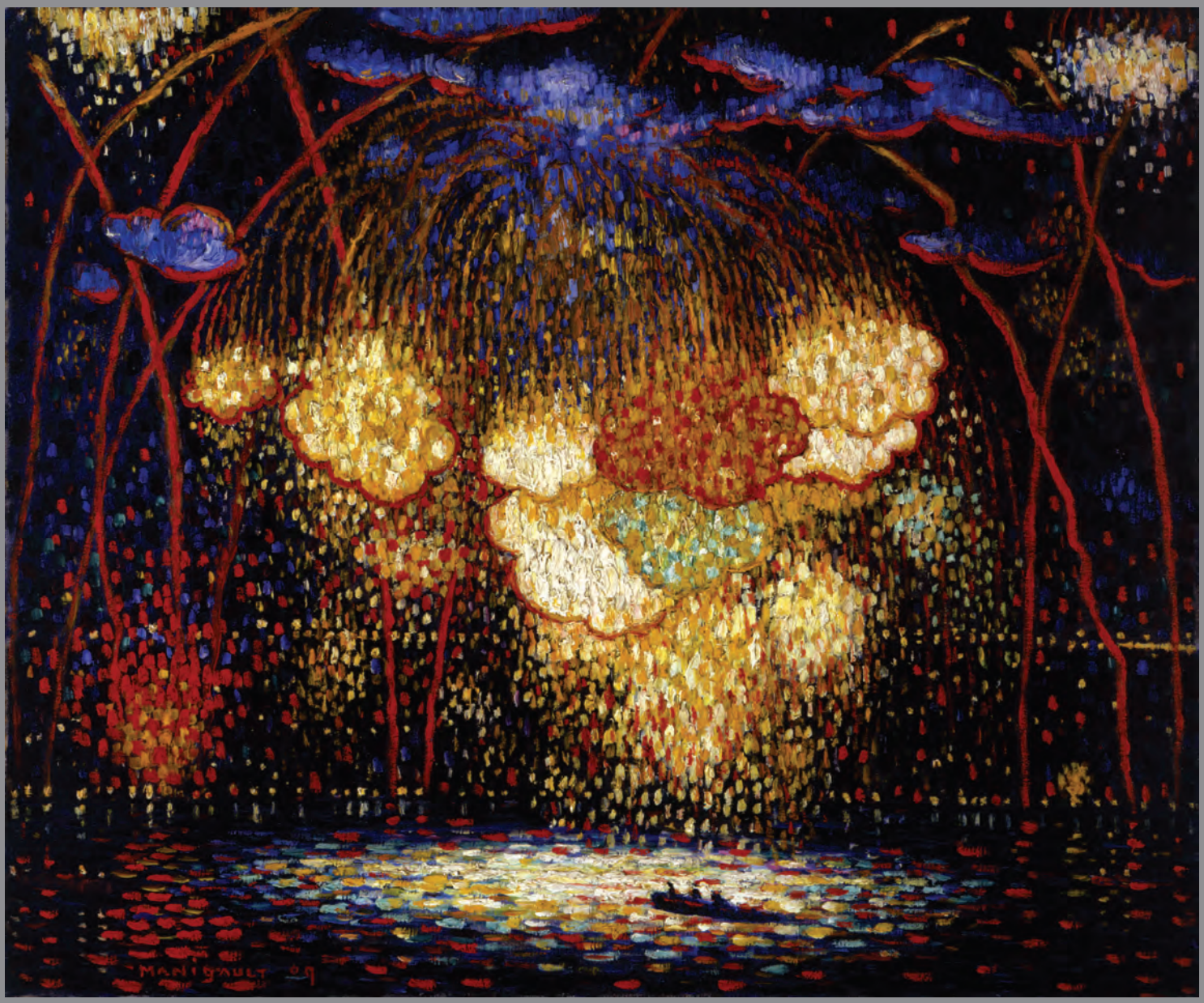
EMERGING INFECTIOUS DISEASES®

Emerging Infections Program

September 2015



Edward Middleton Manigault (1863–1923), The Rocket, 1909. Oil on canvas, 20 × 24 in /50.8 × 60.69 cm. Columbus Museum of Art, Ohio, USA; Museum Purchase, Howald Fund II, 1981.009.

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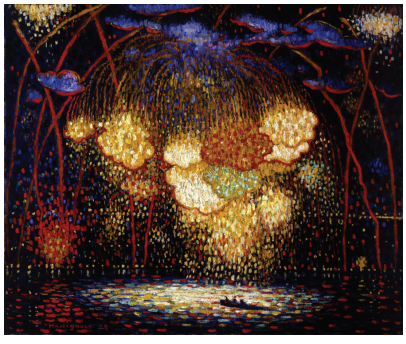

On the Cover

Edward Middleton Manigault (1863–1923)
***The Rocket*, 1909.**

Oil on canvas, 20 × 24 in / 50.8 × 60.69 cm. Columbus Museum of Art, Ohio, USA; Museum Purchase, Howald Fund II, 1981.009.

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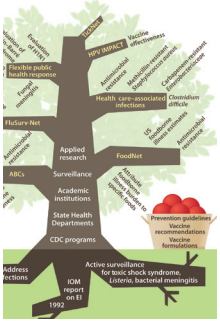

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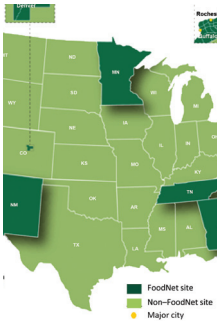

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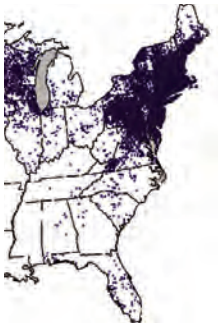
Emerging Infections Program

Medscape EDUCATION ACTIVITY



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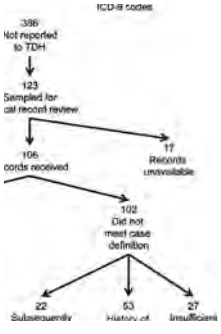

EMERGING INFECTIOUS DISEASES
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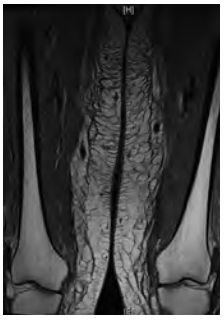
Emerging Infections Program

Synopsis

Medscape EDUCATION ACTIVITY

New treatments, rapid and inexpensive identification methods, and measures to contain nosocomial transmission and outbreaks are urgently needed.



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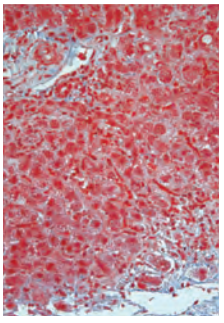

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International Conference on Emerging Infectious Diseases 2015 Poster and Oral Presentation Abstracts http://go.usa.gov/3AwnF

EMERGING INFECTIOUS DISEASES®

20 YEARS

Presenting the ongoing challenge that emerging microbial threats pose to global health

Emerging Infections Program—20 Years of Achievements and Future Prospects

Ruth Lynfield, William Schaffner

"Disease-causing microbes have threatened human health for centuries. The Institute of Medicine's Committee on Emerging Microbial Threats to Health believes that this threat will continue and may even intensify in coming years" (*1*). Thus begins the Institute of Medicine's 1992 Report on Emerging Infections. The Institute of Medicine indicated that "emergence may be due to the introduction of a new agent, to the recognition of an existing disease that has gone undetected, or to a change in the environment that provides an epidemiologic bridge." The recommendations encompassed both the ability to detect (surveillance) and respond to emerging infections. These recommendations laid the groundwork for establishment of the Emerging Infections Program (EIP).

This issue of Emerging Infectious Diseases marks the 20th anniversary of the EIP. Sponsored and organized by the Centers for Disease Control and Prevention (CDC), the EIP is a multifaceted collaboration of CDC with 10 state health departments and their academic partners, with the goal of conducting a portfolio of work that can be characterized as enhanced public health surveillance and applied research to detect, prevent, and control emerging infectious diseases. Collaboration derives from the Latin word "collaboratus," meaning to labor together. The collaboration has been profound and successful, with marked commitment, creativity, and passion contributed by all participants.

This special issue incorporates a Festschrift for the EIP, celebrating the accomplishments of this distinctive enterprise over the past 2 decades. The first article of the series uses a tree metaphor to describe the history of the EIP over the past 20 years and discusses future directions for the network. The following article provides a state-based perspective, which includes the enhancement of public health infrastructure and the development of new academic and public health partnerships. Another article describes the considerable training and teaching activities undertaken by EIP investigators. Although training was among the consortium's explicit goals when EIP was initiated, its funding has been evanescent, thus requiring commitment and imaginative flexibility to create training opportunities in the context of active investigations. However, EIP investigators have derived great pleasure in training the next generation of public health epidemiologists, and this has yielded dividends for mentees, mentors, and public health.

These initial articles are followed by a series of reviews that summarize and assess core EIP areas and some related noteworthy projects. The network has successfully established population-based surveillance for many pathogens of public health importance and has been able to provide insights into risk factors for disease, and characterization of pathogens. EIP data have been used to inform public health recommendations for the prevention and control of multiple infectious diseases and to evaluate public health

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Guest Editors

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interventions. Not resting on their laurels, the authors of these articles also look to future challenges, including those directly related to the infections, as well as others imposed by health inequities and changes in technology. A series of original research contributions by EIP investigators and their collaborators follows the reviews.

The scientific work of the EIP is directed through a genuinely collaborative steering committee comprised of lead investigators from all sites in the field, as well as CDC. It is co-chaired by a CDC investigator and a site senior investigator. Priority-setting discussions are open and genial, informed equally by national views and local perspectives. Formal votes are rare; consensus building is the norm. The participants have longevity; many have been with the program since its inception and have nurtured it through 2 decades of administrative, fiscal, and scientific labyrinths. As such, the participants have become true partners and value the mutual trust, sense of harmony, and friendships that have flourished over the years. These qualities, along with a shared commitment to science-based public health practice, have led to the success of the EIP and bode well as the network looks forward to tackling the next generation of emerging issues of public health importance.

Reference

1 Lederberg J, Shope RE, Oaks SC Jr, editors. Emerging infections: microbial threats to health in the United States. Washington (DC): The National Academies Press; 1992 [cited 2015 Jun 18]. http://www.nap.edu/catalog/2008/emerging-infections-microbial-threats-to-health-in-the-united-states

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Cultivation of an Adaptive Domestic Network for Surveillance and Evaluation of Emerging Infections

Robert W. Pinner, Ruth Lynfield, James L. Hadler, William Schaffner, Monica M. Farley, Mark E. Frank, Anne Schuchat

"The best time to plant a tree was 20 years ago;
the second best time is now." —Chinese Proverb

Through the metaphor of an adaptive, organic entity—a tree with roots, a trunk, large limbs and smaller branches, fruits, and seeds (Figure 1)—this article describes the Emerging Infections Program (EIP), reflects on this network's accomplishments over the past 20 years, and considers opportunities and challenges for the future. Other articles in this 2015 20th anniversary issue of Emerging Infectious Diseases focusing on the EIP expand on many of the ideas introduced here, providing additional discussion, details, and references.

Roots

The concepts of emerging infectious diseases are now familiar to the scientific community and the public. However, it took a 1992 Institute of Medicine report to emphasize the dynamic and modern factors that cause infectious diseases to emerge and re-emerge and to put to rest the idea of infectious diseases as a solved problem, a worry for earlier times (*1*). The Centers for Disease Control and Prevention (CDC) Plan to Address Emerging Infections, released in April 1994, provided recommendations for action by CDC and other public health agencies (*2*). The CDC Plan highlighted the foundational role of surveillance and included in the recommendations creation of a network comprising state public health agencies, academic institutions, and CDC for special surveillance and applied public health research. The EIP sprang from these recommendations.

Even before that time, active, population-based surveillance projects dating to the 1970s had provided a general model for the EIP. Active surveillance and related research conducted through collaborations between CDC and health departments generated information on the burden of and risk factors for toxic shock syndrome, listeriosis, *Haemophilus influenzae* type b (Hib) and group B *Streptococcus* (GBS) infections, and meningococcal disease (*3*–*6*). An earlier population-based active surveillance effort on bacterial meningitis conducted in Bernalillo County, New Mexico, provided a similar model (*7*). The approach—population-based, active, laboratory-based surveillance, sometimes coupled with collection of disease-causing isolates and always including key epidemiologic information—was incorporated into today's EIP activities.

Whereas earlier activities focused on a single disease or a small number of diseases and activities and operated through contracts between CDC and health departments, from the beginning the EIP dealt with multiple public health issues concurrently; engaged experts in state public health agencies, academic institutions, and a variety of CDC programs; and operated as a consortium in which stakeholders have mutual responsibilities for setting priorities, planning and executing activities, and synthesizing and communicating results (*8*,*9*).

Trunk

Understanding the urgency, challenge, and complexity of its mission and the need for a flexible model to support it, the EIP built a network of collaborator sites, each contributing to shared governance, and established a strategic approach to guide projects. These elements serve as the trunk, or supportive infrastructure, for EIP efforts.

The number of sites increased—from 4 in 1994 to the current number of 10 by 2002—as EIP activities demonstrated success, the need for broader geographic and demographic representation was recognized, and funds became available (Figure 2). EIP sites involve state health department personnel and key collaborators in academic institutions; each site engages others to conduct activities, including clinical laboratories and infection control professionals throughout each EIP area. The 10 EIP sites, together with several CDC programs and a coordinating unit

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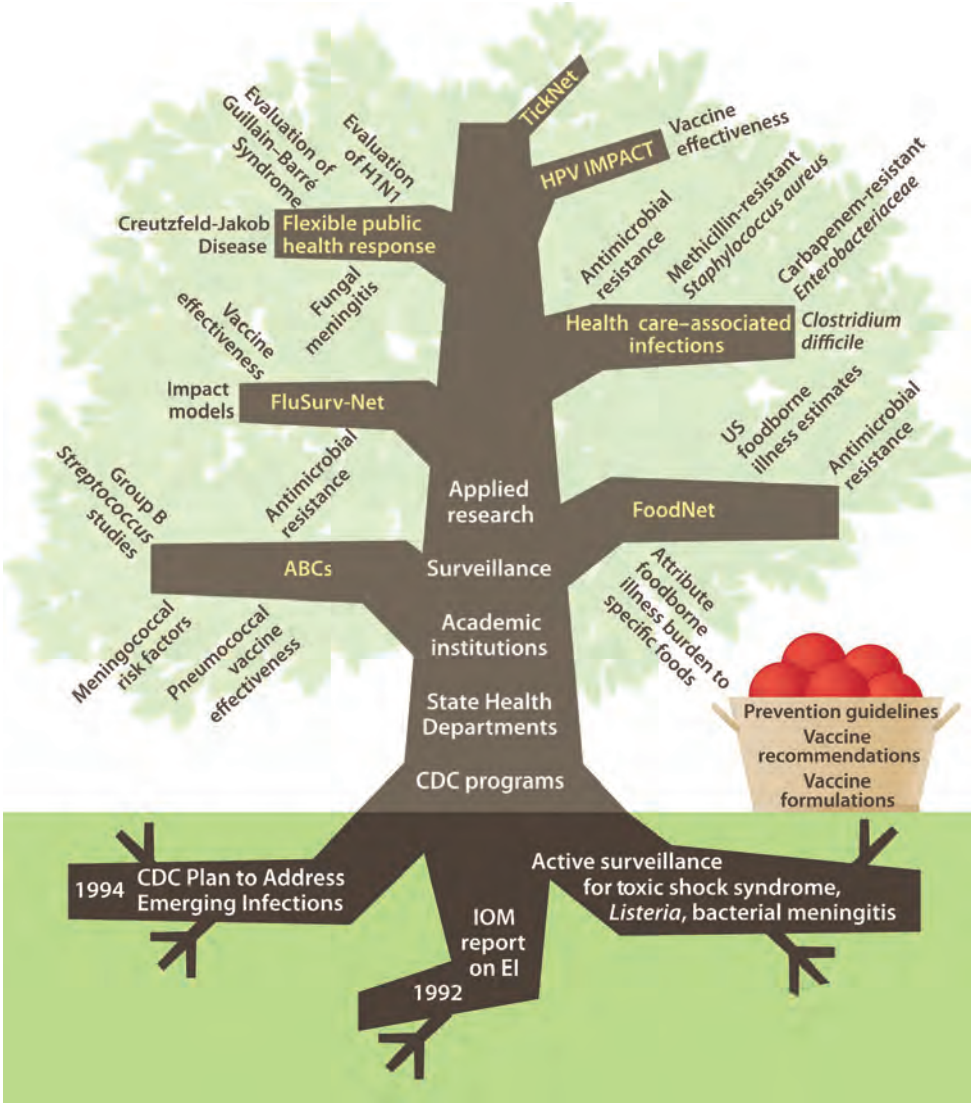

Figure 1. Structure and development of the Emerging Infections Program, United States. ABCs, Active Bacterial Core Surveillance; CDC, Centers for Disease Control and Prevention; IOM, Institute of Medicine; EI, emerging infections; HPV, human papillomavirus.

at CDC, form the EIP network. EIP support comes from core funding intended to maintain and support the network and invest in key activities. In addition, other sources support specific EIP activities. For example, funding from the US Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Food Safety Initiative of CDC have supported foodborne diseases work; the immunization program of CDC supports vaccine effectiveness evaluation and related surveillance of vaccine-preventable disease. Extramural funding for EIP cooperative agreements has ranged from $2.3 million for 4 sites in 1995 to an average annual total of $33.8 million for the current 10 sites during 2010–2014.

As early as the first EIP meeting in November 1994, principals at CDC and EIP sites (including representatives from state health departments and academic partners) formed an EIP Steering Group to provide guidance and strategy for EIP activities. By the time of the Steering Group meeting in November 1996, the group had adopted guiding principles and approved a framework for evaluating ideas for new projects, which has guided assessment of potential new areas of work and strategic directions (Table).

Responsibilities and authorities are distributed across the network's membership. State public health agencies have legal authority for conducting surveillance; in this context, academic partners function as agents of the state health departments. CDC has responsibility for expending and managing federal funds invested in the EIP. Resources come from several funding streams, and each source requires accountability for ensuring that funds are spent well on appropriate activities. This distribution of responsibilities and authorities, coupled with the need for ensuring that the EIP can respond nimbly to emerging issues, has meant that governance works flexibly, not rigidly—through negotiations

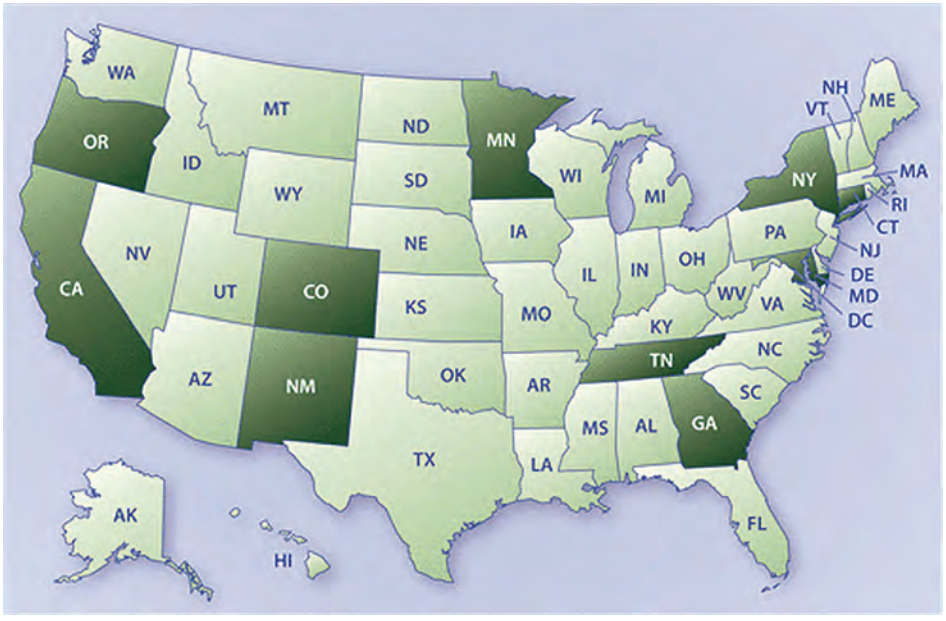

Figure 2. The Emerging Infections Program (EIP) and its key partnerships, United States. Dark shading indicates locations of EIP sites (year established are indicated in parentheses). Minnesota: Department of Health, St. Paul, and Association of Professionals in Health Control, St. Paul (1995); Oregon: Oregon Public Health Division, Portland, and Oregon Health Sciences University, Portland (1995); California: Department of Public Health, Sacramento, and University of California School of Public Health, Berkeley (1995); Colorado: Department of Public Health and Environment, Denver, and University of Colorado Health Sciences Center, Denver (2000); New Mexico: Department of Health, Santa Fe, and University of New Mexico Indian Health Service, Albuquerque (2002); New York: Department of Health, New York, and University of Rochester, Rochester (1997); Connecticut: Department of Public Health, Hartford, and Yale University School of Public Health, New Haven; Maryland: Department of Health and Mental Hygiene, Baltimore, University of Maryland, College Park, and Johns Hopkins University, Baltimore (1997); Tennessee: Department of Health, Nashville, and Vanderbilt University, Nashville (1999); Georgia: Department of Public Health, Atlanta, Emory University School of Medicine, Atlanta, and Atlanta Veterans Administration Medical Center, Atlanta.

and consensus—for the network as a whole and also in each project area. If one considers the distribution of interests and authorities, this model has proven productive. In addition to internal governance, EIP work has benefited from external reviews that provided advice and guidance on strategic directions, and from representatives of professional organizations (e.g., Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Council of State and Territorial Epidemiologists, American Society for Microbiology) serving on several EIP steering committees.

EIP activities generally fall into the categories of surveillance, applied research, and enhanced and flexible public health practice. Active, population-based and laboratory-based surveillance, with collection of disease-causing isolates linked to epidemiologic information from case reports, forms the foundation of many EIP activities. This foundation accurately documents the burden of disease and key characteristics of disease-causing microbes and supports special applied research activities, such as evaluation of vaccine effectiveness and epidemiologic risk factor studies. On several occasions, the EIP has proved its flexibility and provided enhanced responses to precipitously emerging issues.

Limbs and Branches

With an established network of sites, governance, and a strategy in place, the main limbs, or programs, of the EIP grew in 4 broad thematic areas: invasive bacterial diseases; foodborne diseases; health care–associated infections; and influenza. Each program contains a portfolio of established and newer projects. Leveraging EIP resources flexibly as needed to provide fast public health responses to emerging outbreaks is a fifth limb of the EIP tree. Other branches fill out the tree.

Active Bacterial Core Surveillance

Active Bacterial Core Surveillance (ABCs) of the EIP determines the incidence and epidemiologic characteristics of invasive disease caused by bacterial pathogens, including *Streptococcus pneumoniae*, groups A and B *Streptococcus*, *H. influenzae*, *Neisseria meningitidis*, and *Bordetella pertussis* (*10*,*11*). ABCs activities comprise surveillance and studies to better understand diagnostics, risk factors for disease, and vaccine effectiveness.

Foodborne Diseases Active Surveillance Network

The Foodborne Disease Active Surveillance Network (FoodNet), the principal foodborne disease component of the EIP, is a collaborative venture among the 10 EIP sites, the USDA and the FDA. This network monitors foodborne disease caused by bacterial and parasitic pathogens (*Campylobacter*, *Cryptosporidium*, *Cyclospora*, *Listeria*, and *Salmonella* spp.; Shiga toxin–producing *Escherichia coli* O157 and non-O157 *E. coli*; and *Shigella*, *Vibrio*, and *Yersinia* spp.) (*12*).

Table. Guiding principles for the Emerging Infections Program complied from notes of the meeting of the EIP Steering Group, November 13–14, 1996, United States*

Guiding principles
EIP network is a national resource for surveillance, prevention, and control of emerging infectious diseases. EIP activities go beyond the routine functions of health departments in ways that enable challenging new public health questions to be answered.
Core EIP activities target the most pressing issues in infectious disease and are selected with regard to what is appropriate, in particular, for the EIP network (including considerations such as the burden of disease, preventability, and providing resources not provided through categorical funding)
EIP maintains sufficient flexibility for emergency response and to address new problems as they arise.
Training is a key function of EIP (public health students, laboratory personnel, preventive medicine residencies, infectious disease fellows)
EIP network develops and evaluates public health practices and transfers what is learned to the public health community (e.g., computerized transfer of data, molecular epidemiology, accomplishing public health work successfully in a changing health care environment).
EIP network should give high priority to projects that lead directly to prevention of disease.

*EIP, Emerging Infections Program.

Influenza Hospitalization Surveillance Network

Through the Influenza Hospitalization Surveillance Network, the EIP, along with additional states, conducts surveillance for laboratory-confirmed influenza-related hospitalizations in children and adults (*13*). The influenza program at CDC uses this surveillance information from EIPs, together with surveillance for other aspects of influenza to develop a full annual picture of influenza and the effect of vaccination efforts in the United States.

Healthcare-Associated Infections Community Interface

The Healthcare-Associated Infections Community Interface (HAIC) investigates major and time-sensitive questions about emerging health care–associated infection (HAI) threats and antimicrobial drug resistance in the United States. The in-depth approach of the EIP to surveillance that monitors HAI diseases in health care institutions and the community and related research activities complements the broader approach used by the National Healthcare Safety Network (*14*).

Other Branches

Other EIP branches include earlier projects on unexplained deaths, encephalitis, hepatitis, and current TickNET and human papillomavirus (HPV) IMPACT projects (*15*). Surveillance to identify causes for unexplained deaths with characteristics of infectious diseases was conducted during the early years of the EIP (*16*). Subsequently, EIP investigators in some sites focused on the clinical challenges in diagnosing encephalitis and resultant difficulties in epidemiologic characterization, and undertook a several-year project on encephalitis. Beginning by comparing and validating several diagnostics tests, this project estimated the burden and honed characterizations of encephalitis syndromes in relation to causative agents (*17*). TickNET is a network of 5 EIP sites created in 2007 to foster collaboration on surveillance, research, education, and prevention for tickborne diseases. HPV IMPACT conducts a postlicensure evaluation of HPV vaccine in 5 EIP sites (*18*).

Flexible Responses to Emerging Issues and Outbreaks

Flexibility to respond is a foundational principle for the EIP. There are several examples of the EIP's timely engagement in urgent situations.

Creutzfeldt-Jakob Disease, 1996

In 1996, an expert committee to the government of the United Kingdom recognized cases in humans of a new variant Creutzfeldt-Jakob disease (CJD) and concluded that the agent responsible for bovine spongiform encephalopathy might have spread to humans. The EIP then rapidly developed active CJD surveillance in 5 sites. This surveillance, coupled with other reviews of national CJD mortality rates, provided some assurance that the new variant CJD had not spread to the United States and helped substantiate effectiveness of death certificate reviews in identifying CJD deaths in the United States (*19*).

Hib Vaccine Shortage, 2008

When an Hib vaccine shortage occurred in the United States during 2008, the EIP contributed to evaluating the potential effect of deferred doses through active surveillance in the ABCs. In addition, EIP sites in Georgia and Minnesota evaluated nasopharyngeal carriage of Hib (*20,21*).

Influenza A(H1N1)pdm09, 2009

The EIP made contributions during the influenza pandemic in 2009, not only through surveillance of hospitalizations caused by influenza but also by conducting a key evaluation of vaccine safety during the immunization campaign that year. Because of the prior association between Guillain-Barre syndrome and the 1976 vaccine against H1N1 subtype influenza virus, the EIP was engaged to conduct enhanced surveillance to estimate the magnitude of any increased risk for Guillain-Barre syndrome after administration of vaccine against influenza A(H1N1)pdm09 virus. The EIP findings, that the excess risk was comparable with that associated with prior seasonal influenza vaccines and

smaller than that observed in 1976, provided evidence for sustaining the vaccination campaign (*22*).

Fungal Meningitis Epidemic, 2012

Beginning in 2012, Tennessee EIP staff first detected and then provided leadership in a multistate investigation of fungal meningitis. This outbreak was caused by use of contaminated medication and resulted in 751 cases and 64 deaths across 20 states (*23*,*24*).

Fruits

The EIP has borne fruit in several areas. These areas include postlicensure evaluation of vaccines, foodborne diseases, antimicrobial resistance, and health care–associated infections. The EIP has communicated its findings in nearly 1,000 publications.

Vaccine Development and Policy

The EIP has provided critical elements of the evidence base to support US immunization policy, including addressing the burden of disease, defining population groups at higher risk, evaluating cost-effectiveness of various vaccine recommendations, and determining duration of protection after widespread use. Initial recommendations for 7-valent pneumococcal conjugate vaccine (PCV7), 13-valent pneumococcal conjugate vaccine, and meningococcal conjugate A/C/Y/W-135 vaccines were supported by ABCs data, and the HPV IMPACT project provided outcome data that helped evaluate early effects of HPV vaccine implementation (*10*,*25*,*26*). The EIP's laboratory-based surveillance and characterization of circulating strains contributed to development and recent recommendation for use of meningococcal B vaccines and group A streptococcal vaccines under development (*27*,*28*).

Formulating, Implementing, and Evolving an Effective Public Health Prevention Strategy against Perinatal GBS Disease

A series of surveillance and prevention studies from ABCs showed the preventable burden of early-onset (GBS) infections, evaluated the relative effectiveness of initial screening vs. risk-based prevention strategies, provided assessments of prevention guidelines uptake and effect, and identified missed opportunities for additional prevention. A retrospective cohort study (*10*) conducted by using ABCs infrastructure showed that prenatal screening was 50% more effective than the risk-based strategy of directing intrapartum antimicrobial prophylaxis. These data directly resulted in revised GBS prevention guidelines by providing compelling evidence for the recommendation to implement universal prenatal GBS screening. Application of GBS prevention strategies in the era of the EIP has contributed to prevention of ≥85,000 early onset GBS cases (*10*).

Guiding and Monitoring Food Safety Efforts

EIP FoodNet has provided standard surveillance data used by federal agencies—including the FDA, the USDA, and CDC—to assess national trends and progress in reducing foodborne diseases caused by bacterial and parasitic pathogens (*12*), especially in the context of implementing the Food Safety Initiative in 1997 and, more recently, the Food Safety Modernization Act in 2011. Studies conducted at FoodNet sites have also provided many data that contributed to estimates of the burden of foodborne pathogens in the United States in 1999 and in 2010 (*12*). In 1999, studies of antimicrobial drug resistance in *Campylobacter* spp. provided data connecting fluoroquinolone use in animals with emerging fluoroquinolone resistance in human cases of campylobacteriosis (*29*). The FoodNet Population Survey has produced a periodic atlas of specific food consumption prevalence in EIP sites (*12*). The atlas has not only provided baseline data to guide and monitor food safety educational efforts but has become a standard source of data for identifying suspect food in outbreaks caused by widely distributed foods (*9*,*12*).

Investigating and Responding to Antimicrobial Resistance and Health Care–Associated Infections

Over the past 2 decades, the EIP has strengthened the evidence base regarding several antimicrobial drug–resistant pathogens. EIP projects contributed data to the CDC report on Antibiotic Resistance Threats in the United States, 2013, a widely publicized report that outlined the extent of the public health threat of antimicrobial drug resistance (*30*). This report helped prompt development of a National Strategy to Combat Antimicrobial Resistance in Bacteria, issued in March 2015 (*14*).

The EIP has studied antimicrobial drug resistance in invasive pneumococcal disease, methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae*, infections with *Candida* species, and patterns of antimicrobial drug use. The program documented a decrease in drug-resistant invasive pneumococcal isolates after widespread use of PCV7; emergence of resistant serotype 19A, which was not included in PCV7; and another decrease in drug-resistant pneumococcal disease after use of 13-valent pneumococcal conjugate vaccine, which included 19A (*30*,*31*). Analysis of outpatient drug prescriptions and ABCs data found that high use of antimicrobial drugs was correlated with the proportion of nonsusceptible invasive pneumococcal disease, which suggested that local prescribing practices contribute to local drug resistance patterns (*32*). The EIP was instrumental in describing the emergence of community-associated MRSA (*30*), the burden of invasive MRSA (*10*), and a decrease in rates of health care–associated MRSA (*33*). The network determined the

burden of infections with *C. difficile* (*34*) and established surveillance for carbapenem-resistant *Enterobacteriaceae* (*35*). Finally, because antimicrobial drug resistance is driven by use of these drugs, the EIP has conducted prevalence surveys to determine the frequency of infections and use of these drugs in hospitals (*14*).

Seeds

The EIP has planted seeds in the United States and abroad. EIP training, consultation, and collaboration activities have made substantial contributions to public health efforts.

Training in the United States

The EIP has engaged many health care professionals in training, among them numerous master's-level and doctoral-level students. These students have worked on EIP projects that have fulfilled the thesis or practicum requirement for their degree, and many have resulted in publications in peer-reviewed journals and public presentations. In addition, EIP site personnel provide scientific presentations and updates on emerging infectious diseases to local health and public health partners, and several EIP sites hold annual conferences and symposia in their regions (*36*).

EIP-Like Activities Abroad

Surveillance methods, study protocols, and results of EIP work have had effects around the world. An integrated infectious disease and specimen characterization surveillance system in South Africa, modeled after ABCs, has provided valuable information on invasive bacterial, diarrheal, and fungal infections and the effect of pneumococcal and Hib vaccines, and on decreasing opportunistic infections in conjunction with antiretroviral treatment among HIV-infected populations. Data from the ABCs PCV7 vaccine effectiveness study conducted when a vaccine shortage resulted in substantial numbers of children receiving <4 doses of vaccine provided information on partial schedules that supported licensure of 3-dose schedules in the United Kingdom and other countries. Economic analysis that incorporated indirect and direct effects of PCV, derived from EIP data, provided pivotal information for vaccine introduction decisions in countries where initial assessments, before recognition by ABCs investigators that there were indirect benefits, had led policy makers to conclude that the vaccine was too costly to be used routinely. The EIP model spawned International EIPs in Thailand and Kenya (*37*) and was adapted later to regional Global Disease Detection Centers established by CDC and ministries of health in other countries.

Changes in the Climate for EIP

Whereas weather changes often—hourly, daily, and seasonally—climate changes occur more slowly but may have profound effects. From its origins, the EIP has been in the habit of responding flexibly to the severe weather of outbreaks and emerging diseases. Now, however, the broader scientific, technological, and cultural climate in which public health agencies operate and in which emerging infections are addressed is changing substantially, requiring the EIP to adapt.

Culture-Independent Diagnostic Tests and Advanced Molecular Detection

EIP active surveillance for bacterial diseases has depended on isolation of the disease-causing organism. Case finding started in clinical laboratories, and case definitions have included isolation of an organism as part of the case definition (e.g., invasive pneumococcal disease—isolation of *S. pneumoniae* from a normally sterile body site). Clinical diagnoses are increasingly being made through culture-independent diagnostic test (CIDTs), particularly nucleic acid–based tests. Although CIDTs might represent advances in modern medical practice, they can also confound EIP surveillance. Culture-independent diagnostic tests vary in their performance characteristics, and also their market share across EIP sites, which can influence incidence measurements, potentially causing discontinuity of data or requiring modeling to estimate incidence in a way that has not been previously needed. Moreover, the EIP has relied on isolates for antimicrobial drug–susceptibility testing and molecular epidemiology, which cannot be conducted—or conducted in the same way—if there are no longer clinical isolates. EIP surveillance methods, analytic methods, and case definitions will need to adapt, as will laboratory methods applied for drug susceptibility and molecular typing in EIP projects.

Even as CIDTs might challenge the continuity and quality of surveillance data, advances in laboratory technology also present new opportunities. For example, the EIP is engaged in the new advanced molecular detection (AMD) initiative at CDC to explore and advance application of modern molecular technologies to the practice of public health. With its huge asset of collections of population-based and epidemiologically well-characterized strains, the EIP is well positioned to apply AMD methods, such as whole-genome sequencing and metagenomics. As the EIP applies these powerful new tools to characterize strains and understand pathogenesis, they will enhance the quality of the network's science and contribute to the transformation of public health practice that the AMD initiative provides (*38*).

Information Technology and Electronic Health Records

Systematic review of paper medical records by EIP surveillance officers has been central in developing high-quality information for EIP surveillance and special studies. As

electronic health records evolve, this historical approach is disappearing and new efforts by EIP staff are required to gain appropriate and ready access to electronic records and new skills are needed to use them effectively. However, the potential for more efficient, powerful, and innovative use of modern health information technology can outweigh the problems caused by the transition from paper to electronic health records. Instead of transcribing data from charts into EIP surveillance and study forms, well-structured outputs from electronic records can save substantial staff time and resources. Also, use of structured or even ad hoc queries could make EIP surveillance and research projects more flexible and powerful. For example, EIP HAI surveillance uses queries of laboratory-automated culture and susceptibility systems to identify patterns that fit the case definition of multidrug-resistant *Enterobacteriaceae*. Moreover, modern geographic information systems technology offers tremendous possibilities for complementing disease surveillance with monitoring distribution of disease vectors. Recently, the EIP has identified a standard approach for geocoding cases. Adoption of this approach across EIP projects will enable researchers to connect information about cases from different EIP projects (e.g., influenza and pneumococcal pneumonia), which, when linked with other geospatial data, such as socioeconomic or climate or land use data, might help clarify underlying determinants of health and health disparities and the extent to which these pathways are similar across different diseases.

Health Reform and Public Health Practice

Health reform in the United States is affecting the way persons are obtaining health care and is also influencing the range of preventive services available, how they are delivered, and how they are funded. As the relationship between clinical care and public health evolves, there might be a role for the EIP in filling scientific gaps at the population level. The EIP could participate in assessment of the effect of health care reform on health department infectious disease control practice (e.g., evaluation of the role of health departments in direct delivery of clinical services for infectious diseases, such as immunization for tuberculosis and sexually transmitted diseases).

Conclusions and New Directions

The EIP model—close collaboration among state and federal public health agencies along with academic institutions and generation of reliable surveillance information coupled with special studies to address key policy and prevention issues that generally use a population-based approach—has provided numerous dividends for public health work in infectious diseases. The EIP tree is flourishing.

Public health issues other than infectious diseases might also benefit from the EIP model. For example, opioid overdose in the United States, with its recent epidemic-like emergence, might be one such issue. During the coming year, the EIP will explore this idea through projects at 2 sites aimed at strengthening the scientific base for prevention of opioid overdose.

A central premise of the Institute of Medicine report on emerging infections was that the emergence and reemergence of infectious diseases are a consequence of dynamic processes and factors: societal events; health care; food production; human behavior; environmental changes; public health infrastructure; and microbial adaptation (*1*,*2*). Taking these factors into account, the EIP developed into a productive, flexible, and adaptive public health and scientific network. Although current circumstances differ substantially from when the network was founded, in challenges to the public's health and in tools to address them, this vision of an adaptive EIP remains apt. The aim of practicing consequential epidemiology has motivated persons who have engaged in the EIP; we hope this tenet will also guide another generation of public health professionals who will cultivate the EIP over the next 20 years (*39*).

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Emerging Infections Program—State Health Department Perspective

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The Emerging Infections Program (EIP) is a collaboration between the Centers for Disease Control and Prevention and 10 state health departments working with academic partners to conduct active population-based surveillance and special studies for several emerging infectious disease issues determined to need special attention. The Centers for Disease Control and Prevention funds the 10 EIP sites through cooperative agreements. Our objective was to highlight 1) what being an EIP site has meant for participating health departments and associated academic centers, including accomplishments and challenges, and 2) the synergy between the state and federal levels that has resulted from the collaborative relationship. Sharing these experiences should provide constructive insight to other public health programs and other countries contemplating a collaborative federal–local approach to collective public health challenges.

In 1994, the Centers for Disease Control and Prevention (CDC) created the domestic Emerging Infections Program (EIP) as part of the response to the 1992 Institute of Medicine report recommending "the development and implementation of strategies that would strengthen state and federal efforts in U.S. surveillance" (*1*,*2*). The EIP was established as a collaborative population-based surveillance program involving CDC, selected state health departments, and their chosen academic institution partners. The major objective of the EIP was to conduct active population-based surveillance for a range of domestic emerging infectious diseases for which either no surveillance was occurring or state-level surveillance was occurring but "gold standard," consistently high-quality surveillance was needed. The selected state health departments needed to engage clinical laboratories and infection control professionals throughout their jurisdictions. The relationship between CDC and the state health departments chosen to foster the EIP objectives has been a collaborative one, not purely a contractual relationship. Using a cooperative agreement funding mechanism, the federal, state, and academic collaborators have had shared responsibilities for setting priorities, planning and executing activities, and synthesizing and communicating results (*3*).

The infrastructure and expanded capacity that has resulted in terms of resources and collaborative relationships with CDC, between sites, and within each participating state have greatly enriched public health practice at each site and provided multiple state-based "laboratories" to pilot a variety of surveillance initiatives with possible national public health implications. The results have been remarkable: data to drive local and national public health initiatives have been gathered; state laboratory capacity to support surveillance has been updated and expanded, providing a model for expansion in other states; health threats from emerging infectious diseases have been identified and brought to national attention, and their epidemiology has been described; new methods to conduct surveillance have been piloted and adopted; staff in academic centers have become involved in public sector public health practice and research and expanded on them; and training and practice opportunities for public health students—the future epidemiology workforce—have multiplied.

In this article, our objectives are to describe 1) highlights of what being an EIP site has meant for participating health departments and associated academic centers, including accomplishments and challenges, and 2) the synergy between the state and federal levels that has resulted from the collaborative relationship. We hope that sharing these experiences will provide constructive insights to other public health program areas and other countries that are contemplating a collaborative national–local approach to collective public health challenges.

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Health Department Infrastructure and Surveillance Enhancements

Several critical state-level, surveillance-related infrastructural enhancements have resulted from being an EIP site. First, federal EIP funding has been substantial. In 2014, EIP sites received an average of $3.6 million for personnel (including indirect costs), laboratory support, and supplies for all EIP projects in which they participated. This funding paid for a range of staff members, from 22 full-time equivalent (FTE) persons (spread over 27 positions) in the site with the smallest amount of personnel support to 58 FTEs (spread over 80 positions) in the site with the highest level of personnel support. The FTEs included staff in collaborating academic centers but excluded students in training positions.

Having additional epidemiology staff made it possible to conduct gold-standard surveillance for all diseases of EIP interest, with routine auditing of laboratories becoming an accepted feature of laboratory surveillance, thereby ensuring as close to 100% reporting from laboratories as possible. The experience and contacts from these efforts have made it possible for those running programs for non-EIP diseases (e.g., HIV, tuberculosis, sexually transmitted infections) to incorporate audits into their surveillance activities.

The additional resources, also made possible expansion of laboratory capacity to support surveillance. Additional staff enabled processing and storage of specimens of organisms from persons with invasive pneumococcal disease, group A *Streptococcus* (GAS) disease, and bacterial foodborne illness to enable typing and antimicrobial susceptibility testing, critical to the expanded surveillance role EIP sites have served for these infections. Updated laboratory capacity to perform pulsed-field gel electrophoresis enabled the EIPs to be in the forefront of identifying and investigating foodborne pathogen clusters and methicillin-resistant *Staphylococcus aureus* (MRSA) strains (*4*–*7*).

Second, incorporating laboratories, hospital infection prevention and control staff, and infectious disease physicians into the EIP sites by actively seeking their support and developing ways to share the information gathered from active surveillance has resulted in truly collaborative networks in each EIP site. Interest is such that in many sites EIP updates are a routine feature of grand rounds in some hospitals. Such interactions have resulted in more efficient and effective networks for communication and data dissemination, more efficient surveillance, and a sense of partnership among many of those involved (e.g., public health professionals, infectious disease clinicians, infection control practitioners, laboratorians) in contributing toward emerging infections work. These networks were used effectively during 2001–2003, before bioterrorism-related preparedness funding became available to support extensive communication systems in all states.

Third, in 2010, the EIPs began to conduct surveillance for health care–associated infections. Addition of capacity in this area has enabled EIP sites to move beyond encouraging hospitals to enroll in the National Healthcare Safety Network and produce annual reports of infection rates by hospital. EIP sites have established systems for ascertaining the number of central line–associated bloodstream infections within their entire catchment populations. Associated validation studies have identified limitations of definitions and enabled more complete case ascertainment. Methods have been established to enable estimation of the total number of nosocomial infections among hospitalized patients, setting the stage for repeated estimation to monitor trends over time (*8*). Interventions have been developed and studied for their effectiveness in some sites through communitywide collaboration.

Added Value of Academic Center Collaboration

Collaborations with academic health centers have enabled much greater flexibility in the types of surveillance and special studies that the EIPs and, correspondingly, the respective state health departments can undertake. These collaborations not only provide ready access to students looking to participate in research and public health practice projects but also provide easier access for hiring staff for specific short-term projects, making special risk factor studies easier to conduct. In addition, academic center–based staff can conduct intensive surveillance in smaller catchment areas, and interested faculty can collaborate in and enhance population-based surveillance research projects, including tying them into their clinical networks and efforts to seek funding. In Connecticut, for example, faculty from the Yale School of Medicine have taken advantage of, become involved in, and enhanced EIP surveillance for ehrlichiosis, neonatal sepsis, group A GAS disease, chronic liver disease, and precancerous cervical lesions caused by human papillomavirus (HPV) infection; they also have contributed to design and analysis of studies of the effectiveness of pneumococcal, rotavirus, and HPV vaccines. Infectious disease faculty and fellows at the Oregon Health and Science University have contributed to Oregon's studies of *Clostridium difficile* diarrhea, emerging *Cryptococcus gattii* infections, nontuberculous mycobacterial infections, and surveillance and control of carbapenem-resistant *Enterobacteriaceae*. In Minnesota, collaborations with investigators at the University of Minnesota have enabled studies such as the assessment of variant influenza, matching of antimicrobial-resistant bacteria causing infections in animals with those causing infections in humans, and MRSA infections. In Tennessee, fellows and faculty from the Vanderbilt University School of Medicine have used local EIP data in studies of racial, geographic, and socioeconomic differences in the

distribution of pneumococcal serotypes causing invasive disease, group A GAS intracranial infections, invasive pneumococcal infections in patients with sickle cell disease, neonatal early-onset group B *Streptococcus* (GBS) disease, and hospitalizations for influenza. The training relationship established between the Tennessee Department of Health and Vanderbilt University led directly to the prompt recognition and investigation of a recent large, multistate outbreak of fungal meningitis caused by a contaminated injectable steroid product. In Maryland, faculty from Johns Hopkins University designed and led a multisite study using EIP data on risk factors for invasive meningococcal disease among high school students.

Local Use of Data

Being an EIP site has meant conducting surveillance and obtaining local data for diseases for which the site was not previously conducting surveillance, implementing and evaluating prevention activities that could be or were being used without evaluation by other states, and using the data to reinforce existing or establishing new local disease control guidance. Diseases with new surveillance data for local use have included neonatal GBS and MRSA infections, invasive GAS disease and pneumococcal disease, non-O157 Shiga toxin–producing *Escherichia coli* (STEC), hospitalizations for influenza, *C. difficile* diarrhea (community- and health care–associated), and precancerous lesions caused by HPV infection. Diseases with data that have enabled local reinforcement and enhancement of prevention efforts include neonatal GBS, meningococcal disease, pneumococcal disease, influenza, salmonellosis, and HPV infection. As a result of having and using these data at a local level, EIP sites have become a resource to other states about how such data can be used.

Site Contributions to the National EIP—Innovation and Synergy

The state-based EIP sites have contributed to the larger EIP in more ways than conducting the agreed-upon surveillance projects and special studies that have provided national-level data leading to new understanding and prevention initiatives on many fronts (*3*). In particular, these sites have been a source of ideas to be considered for new priority EIP projects, multiple and often independent "laboratories" for working out surveillance methods to meet changing needs, an attraction for local academic center staff to become involved and generate spin-off studies, and sources for training of future public health practitioners.

Innovation

The EIP has a Steering Committee comprising representation from CDC, participating state health departments, and their academic partners from all sites that meets at least annually to discuss administrative matters, progress, and future scientific direction. Although CDC staff usually lead the discussion, goals and priorities are determined collaboratively. Projects originally proposed by EIP sites that have shaped EIP priorities include surveillance for community-associated MRSA (1996 Steering Committee meeting), surveillance for community-associated *C. difficile* infections (2006 FoodNet Steering Committee meeting), and routine analysis of data using area-based socioeconomic measures (2012 Steering Committee meeting). These ideas cut across internal CDC boundaries at the time they were proposed. MRSA and *C. difficile* infections had been largely considered nosocomial problems, housed in CDC's Division of Healthcare Quality Promotion. Initially, finding the right group at CDC to take an interest in the community perspective proved challenging. Measurement and ongoing monitoring of health conditions and risk factors incorporating measures of socioeconomic status other than race/ethnicity was neither centralized nor a routine concern for most CDC infectious disease programs. As a result, the Steering Committee established a Health Equity Working Group to develop standards and set the agenda for incorporating measures of socioeconomic status into routine EIP surveillance (*9*).

EIP sites also have piloted methods testing the feasibility of conducting population-based surveillance for new conditions and responding to changing laboratory technology. EIP sites piloted various forms of surveillance for community-associated MRSA for several years before settling on a common method (*6*,*7*,*10*,*11*). Collectively, a subset of sites piloted a standardized surveillance method for both community- and hospital-onset *C. difficile* infections, a successful endeavor that resulted in its becoming a core EIP surveillance project (*12*,*13*). Similarly, a subset of EIP sites piloted a standard method for surveillance for precancerous lesions for cervical cancer, demonstrating that the method was feasible. Surveillance for HPV cervical cancer precursors is now a core project for 5 EIP sites (*14*) and is contributing substantially in the assessment of the effectiveness of the vaccine at a population level. When some laboratories stopped performing cultures for *E. coli* O157 and switched to testing for Shiga toxin, the ability to detect outbreaks and monitor trends in *E. coli* O157 was threatened. A pilot project at an EIP site demonstrated the feasibility of turning this crisis into an opportunity to conduct surveillance for both non-O157 and O157 STEC by having the state laboratory culture all Shiga toxin–positive broths into which feces had been inoculated (*15*). Subsequently, surveillance for non-O157 STEC became part of core FoodNet surveillance, and these infections are proving to be even more common than infection by the prototypical *E. coli* O157 strain. Finally, the periodic EIP-sponsored FoodNet Population Surveys have measured frequencies of consumption of a variety

of foods, including selected high-risk foods (e.g., alfalfa sprouts, unpasteurized milk). When such data were used in EIP sites as background rates in binomial probability calculations, they enabled rapid identification of food vehicles in outbreaks of salmonellosis, campylobacteriosis, and *E. coli* O157 infection (*16–18*). This method, coupled with confirmatory evidence from food tracebacks, case–control studies, or food testing, is now routinely used in many jurisdictions around the country (*19–21*).

Synergy

Collaborations with academic centers also have provided fertile ground for academic researchers to take advantage of the special surveillance projects being conducted in their midst to conduct spin-off projects, sometimes with funding from non-CDC sources. For example, in Connecticut, Yale University researchers have taken advantage of surveillance for ehrlichiosis, GAS, and HPV to conduct special studies beyond those commissioned through the EIP (*22–26*). Oregon's high rates of disease caused by a clone of serogroup B *Neisseria meningitidis* led to a case–control study demonstrating a strong association with exposure to second-hand tobacco smoke (*27*) and to laboratory studies demonstrating the ability of *N. meningitidis* to alter its capsular polysaccharide (*28*). In Minnesota, academic partners have undertaken special studies of *S. aureus* (*29*) and GBS (*30*). In New York (Rochester) and Tennessee, the extent to which EIP surveillance for laboratory-confirmed influenza underestimated influenza-related hospitalizations in children was identified through collaboration and comparison with a research study with a different design than the EIP influenza surveillance (*31*).

Site-Specific Analyses

EIP sites own their site-specific data and can conduct and publish analyses of these data independently of direct CDC involvement. This ownership has greatly expanded the dissemination of EIP surveillance findings (2 sites alone have published 151 local analyses of data in peer-reviewed publications [online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/9/15-0428-Techapp1.pdf]). In addition, any site wanting to analyze all-site data can make a formal proposal to do so to the Steering Committee which if approved, gives it access to the de-identified all-site dataset (see online Technical Appendix for list of multisite publications led by 2 EIP sites). Overall, this flexibility has resulted not only in expanded dissemination of findings but also in expanded analytic creativity and data analysis capacity, and use of data for local and national purposes.

Training

In another article in this issue, Vugia et al. have summarized the contribution of EIP sites to training of the current and future public health workforce (*32*). Although some training generated by EIP projects has occurred during the course of the CDC-based Epidemic Intelligence Service program and other CDC-based staff have gotten experience with data analysis, most training has occurred at the EIP sites as a result of the partnership in each site with an academic center. In 1 site alone, >190 students received training experiences during 1995–2014 (*32*). Of these, 75 students used their experience to fulfill thesis requirements, and 29 published an article in a peer-reviewed journal.

Challenges

Although being an EIP site has provided multiple benefits for the state health department and academic center at each site, these benefits have come with some challenges. These challenges include data management; need for frequent human subjects committee reviews of special surveillance and nonsurveillance protocols, often by multiple institutions; and dedicated staff to manage complex budgets and contracts. The funding received by sites does not include the substantial in-kind resources necessary to conduct a large multicomponent program, which also must be integrated with existing public health programs.

EIP sites have found that conducting surveillance and research activities requires attention to the logistics of data acquisition, storage, and distribution. Increasing quantities of data have required development within EIP sites of expanded data storage and handling capacity and increased facility with data systems. Many sites have developed home-grown systems capable of gleaning data electronically, making the data available for epidemiologic analysis, while exporting required fields to CDC for multisite data aggregation. Such systems need built-in flexibility—for example, ready ability to add new conditions or variables of relevance to public health stemming from the sorts of emerging disease problems on which EIPs are called to address. Informatics expertise has proved essential.

In many sites, the EIP is the major source of protocols submitted to institutional review boards (IRBs). Whether a given EIP endeavor constitutes "research" meeting the federal definition (i.e., "designed to develop or contribute to generalizable knowledge" [*33*]) is not always clear because analysis of routinely collected surveillance data may provide knowledge that is, at least in some sense, generalizable. CDC routinely analyzes data generated by state public health agencies in the course of ascertaining and controlling reportable diseases to identify new risk factors and trends that may well be generalizable; not surprisingly, CDC and state health departments often have arrived at different determinations as to whether a given EIP activity constituted research. Moreover, some university collaborators consider any study in which its students are engaged to be research, requiring the protocol's review by its IRB. The requirement

that all IRBs approve the final protocol, and the multiplicity of IRBs (including those of individual hospitals, reviewing and imposing their own requirements on each protocol) for a 10-site EIP study involving university collaboration, can consume considerable time and effort.

With time, activities and expectations for EIPs have expanded, a fact welcomed by most sites. However, funding for the administrative work required by such expansions, including budget, contracts, and IRB tracking, and for hiring experienced epidemiologists to lead new projects has not always kept pace. EIPs note that funding increasingly must be directed to specified projects, leaving them with little flexibility and reduced ability to move beyond collecting data to writing articles for publication or crafting new protocols. As a consequence, such activities are increasingly left to CDC, jeopardizing some of the synergy of the collaborative partnership.

Given the challenges we describe and the frequent necessary coordination of surveillance and epidemiologic activities between local hospitals, laboratories, health departments, and state and federal partners, the structural setup that most EIP sites worked out is one in which the program is located within the lead state health department with or without a co-location within the lead partner school of public health or medicine.

Summary

The collaborative nature of the EIP has resulted in enhanced surveillance and laboratory capacity and communication networks in the 10 state public health departments. In addition, it has enriched research and public health training at the partner academic centers and produced synergy with the involved CDC programs, broadening the creativity and data analytic and dissemination capacity of all involved entities.

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Dr. Hadler has worked with the EIP since its inception in 1995, first as the Connecticut State Epidemiologist and more recently based at the Yale School of Public Health, where he is Clinical Professor of Epidemiology. He was a member of the EIP Steering Committee during 1995–2008.

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etymologia

Surveillance [sər-vāl'əns]

From the French *surveiller*, "to watch over," public health surveillance has its roots in 14th-century Europe. In an early form of surveillance, in approximately 1348, the Venetian Republic appointed guardians of public health to detect and exclude ships that carried plague-infected passengers. In 1662, English demographer John Graunt analyzed the mortality rolls in London and described a system to warn of the onset and spread of plague. Until the 1950s, "surveillance" referred to monitoring a person exposed to a disease; the current concept of surveillance as monitoring disease occurrence in populations was promoted by Alexander Langmuir of the Communicable Diseases Center (now the Centers for Disease Control and Prevention).

Image courtesy Phillip Martin clip art, http://architecture.phillipmartin.info/

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Training in Infectious Disease Epidemiology through the Emerging Infections Program Sites

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One objective of the Emerging Infections Program (EIP) of the US Centers for Disease Control and Prevention is to provide training opportunities in infectious disease epidemiology. To determine the extent of training performed since the program's inception in 1995, we reviewed training efforts at the 10 EIP sites. By 2015, all sites hosted trainees (most were graduate public health students and physicians) who worked on a variety of infectious disease surveillance and epidemiologic projects. Trainee projects at all sites were used for graduate student theses or practicums. Numerous projects resulted in conference presentations and publications in peer-reviewed journals. Local public health and health care partners have also benefitted from EIP presentations and training. Consideration should be given to standardizing and documenting EIP training and to sharing useful training initiatives with other state and local health departments and academic institutions.

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The Emerging Infections Program (EIP), funded by the Centers for Disease Control and Prevention (CDC), is a national network for population-based surveillance and epidemiologic studies of emerging infectious diseases in the United States. Since its inception in 1995, the EIP has grown from 4 initial sites to its current network of 10 sites involving state health departments (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) and collaborators in academic institutions, local health departments, health care facilities, and clinical laboratories, as well as in CDC and other federal agencies (*1*). One of the objectives of the EIP is to "Provide training opportunities in infectious disease epidemiology…" (*2*). Training opportunities were to be based on EIP activities, primarily active or enhanced surveillance and applied research on the prevention and control of emerging infectious diseases, most of which fall under the rubrics of invasive bacterial diseases, foodborne diseases, influenza, and health care–associated infections (*1*). Because there has been no dedicated funding or standard guidelines for the EIP training objective, each site has determined what training to provide, to whom, and how.

Most EIP sites are directed by a partnership of co-directors from a state health department and a local/regional school of public health or school of medicine, to maximize the strengths of both institutions. Many senior EIP staff at state health departments hold voluntary faculty appointments at their local schools of public health or medicine. In addition, each EIP site collaborates extensively with its local health departments, health care facilities, clinical laboratories, and other nearby academic institutions. We contacted all 10 EIP sites to ascertain the extent of training performed during the first 2 decades of the program and develop recommendations for further improving these activities as the program moves forward.

EIP Trainees and Training Opportunities

By the 20th year of the EIP, all 10 sites had hosted a variety of trainees. Not all sites have consistently documented all training activities, but adequate information was available

to provide an overall picture of the types of trainees and the spectrum and depth of their activities. Trainees have included undergraduates; graduate students (candidates for master of public health [MPH], doctor of public health, doctor of philosophy, and doctor of medicine degrees); postgraduate fellows; medical residents or infectious disease fellows; CDC Epidemic Intelligence Service officers; and laboratory personnel. Most trainees came from local schools of public health or medicine, but many also came from distant institutions (including international). Connecticut EIP trainees, for example, have come from 18 different colleges and universities, with most from the Yale School of Public Health.

All 10 EIP sites have had trainee projects that were used for graduate student theses or practicums. At the Connecticut EIP, >190 students received training from 1995 through 2014. Of these, 75 used their experiences to fulfill thesis requirements, and 29 published their work in a peer-reviewed journal. Similarly, at the Minnesota EIP, 116 master's theses and 7 doctoral theses were written on the basis of EIP data, and at least 15 of these were subsequently published in peer-reviewed literature. Examples of EIP surveillance and epidemiologic projects on which trainees have worked illustrate the wide variety of emerging infectious disease issues and datasets available to trainees (Table). Projects have included site-specific data as well as data from several participating EIP sites.

Undergraduate and graduate students have also been employed on a part-time or short term basis at several EIP sites. These students typically worked on implementing EIP surveillance activities and epidemiologic investigations, including data collection, entry, analysis, and reporting. Many EIP trainees have subsequently entered the public health workforce at the local, state, and federal levels (including CDC and the Food and Drug Administration), and some have become permanent employees at the sites where they trained. Others have gone on for additional study or have taken positions in hospitals and academia.

Symposia/Regional Conferences

Most EIP sites regularly provided scientific presentations, symposia, and updates on emerging infectious diseases to local health care and public health partners. For example, the Minnesota EIP has sponsored 20 annual 1- or 2-day conferences on "Emerging Infections and Clinical Medicine," with an average of 275 attendees each year. In fall 2014, the Tennessee EIP conducted its 15th Annual Scientific Presentation Day program, hosting ≈300 attendees from across Tennessee, and the California EIP held its 14th annual "Under Surveillance" symposium with 131 attendees from the San Francisco Bay area. In March 2015, the Georgia EIP hosted its 12th Annual EIP Meeting, with ≈230 attendees. Attendees served by these regional conferences have included public health nurses, epidemiologists, laboratorians, hospital infection control practitioners, students, and health care providers.

Examples of Local Training Activities

Connecticut EIP

Connecticut EIP staff from the state health department and Yale EIP co-teach a full semester seminar course, "Investigation of Disease Outbreaks," for MPH students at the Yale School of Public Health; 257 students took the course during 1999–2014. This popular practical course on applied field epidemiology highlights many of the innovative surveillance and analytic epidemiology methods developed by the EIP network. EIP staff have collaborated with the Connecticut Department of Public Health's Food Protection Program to provide a variety of training opportunities to local health departments on topics that included foodborne disease surveillance and outbreak detection, investigation, and response. EIP staff have served as speakers at annual statewide environmental health training programs and regional recertification training workshops for local sanitarians. In 2011 and 2013, EIP staff provided training in outbreak response to a multidisciplinary audience comprised of public health nurses, sanitarians, laboratorians,

Table. Examples of surveillance activities and epidemiologic projects involving trainees, Emerging Infections Program sites, United States, 1995–2014

Surveillance and epidemiologic projects
A. Invasive bacterial diseases
a. Invasive pneumococcal disease
b. Pneumococcal conjugate vaccine effectiveness
c. Pneumococcal carriage
d. Invasive group B streptococcal disease
e. Invasive group A streptococcal disease
f. *Neisseria meningitidis* infections
B. Foodborne diseases
a. *Salmonella* infections
b. *Salmonella* antibiotic resistance
c. *Shigella* infections
d. *Campylobacter* infections
e. Shiga toxin–producing *Escherichia coli* (STEC), O157, and non-O157
f. *Cryptosporidium* infections
C. Health care–associated infections
a. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections
b. *Clostridium difficile* infections
D. Influenza
a. Influenza surveillance
b. Influenza A(H1N1) hospitalizations
c. Guillain-Barré syndrome surveillance
E. Other diseases or conditions
a. Unexplained illness and death surveillance
b. Fungal infection surveillance
c. Tickborne disease surveillance
d. Acute/chronic liver disease surveillance
e. Encephalitis etiology
f. Human papillomavirus vaccine effectiveness

and epidemiologists, using the Council to Improve Foodborne Outbreak Response Toolkit (*3*).

Georgia EIP

Since 2011, the Georgia EIP has offered a 1-year fellowship for infectious disease fellows in their third year at the Emory University School of Medicine. Under the supervision of the Georgia EIP co-director at Emory, the fellow is trained in the use of SAS statistical software and other analytic tools and is expected to present study results at a regional or national meeting and submit a manuscript to a peer-reviewed journal.

New Mexico EIP

New Mexico EIP staff have helped develop and implement a curriculum for second-year medical students that provides a service-learning opportunity in infection control and prevention in outpatient settings. A pilot study conducted in 2013 (and an expanded offering in 2014) involved 19 medical students with the following results: 1) increased medical student awareness and knowledge of infection control practices and their role in the ambulatory care setting, 2) provided feedback to the practices concerning quality improvement recommendations, and 3) increased awareness among community health settings of best practices in infection control.

Tennessee EIP

Tennessee EIP staff have provided annual outbreak training to public health personnel statewide for >14 years. Training exercises have frequently focused on pathogens and diseases being monitored by EIP and have included hands-on training in the evaluation of surveillance systems and in outbreak detection, investigation, and response. Trainees have included nurses, epidemiologists, laboratorians, and environmentalists, with attendance ranging from 100 to 250 each year. Beginning in 2010, Tennessee EIP FoodNet staff have conducted a course for MPH students at Vanderbilt University on public health surveillance, focusing primarily on EIP-related topics.

Training Contributions of EIP Sites

The EIP has made substantial contributions to the training objective in CDC's plan to address emerging infectious diseases in the coming century (*2*). A strength common to EIP sites is the level of engagement of the involved health departments and universities in using epidemiology to address practical questions of public health importance. EIP trainees enjoy the mentorship of academicians and governmental public health practitioners and have a foundation on which to hone skills in disease surveillance, data systems, descriptive and analytic epidemiology, and, in many cases, shaping policy.

The EIP provides a unique opportunity for students at all levels to experience real-world, applied public health, in the context of their academic training. Trainees find it invaluable to participate personally and collaboratively in all levels of a public health activity, from hypothesis generation and data collection to data analyses and final drafting of a report. The training provided by EIP sites is on-the-job training, usually with a one-on-one mentoring relationship between trainee and supervisor. Training capacity is frequently limited by the number of principal investigators and supervisors available to serve as mentors. The large amount of time dedicated to working with trainees is a testament to the commitment that EIP sites make to training the next generations of health care and public health professionals.

Thousands of local public health and health care partners have benefitted from annual local EIP symposia and presentations. The symposia have provided valuable continuing education and opportunities for local and state public health and health care professionals to meet and share experiences as they address critical issues in their communities. The symposia also illustrate how data collected locally can be used to create national public health policy.

Strengthening and Expanding EIP Training

As the EIP continues to carry out its public health mission, reevaluating its training objective and building on past successes will be essential. Efforts to standardize, network, and share training opportunities can strengthen and expand the EIP training objective to benefit future public health professionals through public health service and research on emerging infectious diseases.

EIP training activities should be systematically documented at all sites in a standardized manner, and EIP trainees should be asked to provide a formal evaluation of their training experience. Standardized documentation of these training experiences will allow future evaluation and potential improvement benefitting trainees and supervisors, as well as the partner institutions involved. Such objective assessments can be used to document the utility for dedicated funding to support the training mission of the EIP network.

Several EIP sites have developed additional training initiatives that involve implementing projects specific to their site, to the benefit of local public health and health care students and professionals. Efforts should be made to share these experiences among EIP sites and with non-EIP state health departments, many of whom already partner with local schools of public health or medicine. Expansion of similar trainings in non-EIP sites could be implemented with moderate funding support.

In conclusion, EIP sites have contributed, and will continue to add, to the training of current and future public health and health care professionals, using EIP population-

based surveillance activities and projects on emerging infectious diseases. Consideration should be given to standardizing and documenting EIP training activities and to sharing useful training initiatives with other state and local health departments and academic institutions. Such efforts can contribute further to the training of the next generation of the nation's public health and epidemiology workforce.

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Twenty Years of Active Bacterial Core Surveillance

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Active Bacterial Core surveillance (ABCs) was established in 1995 as part of the Centers for Disease Control and Prevention Emerging Infections Program (EIP) network to assess the extent of invasive bacterial infections of public health importance. ABCs is distinctive among surveillance systems because of its large, population-based, geographically diverse catchment area; active laboratory-based identification of cases to ensure complete case capture; detailed collection of epidemiologic information paired with laboratory isolates; infrastructure that allows for more in-depth investigations; and sustained commitment of public health, academic, and clinical partners to maintain the system. ABCs has directly affected public health policies and practices through the development and evaluation of vaccines and other prevention strategies, the monitoring of antimicrobial drug resistance, and the response to public health emergencies and other emerging infections.

Active Bacterial Core surveillance (ABCs), a program in the Centers for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) network, was launched in 1995 as part of the CDC strategy to address the worldwide threat of emerging infectious diseases (*1*). The goals of EIP are to detect and investigate emerging pathogens; integrate laboratory science and epidemiology; enhance communication about emerging diseases; and strengthen the state and federal public health infrastructure with regard to surveillance, prevention and control programs. Before establishment of EIP, little was known about the national burden of many of the disease areas now under its surveillance umbrella, which include foodborne diseases, influenza-related hospitalizations, health care–associated infections, and invasive bacterial infections.

ABCs and other EIP activities are collaborations between CDC, state and local health departments, and academic institutions. Originally established at 4 sites (California, Connecticut, Oregon, and Minnesota), by 2003 ABCs added Georgia, Maryland, New York, Tennessee, Colorado, and New Mexico, for a total of 10 sites. The sites represent geographic diversity and approximate the racial composition of the US population (*2*). Currently, the population under surveillance ranges from 19 to 42 million (up to 12% of the US population), depending on the pathogen.

ABCs provides population-based surveillance for select causes of invasive bacterial infections in the community, primarily manifested as bloodstream infections and meningitis. At its inception and continuing today, it includes surveillance for invasive infections caused by group A *Streptococcus* (GAS), *Haemophilus influenzae*, *Neisseria meningitidis*, group B *Streptococcus* (GBS), and *Streptococcus pneumoniae*. Surveillance for invasive methicillin-resistant *Staphylococcus aureus* (MRSA), which had long been recognized as a significant nosocomial pathogen, was added to surveillance in 2004 because it had emerged as a substantial cause of invasive infections in the community (*3*). In 2001, rising rates of pertussis (http://www.cdc.gov/pertussis/surv-reporting.html) and legionellosis (*4*) led to the addition of special surveillance for these diseases to ABCs.

Invasive pneumococcal disease (IPD) provides an example of the power of this large, sustained, population-based surveillance system for evaluating public health interventions and providing feedback for additional prevention measures. Although *S. pneumoniae* is a major cause of invasive infections (e.g., bloodstream infections and meningitis) in the United States and worldwide, IPD is not

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reportable in all states. In the late 1990s, when a new vaccine was being developed, a system was needed to determine baseline rates of IPD, evaluate vaccine effectiveness, and monitor circulating serotypes. After establishment of ABCs to fill the void of tracking the disease burden of IPD and other major causes of invasive bacterial disease in the United States, ABCs detected a large reduction in IPD detected among children <5 years of age (for whom vaccination with 7-valent pneumococcal conjugate vaccine [PCV7] was recommended in 2000) and among adults, who benefited from herd protection. ABCs also recognized an increase in IPD rates caused by *S. pneumoniae* serotypes absent from PCV7; this information resulted in accelerated approval of a 13-valent pneumococcal vaccine (PCV13) that has resulted in further reductions in IPD.

Not all infections captured under ABCs are reportable to CDC. Even for those infections included in the CDC National Notifiable Disease Surveillance System, case counts may be underestimated because they rely on reporting by laboratories and clinicians, whereas ABCs tries to actively identify 100% of the cases within the surveillance area. Additionally, epidemiologic data collected by health departments are often incomplete because of limited resources and the inflexibility of the system to capture variables of interest. Unlike the National Notifiable Disease Surveillance System, ABCs also collects isolates and serotypes and tests them for antimicrobial drug susceptibility. These attributes enable ABCs to fulfill 2 critical objectives: 1) to determine the incidence and epidemiologic characteristics of invasive diseases under surveillance and 2) to determine molecular epidemiologic patterns and microbiological characteristics of these invasive infections.

ABCs Methods

For routine surveillance, a case of invasive bacterial disease is defined as isolation of *H. influenzae, N. meningitidis*, GAS, GBS, *S. pneumoniae*, or MRSA from a normally sterile body site (e.g., blood, joint, pleural, or cerebrospinal fluid) in a resident of the surveillance area. Additionally, cases include ill persons from whom GAS is isolated from a wound or other tissue in the presence of necrotizing fasciitis or streptococcal toxic shock syndrome. Cases of GBS in a mother are also included if GBS has been isolated from the placenta or amniotic fluid in the event of fetal death.

The ABCs approach to surveillance is distinctive; it is active, laboratory based, and population based. The goal is to detect 100% of laboratory-confirmed cases by actively contacting all clinical laboratories that routinely process specimens from residents of the surveillance area. Audits are performed regularly to ensure case capture. Efforts at most sites to make ABCs pathogens reportable to state public health agencies have facilitated participation of almost all laboratories (≈600) that serve the surveillance population. Because the population under surveillance is well-defined, US Census data are used to calculate disease incidence rates within the ABCs population. Because of the large population base, CDC uses ABCs data to estimate the national disease burden after adjusting for race and age distribution in the United States.

Medical records review is used to collect demographics, clinical course, outcome, infection type, underlying conditions, and vaccination history for each case-patient. For most patients, an isolate from the first positive culture is collected. Since 1995, with the exception of MRSA (for which a convenience sample of 100 isolates has been collected since 2005), ≈85% of isolates have been collected from eligible patients. Isolates undergo serologic or molecular typing and standardized antimicrobial drug susceptibility testing at CDC or other reference laboratories. A collection of ≈80,000 *S. pneumoniae*, GAS, GBS, *N. meningitides*, and *H. influenzae* isolates is accessible to ABCs partners and external researchers by request (http://www.cdc.gov/abcs/pathogens/isolatebank/index.html). ABCs MRSA isolates are deposited at the Network on Antimicrobial Resistance in *Staphylococcus aureus*, a repository sponsored by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (http://www.niaid.nih.gov/labsandresources/resources/dmid/narsa/Pages/default.aspx).

The ABCs infrastructure is also used to conduct surveillance for other bacterial diseases and provides a foundation for epidemiologic investigations. Examples include special surveillance for pertussis and legionellosis, case–control studies to assess vaccine effectiveness, and cohort studies to assess the uptake and effectiveness of other public health interventions.

ABCs Effects on Vaccine Development, Evaluation, and Policy Recommendations

Because of the large, representative catchment area and the laboratory-linked, population-based epidemiologic data, results from ABCs have been used in the development and prelicensure evaluation of multiple vaccines. After licensure, ABCs data have been used to formulate policy recommendations and to determine the real-world impact of vaccines (Table 1).

As mentioned earlier, ABCs closely tracked the decline in IPD in children after the introduction of PCV7 (Figure 1). Perhaps a more surprising finding, which would not have been possible without the large ABCs catchment area that includes surveillance among all age groups, was the decline in vaccine-type IPD among adults, particularly those ≥65 years of age (Figure 1). ABCs also identified increased incidence of IPD for serotypes not found in PCV7; particularly serotype 19A. These findings contributed to the accelerated approval of PCV13, which includes serotype 19A,

Table 1. Key uses and findings of Active Bacterial Core surveillance data for vaccine development, evaluation, and policy formulation*

Pathogen	Vaccines	Key uses and findings
Streptococcus pneumoniae	PCV7 and PCV13	Selection of serotypes included in PCV7and PCV13 Informed ACIP recommendations for children <5 y of age Tracking postlicensure declines in cases Documented effectiveness of PCV7 Monitoring incidence of nonvaccine serotypes Accelerated regulatory approval of PCV13 Informed ACIP recommendations for PCV13 use in immunocompromised adults and children
Neisseria meningitidis	Conjugate vaccines, serogroup B vaccines	Informed ACIP recommendations for children 11–18 y of age Informed ACIP recommendations for booster dose Documented vaccine effectiveness Informed ACIP infant meningococcal recommendations Evaluated potential effect on serogroup B disease in United States
Haemophilus influenzae	Hib vaccine	Tracking postlicensure declines in Hib disease Tracking shift toward non-Hib disease; Evaluated effect of vaccine shortages
Group A *Streptococcus*	M-type vaccine (under development)	Estimated degrees of protection against severe group A streptococcal infections
Group B *Streptococcus*	Trivalent vaccine (under development)	Informing development of vaccine to prevent early-onset (within 1 week of life) group B streptococcal disease
Methicillin-resistant *Staphylococcus aureus*	*S. aureus* vaccine (under development)	Determining population groups to target

*ACIP, Advisory Committee on Immunization Practices; Hib, *H. influenzae* type b vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine. An expanded version of this table with references is available in the online Technical Appendix (http://wwwnc.cdc.gov/EID/article/21/9/14-1333-Techapp1.pdf).

and the recommendation for its use in children ≤5 years of age. Rates of IPD have further declined since introduction of PCV13 (Figure 1).

Age- and serogroup-specific ABCs data highlighted the increased risk for vaccine-preventable meningococcal disease among college students, adolescents, and young adults. These findings contributed to the Advisory Committee on Immunization Practices policy recommendation for routine use of meningococcal conjugate vaccines in all persons 11–18 years of age and subsequent recommendations for a booster dose during late adolescence.

Through long-standing surveillance, ABCs was able to document the persistent decline of invasive *H. influenzae* infections among young children after introduction of type b vaccine in the mid-1980s (Figure 2). ABCs surveillance for *H. influenzae* type b (Hib) disease was critical for monitoring how vaccine shortages affected disease rates. Because of the availability of epidemiologic data linked to serotype determination, a shift toward non-Hib disease in adults in the post–Hib vaccine era has been recognized.

Although trend data may show indirect evidence of a vaccine's effectiveness, proof of effectiveness requires a more formal epidemiologic investigation to account for other factors that may influence the decline in disease incidence. The ABCs infrastructure was used to conduct case–control studies that confirmed the effectiveness of conjugate meningococcal and pneumococcal vaccines against invasive disease. These very large studies could only have been done through an integrated network, and they highlight the efficiencies gained by maintaining such an infrastructure.

Serotype and serogroup data from ABCs pathogens are also being used to help with formulation of vaccines and evaluation of the potential effectiveness of vaccines currently under development, including those products targeting GAS, GBS, *S. aureus*, and serogroup B meningococcal disease. ABCs data have been used to predict the effectiveness in the United States of a 26-valent GAS vaccine and now a 30-valent GAS vaccine that is under development. GBS disease burden and serotype data gathered through ABCs have been used to inform development of a trivalent GBS vaccine now in phase I and II trials. ABCs data have been used to determine which population groups would be the best candidates for receipt of *S. aureus* vaccines to prevent invasive MRSA disease and to evaluate the potential effect of serogroup B meningococcal vaccines on disease burden in the United States.

ABCs Effect on Other Prevention-Related Policies and Practices

ABCs and a precursor surveillance system for GBS were used to define the need for guidelines for providing antimicrobial drugs to pregnant women during delivery to prevent early-onset GBS in their newborns; such guidelines were published in 1992 (*5*,*6*) and 1996 (*7*). Without evidence as to which strategy was better, the 1996 guidelines recommended that health care providers could use either a screening or risk-based approach to decide which women should receive prophylaxis during delivery. An ABCs-based cohort study that sampled from a population of ≈600,000 live-born infants at 8 sites demonstrated the value of screening over the risk-based approach. Specifically, universal prenatal screening of

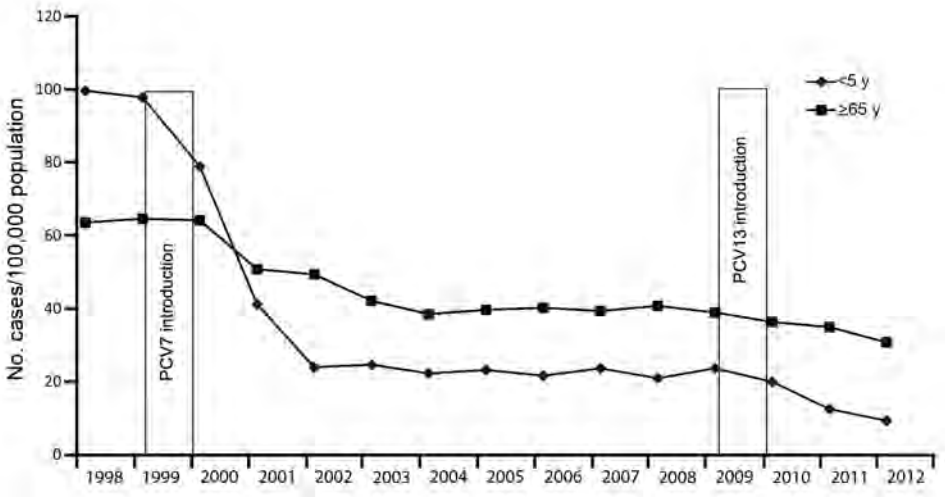

Figure 1. Incidence of invasive pneumococcal disease in children <5 and adults ≥65 years of age, Active Bacterial Core surveillance, United States, 1998–2012. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

pregnant women for vaginal/rectal colonization with GBS and providing antimicrobial drugs during delivery to those who were colonized was ≈50% more effective at preventing early onset GBS than providing prophylaxis to pregnant women on the basis of certain risk factors (*8*). This finding led to issuance of new guidelines in 2002 (*9*) and revised guidelines in 2010 (*10*), which resulted in further reductions in disease. Since the early 1990s, ABCs has documented a ≥80% decline in the incidence of early-onset GBS infection and prevention of an estimated 70,000 cases of early-onset GBS infection (Figure 3).

Guidelines for the prevention of invasive GAS infections were also informed by ABCs surveillance and special studies. An ABCs study found an increased risk for severe GAS infection among household contacts of index patients (*11*). These data, coupled with data that were collected from routine surveillance on the frequency of GAS infection in postpartum women (*12*) and postsurgical patients provided the foundation for the development of CDC policy guidance in households and health care settings (*13*). ABCs surveillance data on the risk for GAS infections among long-term care facility patients also helped inform prevention and control strategies for those settings (*14*,*15*).

Monitoring of Antimicrobial Drug Resistance

The first nationwide estimates of the burden of invasive MRSA were derived from ABCs; in 2005, ≈94,000 cases and ≈18,000 deaths were attributed to invasive MRSA (*16*). Most (≈84%) infections were health care–associated—either hospital-onset (culture obtained >3 days after admission) or health care–associated community-onset (culture obtained from outpatient or within 3 calendar days after admission from a patient with a health care–associated risk factor, which include presence of a central venous catheter within 2 days before MRSA culture or history of surgery, hospitalization, dialysis, or residence of long-term care facility in the 12 months preceding culture date). The prominence of health care–associated community-onset

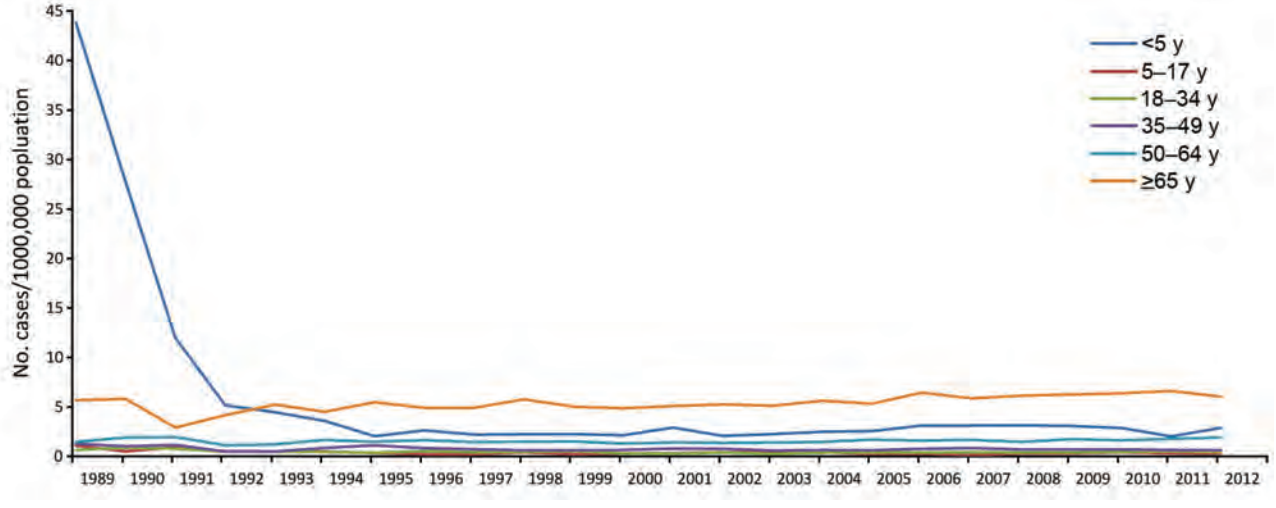

Figure 2. Incidence of invasive *Haemophilus influenzae* disease, by age group, United States, 1989–2012.

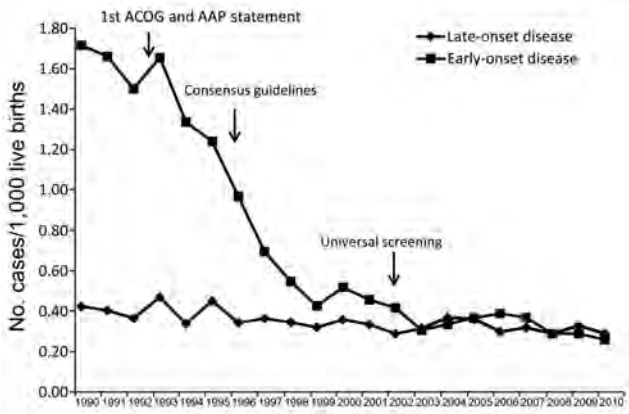

Figure 3. Incidence of early-onset group B *Streptococcus* disease before and after issuance of guidelines, United States, 1990–2010. AAP, American Academy of Pediatrics; ACOG, American Congress of Obstetricians and Gynecologists.

infections was newly brought to light by the ABCs network (*16*). This report led to increased awareness of MRSA infections, and prevention of health care–associated MRSA became a goal for public health agencies and policy makers (*17–19*). ABCs documented a 54% decline in hospital-onset MRSA and a 28% decline in health care–associated community-onset MRSA invasive infections during 2005–2011 (Figure 4) (*20*). An ABCs-based study evaluating risk factors for health care–associated community-onset MRSA infections has just been completed. Despite great progress in reducing health care–associated MRSA infections, rates of invasive MRSA infections in the community among persons without recent health care exposures (community-associated infections) remain largely unchanged, indicating the ongoing need for prevention strategies outside hospital settings (Figure 4) (*20*).

ABCs data showed that, from 1995 through 1998, a large and increasing proportion (up to 25%) of isolates from patients with IPD were resistant to penicillin (*21*). After introduction of PCV7, analysis of ≈43,000 isolates collected from all ABCs sites found a 64% decline in penicillin-nonsusceptible IPD among children <5 years of age and a 45% decline among adults ≥65 years from 1998–1999 through 2008. This finding demonstrated the effectiveness of routine use of pneumococcal conjugate vaccine in children for reducing the spread of resistant strains on a national scale in all age groups (*22*). However, 30% of ABCs isolates from patients with IPD remain resistant to ≥1 antimicrobial drug (http://www.cdc.gov/drugresistance/threat-report-2013/).

In contrast to IPD, GAS infections remain sensitive to penicillin. GAS isolates are collected to monitor the resistance of invasive GAS infections to not only β-lactams but also macrolides and other antimicrobial drugs. ABCs data have documented increasing resistance to erythromycin (currently 8%–11%), a macrolide commonly used for treating pharyngitis in children who are allergic to penicillin (http://www.cdc.gov/drugresistance/threat-report-2013/).

Monitoring antimicrobial drug resistance of GBS across a large geographic area is critical because antimicrobial prophylaxis is widely used to prevent early-onset GBS. GBS isolates from ABCs have remained largely susceptible to first-line prophylaxis and treatment with β-lactams, but for some isolates, β-lactam MICs have been increasing (*23*). Increasing resistance of GBS isolates to clindamycin discovered through ABCs prompted a 2002 change in the second-line prophylaxis recommendation for intrapartum women, from clindamycin to cefazolin for penicillin-allergic women at low risk for anaphylaxis (*9*). Two reports of vancomycin-resistant GBS isolates (1 inside and 1 outside the ABCs catchment area) have recently been published (*24*). Although apparently not widespread, vancomycin resistance is a concerning development that must be closely monitored because it is an alternative agent for prophylaxis in penicillin-allergic patients at high risk for anaphylaxis (*10*).

During 2007–2008, ciprofloxacin-resistant *N. meningitidis* was identified in 3 patients: 2 from Minnesota (within the ABCs catchment area) and 1 from a bordering area of North Dakota (not an ABCs site) (*25*). Although *N. meningitidis* isolates had routinely been collected for serogrouping, resistance testing was not routinely done because previous evaluations had shown low levels of antimicrobial drug resistance (*26*). When the potential problem arose with ciprofloxacin, a commonly used agent for prophylaxis of close contacts, the existing ABCs infrastructure was used to test *N. meningitidis* isolates for antimicrobial drug resistance. No additional ABCs isolates collected during 2007–2011 were found to be resistant to ciprofloxacin, providing reassurance that the chemoprophylaxis policy recommendations continued to be sound (*27*).

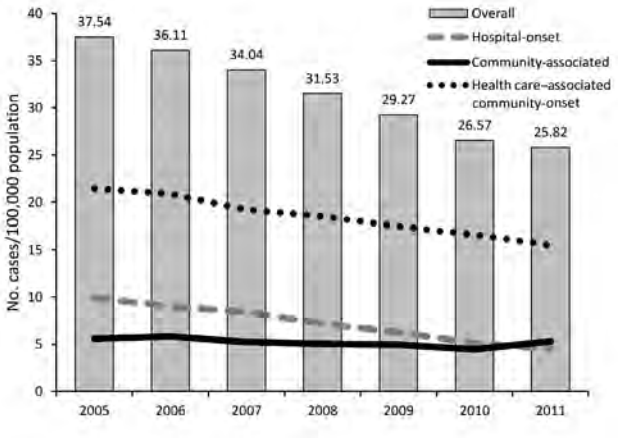

Figure 4. Incidence of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) (defined as MRSA isolated from a normally sterile source) infections, by epidemiologic category, Active Bacterial Core surveillance, United States, 2005–2011 (20).

Response to Public Health Emergencies and Surveillance for Other Emerging Infections

One of the key attributes of ABCs and other EIP activities is flexibility for responding to public health emergencies. After the 2001 anthrax attack, the ABCs infrastructure was used to establish and test a more sensitive and timely system for identifying inhalation anthrax in Connecticut (*28*). After the discovery of severe acute respiratory syndrome in 2002, the EIP infrastructure assisted with surveillance activities and the investigation of suspected cases (*29*). During the 2009 influenza A(H1N1) pandemic, early recognition of IPD among pandemic influenza patients at the Colorado ABCs site led to increased emphasis on pneumococcal disease prevention strategies (*30*). The Tennessee ABCs site helped the Tennessee Department of Health investigate the recent outbreak of fungal meningitis (*31*).

ABCs has also been used as a surveillance platform for other emerging infections, including pertussis and legionellosis. Since the 1980s, the number of reported pertussis cases has been gradually increasing: the 48,277 cases reported in 2012 represent the largest number of cases since 1955 (Figure 5) (http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2012.pdf). From 2000 through 2009, the age-adjusted incidence of legionellosis has almost tripled, from 0.40 to 1.08 cases per 100,000 persons (*4*). Since 2011, enhanced pertussis surveillance has been conducted at 6 sites and legionellosis surveillance at 10 sites. In addition to enhanced surveillance, a study to estimate the effectiveness of maternal vaccination at preventing infant pertussis is under way.

ABCs Effect on Domestic and International Surveillance Programs

A goal of ABCs is to share its methods and experiences with domestic and international partners. In addition to providing materials, methods, and results through its website (http://www.cdc.gov/abcs/index.html), outreach to partners has been provided at multiple national and international conferences. ABCs closely collaborated with the South Africa National Institute for Communicable Diseases in the establishment of a similar surveillance system in that country and in sharing lessons learned and epidemiologic findings (http://www.nicd.ac.za/?page=homepage&id=125). ABCs has also been used as the standard for evaluating and validating less expensive methods for tracking antimicrobial drug susceptibility and measuring vaccine effectiveness—methods that can be used in settings with fewer resources (*32*,*33*).

Challenges and Opportunities

When ABCs began, most cases were identified by reviewing paper laboratory log sheets and computer printouts and most case report forms were abstracted from paper records. The increasing availability of electronic laboratory and medical records may improve timeliness, completeness, and accuracy of reporting (*34*). Ensuring that cases are appropriately captured requires an understanding of laboratory information system codes and periodic reviews of how data are imported. Extracting information and transferring it into usable formats remains a challenge (*35*).

With the exception of surveillance for pertussis and legionellosis, the current ABCs case definition includes only culture-proven disease. Although culture remains the standard for diagnosing invasive infections, the use of culture-independent diagnostic tests will probably increase. Validation of culture-independent diagnostics will remain a major consideration for determining whether culture-independent tests are added to the ABCs case definition.

The growing fields of microbial and human genomics provide ABCs with a potential new role in increasing the understanding of disease transmission and pathogenesis. ABCs is uniquely poised to evaluate the relationship between human and pathogen genetic variation and infectious disease, given that surveillance is population based

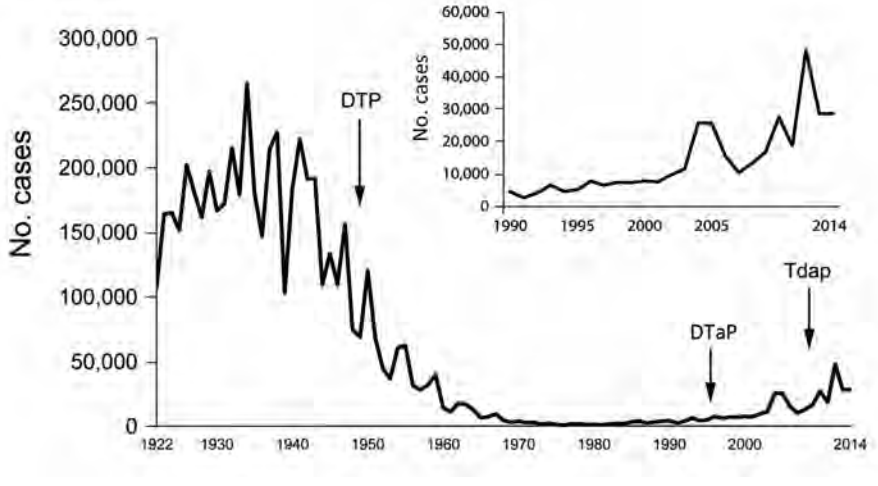

Figure 5. Number of pertussis cases reported to the National Notifiable Diseases Surveillance System, 1922–2014. Inset shows detail view of data for 1990–2014. Sources: Centers for Disease Control and Prevention; National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System, 1922–1949; passive reports to the Public Health Service. Data for 2014 are provisional. DTP, diphtheria, tetanus, pertussis vaccine; DTap, diphtheria, tetanus, acellular pertussis vaccine given to children up to 7 years of age; Tdap, tetanus, diphtheria, acellular pertussis vaccine given to adolescents and adults.

Table 2. Questions left unanswered with regard to Active Bacterial Core surveillance*

Organism or disease	Questions
Streptococcus pneumoniae	Should PCV13 be recommended for adults? What proportion of invasive pneumococcal disease is preventable with vaccine? What other strategies are available to prevent non–vaccine type disease?
Neisseria meningitidis	Should serogroup B vaccines be recommended for routine use in the United States?
Haemophilus influenzae	Are control strategies (e.g., chemoprophylaxis, vaccines) needed for non-Hib disease?
Group B *Streptococcus*	Will antimicrobial drug resistance reduce the effectiveness of intrapartum prophylaxis? What will be the projected effect of vaccines on infant disease? Are there interventions to reduce infant late-onset disease?
Group A *Streptococcus*	What age groups should be targeted for vaccines according to potential effect on invasive disease?
MRSA	Can modifiable risk factors for HACO MRSA be identified? What are effective strategies for preventing infections outside acute-care settings?
Pertussis	Does the acellular vaccine given during pregnancy effectively prevent pertussis in infants? What is the effect of newly emerging *Bordatella pertussis* strain changes on disease epidemiology, clinical presentation, and vaccine effectiveness?
Legionellosis	Why are rates higher among black than white persons and higher among men than women? Why do rates differ by geographic area?

*PCV13, 13-valent pneumococcal conjugate vaccine; Hib, *H. influenzae* type b; HACO, health care–associated community onset; MRSA, methicillin-resistant *Staphylococcus aureus*.

and that bacterial isolates are collected. A study currently under way is using whole-genome sequencing to compare isolates from patients with GAS and necrotizing fasciitis or streptococcal toxic shock syndrome with isolates from persons with isolated bacteremia; another study is planned to examine potential differences in host genomic factors. ABCs is also validating the use of whole-genome sequencing for outbreaks caused by *N. meningitidis*.

In the United States, the leading cause of illness and death is chronic disease. A better understanding of the associations and interactions between chronic diseases and invasive bacterial infections is needed for a better understanding of the pathophysiology, potential interventions, and prognoses for invasive bacterial infections. ABCs surveillance data coupled with other data sources have been used to analyze the influence of chronic diseases on IPD (*36*) and *H. influenzae* infection in adults (*37*). Efforts to analyze the effects of obesity and diabetes on the incidence and severity of ABCs pathogens are under way.

A major goal of ABCs is assessment of public health disparities and promotion of health equity across population groups. ABCs has documented differences in rates of disease across persons of different races; invasive GBS (http://www.cdc.gov/abcs/reports-findings/survreports/gbs12.pdf), pneumococcal (*38*), and MRSA (http://www.cdc.gov/abcs/reports-findings/survreports/mrsa12.pdf) infections are more common among black than white persons. However, racial differences are just one measure of disparity, and categorizing a person's race is becoming increasingly difficult as the United States becomes more multiracial. ABCs analyses have incorporated census tract data to determine the association between area-level poverty and disease incidence (*39*,*40*). In 2013, ABCs started incorporating census tract information into routine surveillance.

Conclusions

ABCs is distinctive among public health surveillance systems in that it is designed to capture nearly all cases of culture-confirmed invasive bacterial diseases over a large, well-defined, and geographically diverse area of the United States. These comprehensive data enable accurate estimations of the national disease burden for severe bacterial infections under surveillance. The collection of isolates in conjunction with epidemiologic data has contributed to the microbiological and molecular characterization of pathogens, which has played a part in the development of vaccines and monitoring of antimicrobial drug resistance. Although the surveillance system alone provides powerful data for informing public health actions, the large ABCs infrastructure provides an efficient and effective platform for engaging in special investigations that would otherwise require additional resources. The infrastructure also provides the flexibility needed to respond to emergencies and to serve as a surveillance platform for other emerging pathogens. Perhaps the greatest strength of ABCs and the reason for its success have been the committed, genial, and long-lasting collaboration among local, state, and federal agencies, academic institutions, and clinical laboratories.

Although ABCs has addressed many questions of public health significance that have directly affected public health policy and practice, many questions still remain (Table 2). To maintain the ability of ABCs to answer questions of high importance, the network must continue to embrace and adapt to the changing public health, laboratory, information technology and medical landscapes.

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Foodborne Diseases Active Surveillance Network—2 Decades of Achievements, 1996–2015

Olga L. Henao, Timothy F. Jones, Duc J. Vugia, Patricia M. Griffin, for the Foodborne Diseases Active Surveillance Network (FoodNet) Workgroup

The Foodborne Diseases Active Surveillance Network (FoodNet) provides a foundation for food safety policy and illness prevention in the United States. FoodNet conducts active, population-based surveillance at 10 US sites for laboratory-confirmed infections of 9 bacterial and parasitic pathogens transmitted commonly through food and for hemolytic uremic syndrome. Through FoodNet, state and federal scientists collaborate to monitor trends in enteric illnesses, identify their sources, and implement special studies. FoodNet's major contributions include establishment of reliable, active population-based surveillance of enteric diseases; development and implementation of epidemiologic studies to determine risk and protective factors for sporadic enteric infections; population and laboratory surveys that describe the features of gastrointestinal illnesses, medical care–seeking behavior, frequency of eating various foods, and laboratory practices; and development of a surveillance and research platform that can be adapted to address emerging issues. The importance of FoodNet's ongoing contributions probably will grow as clinical, laboratory, and informatics technologies continue changing rapidly.

During the late 1980s and early 1990s, recognizing inconsistencies inherent in passive national surveillance systems, epidemiologists at the Centers for Disease Control and Prevention (CDC) proposed creating a population-based active surveillance system to better measure the frequency of enteric infections and their effects on society. However, resources for these improvements were not available. Then, in late 1992 and early 1993, hamburger patties contaminated with *Escherichia coli* O157 caused 732 laboratory-confirmed infections and the deaths of 4 children. After this outbreak, the US Department of Agriculture (USDA) implemented a risk-based meat inspection system. Public health and regulatory officials needed a method to determine whether the changes made by regulatory agencies and the industry were followed by declines in infections. The outbreak had focused attention on the need for reliable data on the incidence of infections caused by enteric pathogens; changes in the incidence over time; and estimates of the actual numbers of illnesses, hospitalizations, and deaths they cause. Therefore, in 1995, with support from Food Safety and Inspection Service (FSIS) of the USDA, CDC established the Foodborne Diseases Active Surveillance Network (FoodNet), an active, population-based sentinel surveillance system. FoodNet monitors changes in the incidence of selected major bacterial and parasitic illnesses transmitted commonly by food, attributes illnesses to sources and settings, and estimates the total numbers of foodborne illnesses in the United States.

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Overview and Purpose

FoodNet, a core part of CDC's Emerging Infections Program, is a collaboration among CDC, 10 state health departments, USDA-FSIS, and the Food and Drug Administration (FDA). Over time, the surveillance area has grown to include ≈48 million persons (≈15% of the US population) in Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee and in selected counties in California, Colorado, and New York (*1*) (Figure 1). More information about the program and its activities is available at http://www.cdc.gov/FoodNet. The cost of funding for the surveillance sites and CDC, typically <$7 million per year, is dwarfed by the economic impact of the illnesses monitored. *Salmonella* infections alone cost ≈$3.6 billion each year in direct medical costs, productivity, and years of potential life lost (*2*).

The community of multidisciplinary FoodNet scientists collaborates to track infections transmitted commonly by food and to study the sources of infections. FoodNet's annual report of confirmed infections caused by major pathogens, published within months of the end of each calendar year, is sometimes referred to as the foodborne illness "report card" for the nation. Public health officials, regulatory agencies, and industry use it to gauge progress in food safety and to determine when new policies and prevention efforts are needed (*3*).

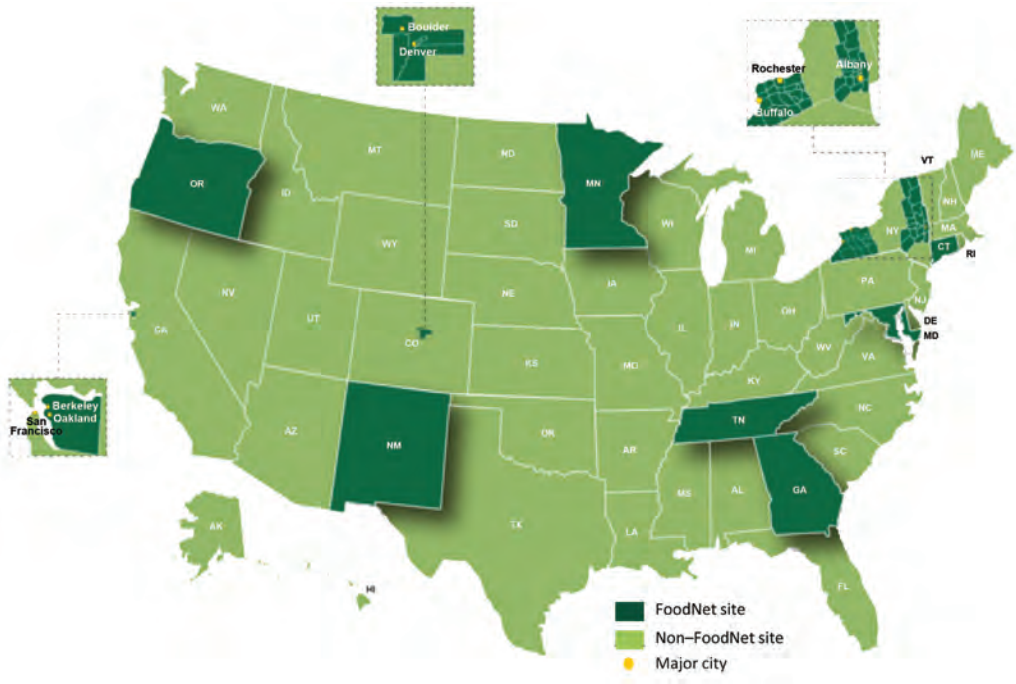

Figure 1. The Foodborne Diseases Active Surveillance Network Surveillance Area, United States, 2004–present.

FoodNet's major contributions include the establishment of reliable, active population-based surveillance of enteric diseases; development and implementation of epidemiologic studies to determine risk and protective factors for sporadic enteric infections; population and laboratory surveys that describe the features of gastrointestinal illnesses, medical care–seeking behavior, food eating patterns, and laboratory practices; and development of a surveillance and research platform that can be adapted to address emerging issues (Table). It is the only US system focused on obtaining comprehensive information about sporadic infections caused by pathogens transmitted commonly through food.

Specific Activities and Selected Accomplishments

Active Surveillance

FoodNet's core activity is active surveillance for laboratory-confirmed bacterial infection caused by *Campylobacter*, *Listeria*, *Salmonella*, Shiga toxin–producing *Escherichia coli* (STEC) O157 and non-O157, *Shigella*, *Vibrio*, and *Yersinia* and parasitic infection caused by *Cryptosporidium* and *Cyclospora*. FoodNet does not track agents for which clinical laboratories do not routinely test (e.g., norovirus). As laboratory practices change, the surveillance system adapts. During the 2000s, culture-independent diagnostic tests (CIDTs) became commercially available to detect Shiga toxin. Recognizing that some laboratories might stop culturing for STEC O157, leading to a perceived decline in infections, FoodNet began surveillance for hemolytic uremic syndrome (HUS) as another way to track STEC O157 infections. Most cases of HUS are caused by STEC O157. As more clinical laboratories began using CIDTs to detect other pathogens, FoodNet responded by gathering data on laboratory practices and on pathogens detected by these tests and by encouraging reflex culturing of specimens that test positive (*4*).

FoodNet staff at each site receive reports of every identification of a pathogen under surveillance from clinical laboratories that conduct tests on patients' specimens ordered by health care providers. They conduct periodic audits to ensure that all pathogens identified are reported (*3*). In 1999, to ensure the validity of data summarized across all sites, FoodNet developed and began tracking metrics related to reporting, a process unusual for CDC programs at that time. For each person with an infection, FoodNet staff collect demographic information and determine whether the person was hospitalized and whether he or she survived. In 2004, FoodNet began collecting data on whether the infection was part of an outbreak and whether the patient had traveled internationally.

FoodNet has the flexibility to conduct special surveillance projects in response to concerns about emerging infectious diseases, as when variant Creutzfeldt-Jakob disease emerged (*3*). In 2010, FoodNet conducted surveillance for *Cronobacter sakazakii* infections and found infection in all age groups, the highest rate of invasive infections in infants, and data suggesting that urine might be a more common site of infection than previously thought (*5*).

Tracking Incidence and Changes Over Time

FoodNet tracks the incidence of infections and HUS to assess the effectiveness of measures aimed at preventing

Table. Major contributions of the Foodborne Diseases Active Surveillance Network (FoodNet), 1996–2015

Contribution	Specific contribution	Example of impact
Reliable active population-based surveillance of enteric diseases	FoodNet publishes incidence data for the previous year every spring. Rich database has comprehensive epidemiology and laboratory information about sporadic infections	Regulatory agencies evaluate their prevention efforts and change policies as a result of FoodNet data. Industry food safety executives use FoodNet data to inform policies. FoodNet data has been used to describe the epidemiology of infections caused by pathogens transmitted commonly through food in 162 publications. (More information is available at http://www.cdc.gov/foodnet/publications/index.html.)
Epidemiologic studies that determine risk and protective factors for sporadic enteric infections	A case–control study of *Listeria* infections showed that infection was associated with eating melons. Case–control studies of *Campylobacter* and *Salmonella* infections showed higher risk for infection among infants that had ridden in a shopping cart next to meat or poultry.	Because of study results, cantaloupe was added to *Listeria* initiative questionnaire, and this addition helped to more quickly identify cantaloupes as the source in the 2011 outbreak. As a result, some retail stores are now providing bags near the meat and poultry counters and are providing wipes for cleaning shopping carts.
Population and laboratory surveys that describe the features of gastrointestinal illnesses, medical care–seeking behavior, foods eaten, and laboratory practices	Estimates were made in 1999 and 2011 of the actual number of foodborne illnesses, including those not confirmed by a laboratory test.	The 2011 estimates were used to help determine the number of illnesses that could be attributed to each major food category. Regulatory agencies are using the latter estimates to guide prevention efforts.
Surveillance and research platform that can be adapted to address emerging issues	In 2008, as more clinical laboratories began adopting culture-independent diagnostic tests (CIDTs) for enteric pathogens, FoodNet responded by gathering data on enteric pathogens detected by these tests.	FoodNet worked with the Council of State and Territorial Epidemiologists to write a proposal to make *Campylobacter* infection diagnosed by either culture or CIDT a reportable condition nationwide. The proposal was approved in 2014, and reporting began in January 2015.

infections and to monitor progress toward national health goals. To measure changes over time and minimize the spurious effect of annual fluctuations, FoodNet has used 2 baseline periods of 3 consecutive years each. The first, 1996–1998, is the initial 3 years of surveillance; the second, 2006–2008, was used to develop the US Department of Health and Human Services Healthy People 2020 goals (*6*). In 2008, FoodNet began also reporting changes from the average annual incidence for the 3 years preceding the year of the report. In 2012, FoodNet began reporting a measure of overall change in the incidence of bacterial foodborne illness. This measure combines data for infections caused by the 6 bacterial pathogens monitored by the network for which >50% of illnesses are estimated to be transmitted by food (*7*). To account for variations in the surveillance area, FoodNet uses a main-effects log-linear Poisson (negative binomial) regression model to assess changes in incidence rates (*1*).

Each spring, FoodNet summarizes preliminary data and changes in incidence for the preceding year (Figure 2) in CDC's Morbidity and Mortality Weekly Report. Public health officials, regulatory agencies, industry, and consumer groups use these data to assess the effect of food safety interventions (*3*). FoodNet has documented significant decreases in the incidence of *E. coli* O157 infections since 1996–1998 and in HUS since 2001, supporting other data indicating that regulatory and industry actions have made ground beef safer (*8*). FoodNet also has documented lack of significant change in the overall incidence of *Salmonella* infections and marked changes in some specific serotypes, indicating that efforts targeting specific serotypes are needed to decrease *Salmonella* infections. In response to these findings and to recent outbreaks, FSIS created performance standards mandating the upper limit of allowable *Salmonella* contamination of chicken parts (*8*). Poultry is also a major source of *Campylobacter* infections (*9*). In 2011, in response to FoodNet data showing little progress in reducing these infections, FSIS issued the first performance standards that limited the allowable contamination of chicken and turkey with *Campylobacter* (*10*).

FoodNet data are used to guide the development of and monitor progress toward national goals and health objectives, such as the US Department of Health and Human Services' high priority goal to reduce *S. enterica* serotype Enteritidis infections from eggs after implementation of the Egg Safety Rule that was passed in 2009 (*6*). FoodNet data also are used to monitor progress on 7 illnesses included in the Healthy People National Health Objectives.

Determining Sources and Outcomes of Infections

Understanding sources and settings of illnesses informs the development of recommendations, regulations, and interventions to reduce illnesses. FoodNet collects data to determine the relative importance of various routes of infection, including nonfood sources. Kendall et al. reported that, with wide variation by pathogen, 13% of persons infected

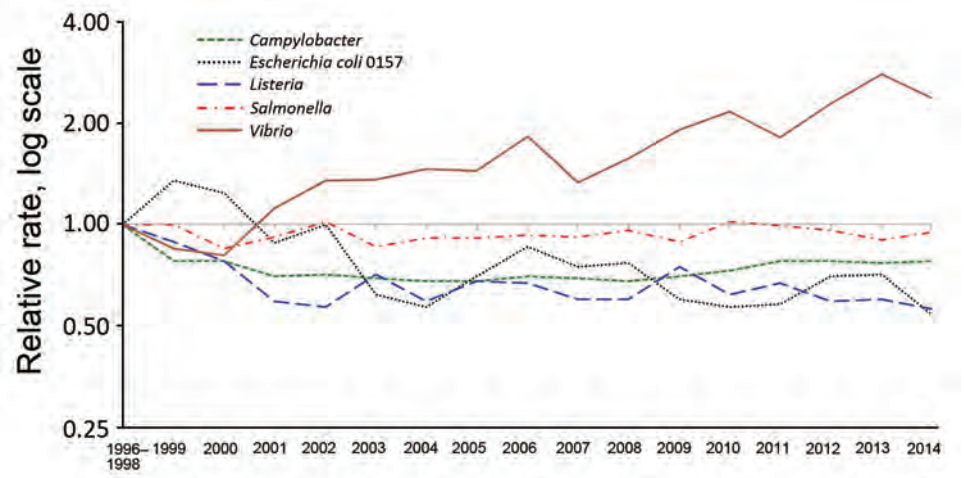

Figure 2. Relative rates of culture-confirmed infections with *Campylobacter*, *Escherichia coli* O157, *Listeria*, *Salmonella*, *Vibrio,* and *Yersinia* compared with 1996–1998 rates, Foodborne Diseases Active Surveillance Network, United States, 1996–2014. The position of each line indicates the relative change in the incidence of that pathogen compared with 1996–1998. The actual incidences of these infections cannot be determined from this graph. Data for 2014 are preliminary.

with a pathogen monitored by FoodNet had recently traveled internationally; the authors identified regions to which travel carries the highest risk for illness (*11*). Hale et al. used data from FoodNet and other sources to estimate that 13% of illnesses caused by 7 enteric pathogens were attributable to contact with animals and their environments (*12*).

FoodNet has identified numerous risky food, environment, and animal exposures through case–control studies of sporadic *Campylobacter*, *Cryptosporidium*, *Listeria*, *Salmonella*, and STEC O157 infections, described in 19 journal articles (more information available at http://www.cdc.gov/FoodNet). It is currently conducting a case–control study of non-O157 STEC infections to assess risk factors and correlate virulence factors with symptoms. These studies have yielded rich data of long-term value. When the FDA needed data on sources of *S. enterica* serotype Enteritidis illnesses before the Egg Rule was implemented, Gu et al. reanalyzed data from an old FoodNet case–control study with a new method and determined that egg-related exposures had the highest attributable fraction (*13*). A case–control study of *Listeria* infections showed an unexpected association with eating melons (*14*). In response, CDC modified the *Listeria* Initiative questionnaire used to interview patients with *Listeria* infection. As a result, when Colorado detected a large *Listeria* outbreak, investigators already had information about cantaloupe consumption from many patients, and the melons were more quickly implicated and removed from the market (*15*). Case–control studies are resource-intensive and so are conducted infrequently. In 2014 FoodNet began routinely collecting exposure data from patients with some *Salmonella* infections and is exploring ways to use these data in models that attribute illnesses to sources.

Population and Laboratory Surveys

FoodNet conducted 5 population surveys beginning in 1996, with only a 2-year gap before the last survey ended in 2007. In addition to obtaining data for estimating illnesses (described in the next section), the surveys asked participants how recently they ate selected foods. These data have been used for many analyses. Shiferaw et al. found a higher proportion of men reported eating pink hamburger and runny eggs, whereas a higher proportion of women ate fruits and vegetables (*16*). The population surveys have been used frequently in outbreak investigations. Epidemiologists compare frequencies of specific exposures reported by outbreak patients with those of a comparable population in the survey to quickly generate, confirm, or refute hypotheses about sources of illness. The ready availability of these data saves time over traditional methods of finding controls (e.g., by random-digit telephone calls, followed by interviews of persons reached who agree to participate) (*17*). During a 2012–2013 multistate outbreak of *S. enterica* serotype Heidelberg infections, 79% of patients reported eating chicken in the week before illness began, significantly higher than the 65% reported in the 2006–2007 FoodNet population survey (*18*). That finding, with other epidemiologic, laboratory, and traceback findings, helped link the outbreak to chicken from 1 producer. The population surveys also have provided a platform for obtaining information quickly in a crisis. When bovine spongiform encephalopathy emerged as a public health concern during the mid-2000s, questions about hunting practices, eating venison, and travel to countries in which bovine spongiform encephalopathy had been reported in animals were added to the 2006–2007 survey (*19*).

FoodNet conducts surveys of clinical laboratories to determine practices. By analyzing data from surveys conducted in 1995, 1997, and 2000, Voetsch et al. determined that variations in laboratory practice by site might explain some of the observed differences in the incidence of STEC O157 infection (*20*). A survey in 2005 found that adherence to recommendations for isolation and identification of *Campylobacter* varied substantially among laboratories

(*21*). A survey in 2007 showed that most laboratories complied with recommendations for testing STEC O157 but not with recommendations for non-O157 STEC (*22*). The laboratory surveys provided essential information for estimating the true number of enteric infections (*23*). In 2012, because of rapidly changing clinical laboratory practices, FoodNet began conducting a survey annually. The 2014 survey showed that CIDT methods were used most often to detect *Campylobacter* and STEC (*4*).

Estimating Actual Foodborne and Acute Gastrointestinal Illnesses, Hospitalizations, and Deaths

FoodNet data are central to estimating the numbers of US foodborne illnesses, hospitalizations, and deaths (*23*,*24*). Regulatory agencies and lawmakers use these estimates to help decide how to allocate resources for prevention. Mead et al. published the first estimates in 1999 in Emerging Infectious Diseases (*24*) using early active surveillance data from FoodNet and data from other sources. By 2010, this article was the most frequently cited article published in this journal. After these estimates were published, FoodNet began addressing data gaps and developing improved methods, resulting in revised comprehensive estimates published by Scallan et al. in 2011 (*23*). Major improvements resulted from the availability of data from >5 times more respondents to population surveys and more detailed information about illnesses reported in those surveys. For both the 1999 and the 2011 estimates, these surveys provided key data on the severity of illnesses, medical care–seeking behavior, and specimen submission. These data and data from FoodNet surveys of laboratories were used to estimate the total number of illnesses for every reported laboratory-confirmed illness of each pathogen. The surveys also provided essential information about the rate of acute gastroenteritis illnesses, which was used to estimate illnesses caused by viral pathogens and by unknown agents (*25*). An important advancement in the 2011 article was separate estimation of the numbers of illnesses acquired domestically and during international travel, enabled by FoodNet's collection of information about recent international travel. These new foodborne illness estimates formed the basis for a ground-breaking analysis estimating the number of illnesses attributed to specific food categories (*26*).

Other Contributions

Linking FoodNet to the National Antimicrobial Resistance Monitoring System (NARMS) has expanded the impact of both surveillance systems. A FoodNet case–control study linked fluoroquinolone-resistant *Campylobacter* infections with eating poultry at a commercial establishment and with international travel (*27*). Data from this study contributed to the body of evidence that led FDA to withdraw approval for the use of fluoroquinolones in poultry (*28*). Krueger et al. conducted a joint FoodNet–NARMS study that showed bloodstream infection was more common among patients infected with resistant than susceptible *Salmonella* strains (*29*). By linking FoodNet and NARMS data, Shiferaw et al. found that *Shigella* isolates from Hispanics and recent international travelers were more likely than other isolates to be resistant to trimethoprim/sulfamethoxazole (*30*). In another study linking these 2 databases, O'Donnell et al. found that two thirds of persons with *S. enterica* serotype Enteritidis infections resistant to nalidixic acid had recently traveled internationally (*31*).

The ability to geocode FoodNet surveillance data and link it to census data has increased FoodNet's ability to examine health disparities. By geocoding *Campylobacter* cases and linking to census tract socioeconomic status (SES) measures, Bemis et al. found the incidence of campylobacteriosis in Connecticut increased as neighborhood SES increased except among children <10 years old, for whom incidence increased as SES decreased (*32*).

The benefits of FoodNet for public health are far-reaching. As experts in surveillance, FoodNet site epidemiologists are often leaders in conducting multistate outbreak investigations, many of which result in industry or regulatory changes that make food safer. Examples include an outbreak of *Salmonella* infections linked to pot pies (*33*), an outbreak of *E. coli* O157 infections linked to spinach (*34*), and the outbreak of *Listeria* infections linked to cantaloupe (*15*). FoodNet site personnel also train local public health nurses, epidemiologists, sanitarians, and laboratorians about foodborne disease surveillance, outbreak detection, investigation, and response. Training helps local public health professionals recognize outbreaks and maintain skills and knowledge needed to respond appropriately.

FoodNet's influence reaches beyond the United States. Australia's OZFoodNet and FoodNet-Canada have modeled some of their activities on FoodNet surveillance, and FoodNet staff have collaborated with scientists from other countries to compare the prevalence of diarrheal illness (*35*). FoodNet scientists have been active in the World Health Organization Global Foodborne Infections Network, which works to enhance the capacity of countries to detect, respond to, and prevent foodborne and other enteric infections.

Challenges and the Future

The importance of FoodNet's ongoing contributions toward developing epidemiologic methods for assessing diseases transmitted commonly by food likely will grow as clinical, laboratory, and informatics technologies continue changing at a rapid pace. Recent and ongoing advances in CIDTs and molecular diagnostics affect FoodNet surveillance. FoodNet's responsiveness to this changing landscape is informing ongoing modifications of national surveillance definitions that CDC and all US states use.

For the near future, although CIDTs serve clinical needs, bacterial isolates remain essential for the molecular subtyping and antimicrobial drug susceptibility testing needed for epidemiologic monitoring, outbreak detection, and public health investigations. Public health laboratories in FoodNet states could become key sites for maintaining public health access to isolates of enteric pathogens obtained by reflex culturing after a positive CIDT. Maintaining access to traditional laboratory methods also is necessary to validate and interpret new technologies. Traditional laboratory methods might be needed to help evaluate the significance of detection using highly sensitive genetic techniques of multiple pathogens in a single specimen. Because FoodNet surveillance is built on clinical and public health laboratory diagnosis, laboratories must have the resources required to meet surveillance needs.

As laboratories adopt whole-genome sequencing to identify and characterize enteric pathogens, the ability to identify subtypes associated with particular reservoirs and particular food sources will increase. Detailed epidemiologic data on exposures of ill persons will be needed to make these associations. At this time, although many state and local health departments obtain exposure information, FoodNet surveillance captures only a limited amount. Obtaining more will involve duplicate data entry or designing information technology systems that can interface with a variety of databases housed at local and state health departments and at CDC.

The advent of CIDTs offers opportunities to conduct surveillance for enteric pathogens not monitored now. Some CIDTs can detect enterotoxigenic *E. coli* infection, which is an important cause of diarrhea in returning travelers and has caused domestic outbreaks (*36*). The large proportion of the US food supply that is imported, including many fruits and vegetables that are eaten raw, provides opportunities for exposure to pathogens from all over the world. Expanding surveillance to enterotoxigenic *E. coli* and other pathogens, after clinical laboratories begin detecting them, could lead to greater insight into the causes and sources of enteric infections in the United States and abroad.

FoodNet population surveys have proven valuable as sources of data about rates and severity of acute gastrointestinal illnesses and medical care–seeking and about food eaten and other exposures among well persons in the community (*16*,*37*,*38*). The lack of a population survey after 2007 means that data needed to update estimates of the impact of illness are not available. Although the frequency that various foods are eaten may have changed, these data are still used because up-to-date data are not readily available from other sources. FoodNet is working with its partners to find ways to fund and conduct more frequent surveys.

Awareness is increasing of the need to combat antimicrobial drug resistance. Four of the 18 threats that CDC reported in Antibiotic Resistance Threats in the United States, 2013, are tracked in FoodNet (*39*).The National Strategy for Combating Antibiotic Resistant Bacteria, announced in 2014 (*40*), aims to slow the emergence of resistant bacteria and prevent the spread of resistant infections. Surveillance data are needed to determine whether strategies to preserve the effectiveness of antimicrobial drugs are working and whether new threats are emerging. FoodNet's longstanding collaboration with NARMS likely will increase further to meet this need.

CDC's information technology method for obtaining surveillance data from FoodNet sites needs updating, including developing the ability to obtain and analyze data by person and to interface with national surveillance systems. FoodNet creates a separate record for each illness diagnosed by the detection of a pathogen; ways to link the record to the ill person are needed to determine whether a person has a co-infection or has sequential illnesses with several pathogens. The existence of a variety of methods for reporting infections to CDC is an ongoing challenge for state health officials. The use of different identifiers for information about the same isolate or illness reported to various CDC surveillance systems (e.g., FoodNet, PulseNet, NARMS) is an obstacle to fully understanding the features of reported infections. FoodNet staff will be engaged in efforts to ensure that national surveillance systems are designed to meet the needs of both states and CDC and that they enable accurate and timely analysis and release of FoodNet data.

The widespread growth of electronic health records in the clinical community presents challenges and opportunities for public health. CDC's Emerging Infections Program is developing informatics capacity to incorporate data streams from electronic health records, electronic laboratory reporting, and other sources of "big data" (e.g., administrative claims data, social media). FoodNet databases at the sites and CDC are increasingly conforming to national data standards, which will facilitate linking to meaningful use of certified electronic health records technology. Rapid access to clinical data will improve surveillance and epidemiologic studies. Informatics capacity is essential for linking FoodNet surveillance data with geographic information systems and other public health databases (e.g., hospital discharge data, vital statistics, NARMS surveillance data). Lessons learned from pilot projects conducted at FoodNet sites could provide an important foundation for developing public health informatics infrastructure nationally. Through multiagency partnership and collaboration, FoodNet has helped improve food safety in the United States in multiple ways. The surveillance network, which began as a project, provides key data for public health analyses and decision-making, and has become an integral part of CDC's work. FoodNet has matured and transformed over the last 20 years and continues to evolve. Changes in diagnostic

practices that affect surveillance and the need for more detailed and precise information about the major sources of infections and how they change over time are just a few of the issues FoodNet will address during the next decade.

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Evaluating Epidemiology and Improving Surveillance of Infections Associated with Health Care, United States

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The Healthcare-Associated Infections Community Interface (HAIC), launched in 2009, is the newest major activity of the Emerging Infections Program. The HAIC activity addresses population- and laboratory-based surveillance for *Clostridium difficile* infections, candidemia, and multidrug-resistant gram-negative bacilli. Other activities include special projects: the multistate Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey and projects that evaluate new approaches for improving surveillance. The HAIC activity has provided information about the epidemiology and adverse health outcomes of health care–associated infections and antimicrobial drug use in the United States and informs efforts to improve patient safety through prevention of these infections.

Health care–associated infections (HAIs) and inappropriate antimicrobial drug use are major threats to patient safety in US health care facilities. For several years, the elimination of infections associated with health care has been a priority of the US Department of Health and Human Services and a "winnable battle" for the Centers for Disease Control and Prevention (CDC) (*1*). Essential to the development and implementation of effective HAI prevention and antimicrobial stewardship policies and practices is a current and comprehensive understanding of the epidemiology of HAIs and drug-resistant pathogens that commonly cause such infections.

The Emerging Infections Program (EIP) network, a CDC-supported, public health surveillance and research network, has conducted population-based surveillance for severe bacterial infections since 1995 through the Active Bacterial Core surveillance (ABCs). This program has successfully characterized the magnitude of infections, the patient populations affected, and risk factors for infections. Until 2004–2005, when the ABCs initiated surveillance for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections, pathogens tracked by EIP were primarily associated with communities rather than with health care. In 2005, CDC's National Nosocomial Infections Surveillance System, a longstanding, hospital-based surveillance system for HAIs, was integrated into the new National Healthcare Safety Network (NHSN). With the rapid expansion of NHSN during 2006–2010, additional complementary approaches were needed to define more fully the epidemiology of HAIs, drug-resistant pathogens, and antimicrobial drug use in US health care settings. Consequently, the Healthcare-Associated Infections Community Interface (HAIC) activity was launched to address this need; to bring together existing EIP HAI-related work into a single organizational structure (except for invasive methicillin-resistant *Staphylococcus aureus* surveillance, which remained part of the ABCs); and to develop further the EIP's involvement and expertise in HAI epidemiology. The HAIC activity was initiated because of a growing need for a flexible infrastructure in which to conduct HAI-related surveillance and applied research activities and because of the increasing role of state health departments in the implementation of reporting and preventing HAIs through regional and statewide collaboration.

Over the past 5 years, the HAIC activity has become a national public health resource for data on urgent and emerging infectious diseases related to health care. The HAIC activity seeks to promote patient safety and health care quality through 2 main initiatives: 1) evaluation of the epidemiology and public health effects of HAIs to understand emerging pathogens and populations at risk; and 2) exploration of innovations to improve national surveillance and evaluation of HAI prevention and control strategies.

Current HAIC Activities and Methods

HAIC activity projects are divided into 2 major categories: 1) pathogen-specific, population- and laboratory-based surveillance (for which 2 projects predated the formation

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of the HAIC activity); and 2) epidemiologic innovations. The HAIC activity currently conducts population-based surveillance aimed at defining the effects of disease and the epidemiology of infections caused by *Clostridium difficile*, *Candida* species (bloodstream infections only), and carbapenem-resistant *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* cultured from urine and sterile body sites (*2*). Although each of these 3 surveillance projects has its own case definition, catchment area, and data collection, all use laboratory-based criteria to identify cases. In addition, all 3 projects collect and submit isolates to CDC for further characterization, and they all collect data from medical records to confirm patient eligibility as a case, obtain demographics, and classify cases as either community associated or health care associated. When disease burden is high and surveillance catchment areas are large, CDC can work with specific EIP sites to develop medical records reviews and isolate sampling strategies that reduce resources needed for surveillance.

In 2008, population-based candidemia surveillance began in 2 EIP sites (Georgia and Maryland) to follow up previous surveillance conducted in the 8-county metropolitan area of Atlanta, Georgia, and in San Francisco, California, during 1992–1993 (*3*) and in Baltimore City and Baltimore County, Maryland, and in Connecticut during 1998–2000 (*4*). The primary objective of the ongoing surveillance is to assess changes in the incidence and epidemiology of these infections, including changes in antifungal resistance. Cases are identified through blood cultures that are positive for *Candida* species in residents of catchment areas. Submission and study of isolates enables a better understanding of antifungal susceptibility patterns among invasive *Candida* isolates; this information is not usually available from hospital clinical microbiology laboratories. Analysis of data collected during 2008–2011 in Georgia and Maryland showed marked declines in candidemia in infants, the group that had the highest rates of infection in the 1990s (*5*). The data also showed relatively stable levels of fluconazole resistance among *Candida* bloodstream isolates (*6*). Subsequent analyses identified increases in echinocandin-resistant and multidrug-resistant *Candida* infections during 2008–2012 (*7*). After sites in Oregon and Tennessee were added in 2011, candidemia surveillance is now conducted in 4 EIP sites, covering a population of 7.7 million persons. Data from this expanded surveillance are used to describe candidemia in these populations and to evaluate the emergence of echinocandin resistance in *C. glabrata* (*8*).

Surveillance for *C. difficile* infections (CDIs) began in 2009 and expanded by 2011 to include all of the 10 EIP sites and a population of ≈11.5 million persons. The objectives of CDI surveillance are to compile national estimates for CDIs associated with the community and with health care, to describe the epidemiology of these CDIs, and to characterize *C. difficile* strains. CDI surveillance captures the broad spectrum of CDI cases that occur in all community and health care settings (including nursing homes and facilities for rehabilitation and acute care) and collects extensive clinical and microbiologic data. CDI cases are defined on the basis of *C. difficile*–positive toxin or molecular assays for catchment area residents ≥1 year of age. Clinical data are used to confirm that patients had symptoms consistent with CDI, and epidemiologic data are used to classify cases into 1 of 3 categories: community associated; community-onset, health care facility associated; and health care facility onset. *C. difficile* isolates are collected from a convenience sample of laboratories and sent to CDC for molecular characterization, which enables comparative analysis of disease characteristics by strain type. Outcome data such as recurrence, hospitalization, and death are also captured.

This surveillance project has contributed substantially to the current understanding of CDI epidemiology in the United States. A recently published analysis of CDI surveillance data estimated that ≈453,000 CDI cases and 29,000 deaths occurred among patients with CDI in the United States in 2011 (*9*). Data from this surveillance project have also been used to evaluate differences in CDI incidence across EIP sites and have illustrated the importance of adjusting for patient factors (e.g., age, gender, and race) and hospital factors (e.g., inpatient days and use of nucleic acid amplification tests [NAAT]) for comparisons among populations (*10*). Data from EIP CDI surveillance have also shown substantial increases in CDI detection because laboratories have adopted NAAT for CDI diagnosis (*11*). EIP surveillance data have also enabled additional advances in the characterization of CDI: identification of outpatient health care exposures (e.g., doctor or dentist visits) among patients with community-associated CDI (*12*); description of the epidemiology of CDI in children, in whom most disease is community associated (*13*); evidence of the association between the North American pulsed-field gel electrophoresis type 1 epidemic *C. difficile* strain and more severe CDI outcomes (*14*); and description of the association between adoption of NAAT by clinical laboratories and implementation of stricter criteria for submitting stool specimens for testing (*15*). The CDI surveillance data are also used to estimate potential effects of reducing antimicrobial drug use on CDI rates (*16*), to estimate the incidence and outcome of CDI infection in nursing home populations (*17*), and to evaluate risk factors for community-associated infection. Ongoing surveillance will also enable measurement of outcomes of prevention efforts associated with inpatient antimicrobial drug stewardship or, potentially, with a CDI vaccine.

The third HAIC activity surveillance project targets multidrug-resistant gram-negative bacilli (MDR GNB).

This project, known as the Multisite Gram-Negative Bacilli Surveillance Initiative (MuGSI), began in Georgia and Minnesota in 2010 as pilot projects and expanded to Oregon in 2011. The impetus for initiating population-based EIP surveillance for MDR GNB was the emergence of CRE in the United States. Patients infected with these organisms have few or sometimes no antimicrobial drug treatment options. The incidence and characteristics of MDR GNB are in flux, so a flexible yet specific surveillance program is needed. The program must be able to adapt to changing laboratory breakpoints and case definitions when needed to better define the impact of these infections, determine the populations at risk, and inform prevention efforts.

The main objective of MuGSI is to describe the epidemiology and population-based incidence of carbapenem-nonsusceptible *Enterobacteriaceae* species and *Acinetobacter baumannii*. The project also seeks to characterize isolates and describe resistance mechanisms among a subset of carbapenem-nonsusceptible *Enterobacteriaceae* isolates submitted to CDC. This surveillance has expanded in recent years to cover a surveillance area of ≈15 million persons in 8 states: Georgia, Oregon, Minnesota, Colorado, Maryland, New Mexico, New York and Tennessee. Initially, cases were defined by carbapenem-nonsusceptible (excluding ertapenem) and extended-spectrum cephalosporin-resistant *Escherichia coli*, *Enterobacter aerogenes*, and *E. cloacae*, *Klebsiella pneumoniae* and *K. oxytoca*, and carbapenem-nonsusceptible (excluding ertapenem) *Acinetobacter baumannii* complex isolated from normally sterile sites or from urine of residents in the surveillance areas. In MuGSI surveillance, most cases are identified through queries of automated susceptibility-testing instruments in clinical laboratories that serve the catchment areas rather than through routine output of summarized test results (often called line listings) generated by laboratory information systems (*18*). This method enables the application of case definitions based on antimicrobial drug susceptibility test results that may be suppressed from routine reports entered into the patient's medical record. Also, depending on the concentration range of drugs tested, the method enables application of the latest breakpoints from the Clinical Laboratory Standards Institute (http://www.clsi.org/) before they have been widely implemented by clinical laboratories. Isolates from EIP sites are being used to evaluate different phenotypic definitions used to identify carbapenemase-producing CRE (*19*). Data from this evaluation have assisted in modifying CRE definitions used for reporting to NHSN and for updating the MuGSI case definition. Finally, MuGSI is uniquely positioned to describe persons with community-associated CRE.

Since its inception, the HAIC activity has also conducted several projects in epidemiology innovations, a major area of growth for the HAIC activity. The largest of these projects is a multicenter HAI and antimicrobial drug use prevalence survey project. This multiphase effort is designed to fill gaps in data collected through NHSN by developing and conducting a national-scale point prevalence survey that estimates the scope and magnitude of all HAIs affecting acute-care hospital patients. This project also describes the nature of and rationale for antimicrobial use in acute care hospitals. The project development began in 2009 with a single-city pilot survey (*20*). A limited roll-out survey was conducted in 22 hospitals in the 10 EIP sites in 2010, followed by the full-scale survey in 183 hospitals across the 10 sites in 2011. Data from the full-scale survey were used to establish the current annual estimates of HAIs in US acute-care hospitals: ≈722,000 infections in 648,000 patients (*21*). The survey showed that surgical site infections and pneumonias were the most common HAIs and also that device-associated infections, which have for many years been the focus of most HAI prevention efforts, accounted for only 26% of all HAIs. *C. difficile* was the most common pathogen causing HAIs; considering the importance of antimicrobial drug use in the epidemiology of CDI, this finding supports CDC's increasing focus on antimicrobial stewardship programs in acute-care hospitals. The antimicrobial drug use component of the survey showed that half of all patients included in the survey were receiving antimicrobial drugs at the time of the survey; furthermore, broad-spectrum antimicrobial drug use was very common, even among patients with community-onset infections and among patients who were not in critical care units (*22*).

The next phase of the prevalence survey, scheduled for 2015, includes a hospital infection control and antimicrobial stewardship practices questionnaire; it also has assessments of the quality of antimicrobial drug prescribing for selected clinical scenarios. The prevalence survey is an effective approach for obtaining broad, situational awareness of HAIs and antimicrobial drug use in different health care settings, particularly those settings where robust, prospective surveillance is not yet available or widely used. These surveys have been used in many other countries, including a European Union survey conducted in 2011–2012 (*23*). The methods for the US survey effort were developed with input from European colleagues, including those in the European Centre for Disease Prevention and Control, in an attempt to enable comparative metrics. We also relied on European colleagues' considerable experience in conducting HAI and antimicrobial use prevalence surveys in long-term care facilities (*24*). We consulted them for input on a pilot EIP HAIC antimicrobial drug use prevalence survey for nursing home HAIs. This pilot was conducted in 9 nursing homes in 4 EIP sites, and expansion to a larger-scale, US nursing home survey in the future is being considered.

Other innovations projects have sought to field-test streamlined, simplified methods for conducting HAI surveillance in NHSN. One example of these short-term innovations projects is a device-associated HAI denominator data simplification project to identify streamlined sampling methods that can replace daily collection of patient- and device-day data (*25*,*26*). Other innovations projects include field-testing of a new surveillance component for CDI and urinary tract infections (UTIs) in long-term care facilities and field-testing of a definition modification of bloodstream infections associated with central lines (*27*). Another innovations project is surveillance for bloodstream infections in dialysis facilities (*28*). EIP sites have also completed work to validate data submitted to NHSN. For example, the Connecticut and New Mexico EIP sites have compared MRSA bacteremia and CDI data collected through EIP's population-based surveillance with MRSA and CDI Laboratory-Identified Event data (http://www.cdc.gov/nhsn/labid-calculator/index.html) submitted to NHSN (*29*). Knowledge gained through these EIP projects has directly affected several NHSN surveillance operations: in 2015, implementation of central line–associated bloodstream infection and catheter-associated urinary tract infection denominator sampling methods (http://www.cdc.gov/nhsn/acute-care-hospital/clabsi/index.html); also in 2015, the addition of selected variables to Laboratory-Identified Event reporting to improve the completeness of case information capturing; in 2014, implementation of the Mucosal Barrier Injury-Laboratory Confirmed Bloodstream Infection definition; and in 2013, clarification of UTI surveillance methods for long-term care facilities.

Data from HAIC activity population-based surveillance projects and from the HAI and antimicrobial drug use prevalence survey have been critical to the development of recent high-profile reports. Of the 18 pathogens or pathogen groups included as serious, urgent, or concerning threats to public health in CDC's first report on antimicrobial threats in the United States, discussions of 7 used estimates from HAIC activity data (*30*). HAIC activity data have also been used to illustrate concepts in public health calls to action in CDC reports: on CDIs (75% of cases had infection occurring outside of hospitals) (*31*), on CREs (92% of CRE episodes occurred in patients with health-care exposures) (*32*), and on the public health problem of incorrect inpatient antimicrobial drug use (37% of antimicrobial drug prescribing in selected scenarios could be improved) (*16*). In addition, data from candidemia surveillance were used in the World Health Organization's first global report on antimicrobial resistance (*33*).

Future of the EIP HAIC Activity

The accomplishments of the EIP HAIC activity have been numerous over a relatively short period of time, including delivery of data that have affected federal policy, programs, and operational approaches of HAI surveillance and prevention. However, as the landscape of HAI and antimicrobial drug–resistant infection prevention changes, the HAIC activity must constantly reassess priorities and direction. Reporting requirements related to HAIs as part of the Centers for Medicare and Medicaid Services quality reporting programs have expanded in recent years; data from the HAI and antimicrobial drug use prevalence survey show that ≈28% of all acute care hospital–related HAIs are now part of the Hospital Inpatient Quality Reporting Program of the Centers for Medicare and Medicaid Services (http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalRHQDAPU.html). The flexibility of the HAIC activity makes it well suited to fill gaps in facility-specific reporting as part of those programs, to contribute data on hospital HAIs not included in reporting programs, and to provide data on the large proportion of infections caused by health care–associated pathogens that occur outside acute care hospital settings. For example, as reporting to NHSN becomes increasingly robust for particular hospital-onset infections, the HAIC activity can adapt its surveillance approach to focus on cases in nonacute care or community settings, locations where high quality data would otherwise be lacking. Thus, the HAIC activity can provide an infrastructure that enables evaluation of progress of prevention efforts.

As reporting requirements become part of nonacute care settings, including long-term care or ambulatory care, the EIP HAIC activity will be well positioned to help determine selection of the highest-priority infection metrics in those settings. Periodic assessment of the spectrum of HAIs through time-limited activities, such as the point-prevalence surveys, will help CDC reassess priority infections for prevention efforts and determine needed modifications to reporting requirements for various types of health care facilities. Over the next decade, the HAIC activity can serve to identify new and emerging challenges involving HAIs occurring across the spectrum of health care delivery.

The HAIC activity can also continue to develop new techniques and respond to emerging and urgent issues related to HAI surveillance and antimicrobial resistance. With knowledgeable, state-based staff and existing networks in health care facilities and clinical microbiology laboratories, the HAIC activity can explore novel approaches to HAI tracking, accommodate shifting case definitions and approaches to defining antimicrobial resistance, and contribute valuable data to inform development and implementation of optimal definitions through ongoing collection and study of isolates linked to well-defined cases of infection.

Besides these functions, the HAIC activity provides an infrastructure for evaluating approaches to the prevention of HAIs and the spread of antimicrobial resistance by

building on research and innovations tested and refined in smaller-scale or academic settings. The activity's surveillance projects have firmly established outcome metrics and can therefore measure patient-centered outcomes after early adoption of new standards in HAI prevention efforts in acute or long-term care settings (e.g., the effects of hospital-based programs to reduce CDI in postdischarge settings). One challenge facing the HAIC activity in implementing these evaluations is the population-based nature of many of its surveillance projects. Currently, cases are defined in part on the basis of residency in the designated catchment area, and new approaches to enable capture of nonresident cases will be needed, particularly for work focused in acute care hospitals.

During the past 5 years, the HAIC activity infrastructure has adapted quickly to new challenges, additional pathogens, and new methods to accomplish its mission. Given the scope of the antimicrobial resistance problem and the aggressive timeline laid out in the US President's September 2014 Executive Order (https://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria), the pace of work will need to be accelerated to make progress in reaching the targets outlined in the National Strategy for Combating Antibiotic-Resistant Bacteria (*34*). These targets include large reductions in incidence of multidrug-resistant *Pseudomonas aeruginosa*, invasive MRSA, CDI, and CRE. Through the EIP HAIC activity, CDC will be better and more rapidly able to identify populations at risk for antimicrobial drug–resistant infections associated with health care settings, to evaluate and refine prevention approaches, and to define critical links between disease severity or prevention and microbe characteristics. Furthermore, this program will serve as one of several that will assess the success of various components of the National Strategy towards achieving targets and providing data to empower public health and health care sectors to make progress toward eliminating HAIs.

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The US Influenza Hospitalization Surveillance Network

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In 2003, surveillance for influenza in hospitalized persons was added to the Centers for Disease Control and Prevention Emerging Infections Program network. This surveillance enabled monitoring of the severity of influenza seasons and provided a platform for addressing priority questions associated with influenza. For enhanced surveillance capacity during the 2009 influenza pandemic, new sites were added to this platform. The combined surveillance platform is called the Influenza Hospitalization Surveillance Network (FluSurv-NET). FluSurv-NET has helped to determine the risk for influenza-associated illness in various segments of the US population, define the severity of influenza seasons and the 2009 pandemic, and guide recommendations for treatment and vaccination programs.

Every year, influenza virus circulates worldwide, causing substantial illness and death and leading to considerable economic losses (*1*). From time to time, new strains of influenza A viruses emerge and cause a global pandemic with devastating consequences (*2*–*4*). Therefore, influenza surveillance programs are crucial for monitoring the timing and severity of seasonal influenza, which virus strains are circulating in a community, and changes in the epidemiology or risk associated with influenza virus infection. These data can be used to plan for vaccine strain selection, to alert the medical community and public health officials about the intensity and magnitude of an epidemic, and to evaluate the effects of intervention programs. In the event of an influenza pandemic, surveillance programs are essential for guiding response efforts and assisting with resource prioritization.

In response to the 2003–04 influenza season, which was relatively severe and caused a large number of deaths among healthy children, the Centers for Disease Control and Prevention (CDC) and 10 state health departments initiated a population-based surveillance system for laboratory-confirmed influenza in hospitalized children <18 years of age (*5*). Surveillance for influenza-associated hospitalizations among children proved to have useful public health implications, such as informing influenza vaccine recommendations over the years (*6*,*7*). Two years later, in 2005, the system was expanded to include surveillance for influenza hospitalizations among adults and was named the Influenza Hospitalization Surveillance Network (FluSurv-NET). FluSurv-NET data have helped determine the risk for illness in various segments of the population, document the severity of specific influenza seasons, and guide recommendations for treatment and vaccination programs. We describe FluSurv-NET, discuss how the system has generated data for public health action, and describe achievements and new directions for improving the system.

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Key Components of FluSurv-NET

The CDC Emerging Infections Program (EIP) platform is the cornerstone of FluSurv-NET and since the 2003–04 influenza season has conducted ongoing, population-based surveillance for children hospitalized with influenza (*5*). Surveillance for adults hospitalized with influenza was added to the EIP platform during the 2005–06 season (*8*). EIP sites include selected counties in California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. To enhance surveillance, using the same EIP hospitalization surveillance protocol and making the system more geographically representative, new sites were added during the 2009 influenza pandemic. FluSurv-NET currently comprises the previously listed 10 EIP sites plus Michigan, Ohio, and Utah. The network encompasses 267 acute care hospitals and laboratories and has a total catchment area of >27 million persons (≈9% of the US population). Distribution of age, sex, race/ethnicity, and health indicators (e.g., population density and percentage of persons at or below poverty level) for persons in the FluSurv-NET catchment area is similar to that for persons throughout the nation.

FluSurv-NET monitors community-acquired, laboratory-confirmed influenza-related hospitalizations, defined as hospitalization of persons residing in the surveillance area at 1 of the catchment area hospitals ≤14 days after or ≤3 days before a positive influenza test result during October 1–April 31 each year. Because of the long-standing relationship between public health officials, academic centers and private hospitals, and laboratories at each participating site, and because of the feasibility of channeling resources to external partners through cooperative

agreements, surveillance can be extended beyond seasonal periods and special projects can be implemented in the FluSurv-NET platform at very short notice.

Surveillance officers (either at an academic center or public health department) are hired and trained to collect information about patients hospitalized with influenza. A laboratory-confirmed influenza case is identified from laboratory logs of diagnostic testing for influenza, patient medical records, infection control practitioners' databases/logs, or weekly calls to catchment-area hospitals. Cases can also be identified by reportable conditions databases at sites where influenza hospitalization is a reportable public health condition (Figure 1). Each positive influenza test result is investigated as to whether it represents a hospitalization event; this process helps avoid data entry duplication. Laboratory testing for influenza is ordered at the discretion of clinicians providing care. Laboratory confirmation is defined by a positive result from viral culture, direct or indirect fluorescent antibody staining, rapid antigen testing, or real-time reverse transcription PCR (RT-PCR). Hospitals are encouraged to send specimens to the public health department laboratory for RT-PCR confirmation and additional virus characterization, including virus subtyping.

Information about patient demographic characteristics and clinical course of illness during hospitalization is collected for each laboratory-confirmed influenza case through review of medical records by use of a standard form (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/9/14-1912-Techapp1.pdf). Clinical data collected depict presence of underlying chronic medical conditions, influenza treatment and vaccination, clinical outcomes during hospitalization (including admission to an intensive care unit, need for mechanical ventilation, and death), and hospital discharge diagnoses. Influenza vaccination status is obtained through review of medical records and vaccination registries, primary care provider, or interview of patients or their proxies.

FluSurv-NET data collection was determined by CDC to be public health surveillance and therefore not subject to CDC Institutional Review Board approval for human research protections. Nonetheless, each participating site determines the need to submit the study to its state and local institutional review boards.

Surveillance

During an influenza season, data collected through FluSurv-NET are reported weekly to the CDC Influenza

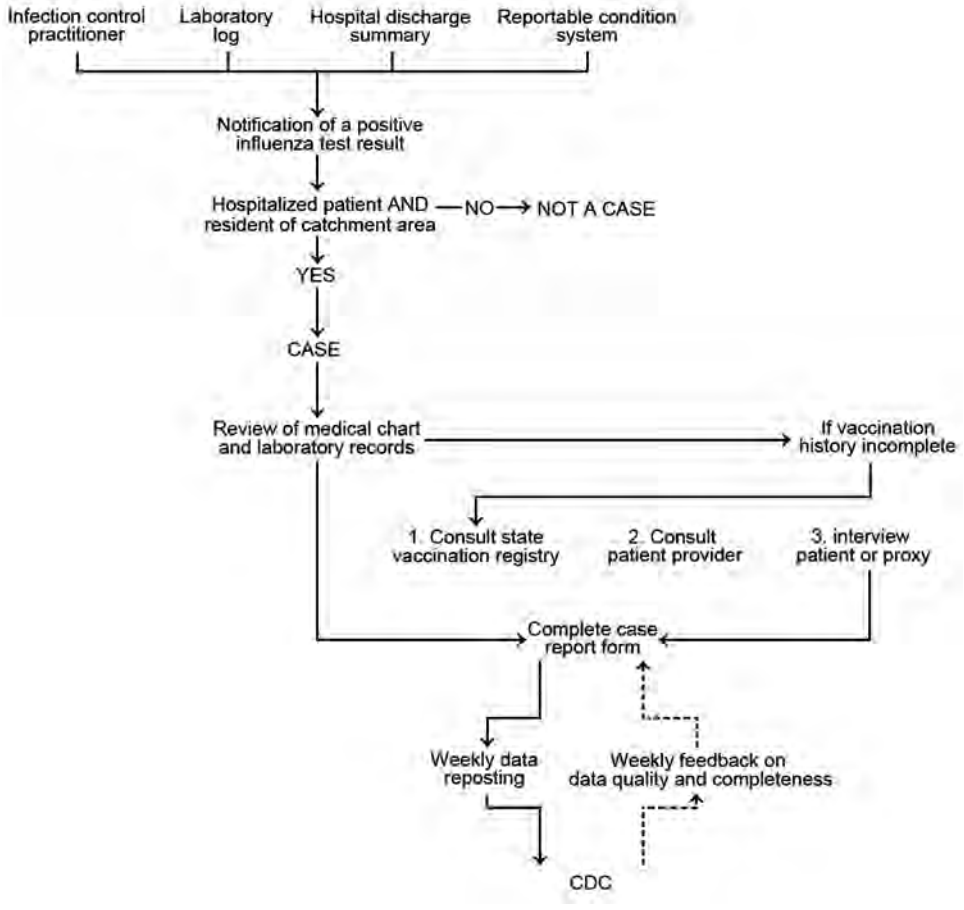

Figure 1. Population-based influenza hospitalization surveillance case ascertainment and review process, Influenza Hospitalization Surveillance Network, United States. Core data transmitted weekly to the Centers for Disease Control and Prevention (CDC) are patient identification number, surveillance site, hospital admission date, patient's date of birth, type of influenza test, and type of influenza virus. Case finding and chart reviews are done manually.

Division (required core variables are surveillance site; hospital admission date; patient's date of birth; type of influenza test; and, if available, type of influenza virus). There is a median lag time of 7 days (range 2–10 days) between date of a positive influenza test result and reporting of core variables to CDC. The primary product of FluSurv-NET is age-specific rates of laboratory-confirmed influenza-associated hospitalizations in the United States, which are calculated by using population denominators from the most recent census data available for each surveillance county catchment area. These rates are made available weekly in a web-based interactive application (available at http://gis.cdc.gov/GRASP/Fluview/FluHospRates.html and http://gis.cdc.gov/grasp/fluview/FluHospChars.html), which can also provide visualization of much of the influenza data collected and analyzed by CDC. This interactive application allows for analyses and visualization of customized data and comparisons across influenza seasons, regions, age groups, and selected patient demographics and clinical characteristics (Figures 2, 3). Selective clinical characteristics posted in the interactive application probably reflect 25%–50% of reported cases with complete clinical information at any given time during the season. Full clinical data for all hospitalized patients are often available after the end of the season, when chart reviews are finalized and providers, patients, or both have been interviewed regarding influenza vaccination.

Useful features of this system include near real-time information about the current influenza season and comparison of rates from previous seasons and by age groups. Data reported from FluSurv-NET are posted on a CDC website in a weekly influenza surveillance report prepared by the Influenza Division and called FluView (http://www.cdc.gov/flu/weekly/). Data posted in FluView are used to respond to media calls, address public information needs, and provide national-level information to local and state health departments for use in interpreting and communicating information about the influenza season in their own jurisdiction.

During the 2009 influenza pandemic, FluSurv-NET provided a crucial source of data for policy and decision making. Demographic and risk factor data from FluSurv-NET were used to develop vaccination prioritization recommendations for monovalent influenza A(H1N1)pdm09 virus vaccine distribution and administration early in the pandemic when the vaccine was in short supply. FluSurv-NET data were also used to demonstrate that persons in some age groups, with conditions such as pregnancy (*9*), and in some racial/ethnic groups were at higher risk for severe health outcomes associated with A(H1N1)pdm09 infection (*10*). In addition, these data contributed to the development of antiviral medication prioritization recommendations in anticipation of antiviral medication shortages.

Hospitalization rate data were used on a weekly basis to brief the CDC director and senior leadership at the Department of Health and Human Services about the severity and magnitude of the pandemic. Furthermore, data from this system were modeled to estimate national disease burden and became a monthly public benchmark for estimating how hard the pandemic was hitting the country. These data confirmed that morbid obesity was a new risk factor for influenza-related complications (*11*) and served as a reminder of the severe toll that influenza can take on persons with concurrent medical conditions, such as children with underlying neurologic disabilities (*12*).

Addressing Critical Public Health Questions

Historically, estimates of the burden of influenza disease have relied on modeling excess influenza-associated hospitalizations by using national hospital discharge data (*13*,*14*). Therefore, results were available retrospectively

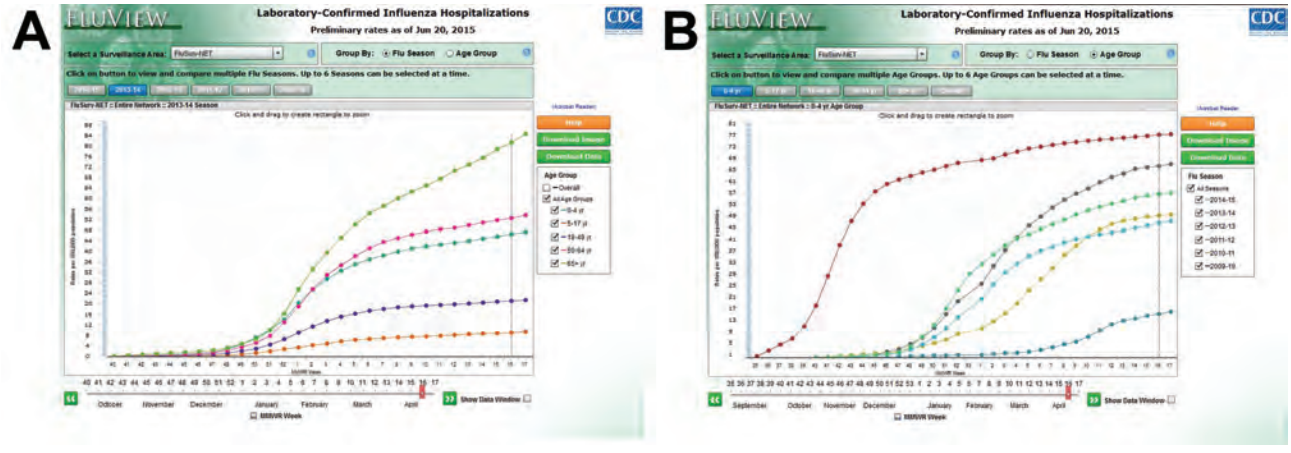

Figure 2. Screenshots of FluView web-based interaction application showing cumulative laboratory-confirmed influenza-associated hospitalizations per 100,000 population, United States. A) Age-specific rates by age groups; B) rates within specific age group, by influenza season. MMWR week defined at http://wwwn.cdc.gov/nndss/document/MMWR_Week_overview.pdf. Data from http://gis.cdc.gov/GRASP/Fluview/FluHospRates.html.

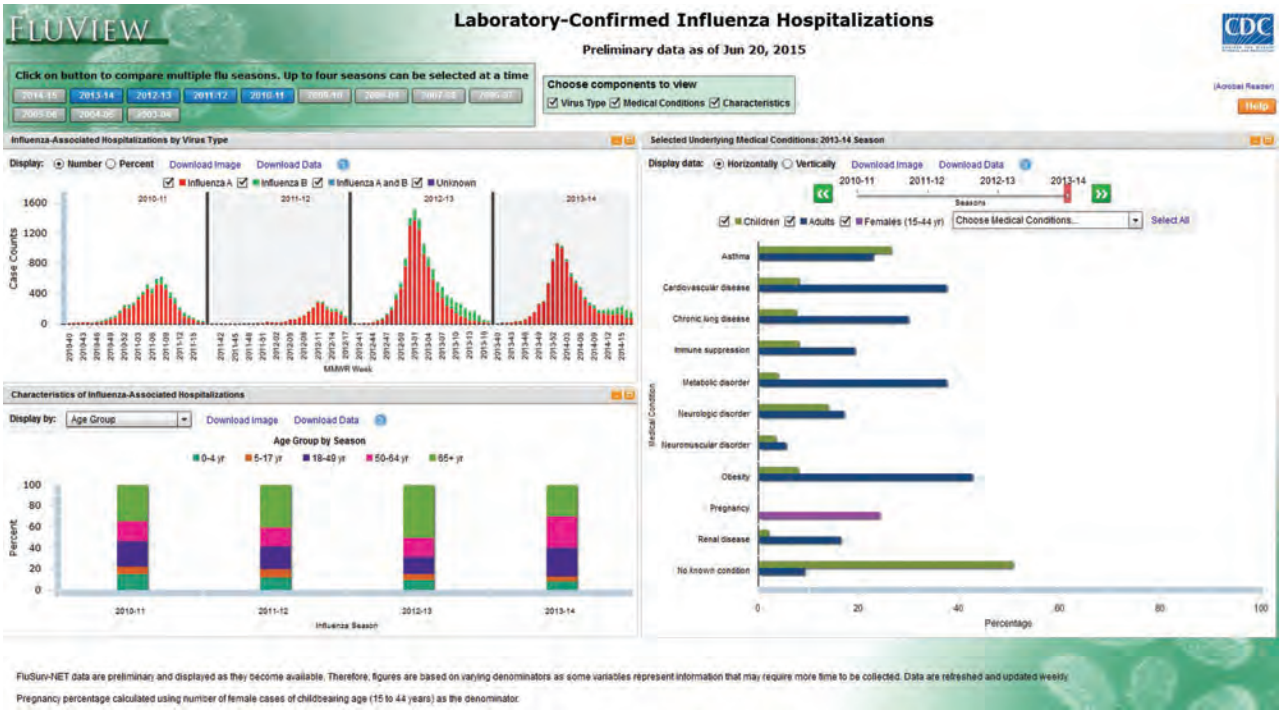

Figure 3. Screenshot of FluView web-based interaction application showing characteristics of hospitalized patients with laboratory-confirmed influenza in the United States by virus type; selected demographic characteristics, by influenza season; and prevalence of underlying medical conditions in children and adults. Data from http://gis.cdc.gov/grasp/fluview/FluHospChars.html.

only, after a 2–3 year delay. This delay precluded the use of burden estimates and season severity assessments to guide hospital resource allocations, control and preventive interventions, and public messaging. However, since the 2009 influenza pandemic, FluSurv-NET has provided a platform for contemporaneous timely assessments of seasonal severity and influenza disease burden estimates (*15*,*16*). The FluSurv-NET disease burden model uses probabilistic models to account for age-specific influenza testing practices and case underreporting and extrapolates data from FluSurv-NET sites to arrive at national estimates. Most recently, it was estimated that from the 2010–11 season through the 2012–13 season, 114,192–624,435 hospitalizations, 18,491–95,390 intensive care admissions, and 4,915–27,174 deaths occurred per year (*16*).

FluSurv-NET data have also been used to evaluate prescription of antiviral medication for hospitalized persons in the United States (*17*,*18*). Influenza antiviral medications are recommended for all hospitalized persons with suspected or confirmed cases of influenza. Despite the increased use of antiviral medications observed during the 2009 influenza pandemic, use of these medications declined substantially after the pandemic, especially among children (*18*) (Figure 4). These results were used to educate clinicians and improve messaging about the use of antiviral medications as a way to accelerate recovery and reduce influenza-associated complications, especially among hospitalized patients.

During the 2009 influenza pandemic, the FluSurv-NET platform was used to evaluate the effectiveness of the monovalent influenza A(H1N1)pdm09 vaccine. Effectiveness of the vaccine for preventing hospitalizations was estimated to be 50% (95% CI 13%–71%) (*19*); through the vaccine effectiveness study, FluSurv-NET contributed substantially to the evaluation of the A(H1N1)pdm09 prevention and control plan. Concerns were also expressed about the monovalent influenza A(H1N1)pdm09 vaccine being associated with Guillain-Barré syndrome (GBS); therefore, another contribution of the FluSurv-NET system during the 2009 influenza pandemic was completion of studies demonstrating a very small association of the monovalent influenza A(H1N1)pdm09 vaccine with risk for GBS (*20*,*21*). The attributable risk was similar to that previously estimated for seasonal influenza vaccine (≈1–2 cases/1 million doses administered), suggesting a low risk for GBS after vaccination (*21*). Data from these studies were used to communicate the safety of the influenza A(H1N1)pdm09 vaccine, thereby improving public trust and government transparency.

Support for Policy Recommendations and Program Evaluations

The best protection against influenza and influenza-associated complications is considered to be annual influenza vaccination. In the United States since 2010–11, influenza

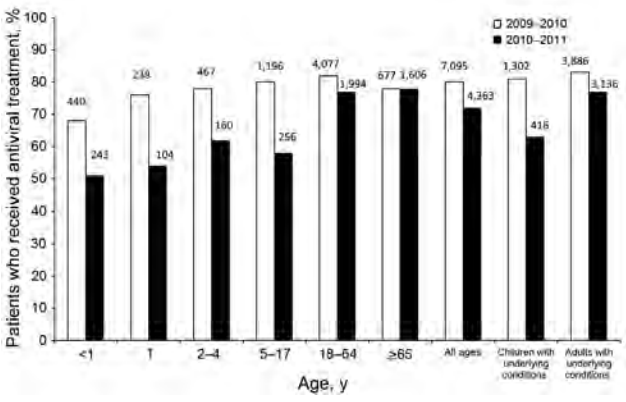

Figure 4. Percentages of children and adults hospitalized with laboratory-confirmed influenza virus infection who received influenza antiviral treatment, during 2009–10 (total hospitalized patients = 8,866) and 2010–11 (total hospitalized patients = 6,040), United States. Numbers above bars denote numbers of patients who received influenza antiviral treatment. p<0.01 for all age groups and categories except for the age group ≥65 years (*18*). Data from FluSurv-NET.

vaccination has been recommended for all persons ≥6 months of age (*22*). However, since the first national influenza vaccination policy was developed in 1968 until 2010, influenza vaccination recommendations were based on risk; groups recommended to receive vaccine were added incrementally over time as evidence was produced with regard to the risk factors for and the burden of influenza among various groups. The rates of severe disease provided by this system have also been used to develop evidence for focusing on new vaccine target groups and ultimately for justifying the current universal vaccination policy (*22*).

In the past, the benefits of influenza vaccination have been evaluated by use of cost-effectiveness studies that assessed vaccination coverage and vaccine efficacy or effectiveness in certain groups of the population (*23*,*24*). However, data from FluSurv-NET have provided a unique mechanism for evaluating the effect of influenza vaccination on a national scale (*15*). While FluSurv-NET data have been used to develop methods for estimating disease burden (i.e., number of cases, medically attended visits, and deaths associated with influenza in the United States) (*15*,*16*), when the number of doses of vaccination administered and the effectiveness of vaccine are applied to these estimates, the effect of the vaccine program can be assessed (*15*,*25*). The continuity of the surveillance system enables estimation of vaccine impact over time, and the value of influenza vaccines can be easily communicated to stakeholders as number of influenza cases, hospitalizations, and deaths prevented each season. The data have shown that the prevented fraction of influenza cases has varied by age group and year (Figure 5). The highest estimate for a prevented fraction was from postpandemic seasons, after influenza vaccine recommendation became universal in the United States (*15*,*25*).

Capacity to Serve as a Platform for Addressing Research Questions

Over the years, FluSurv-NET data have been used to answer various epidemiologic questions of public health relevance. Published studies have confirmed risk factors for severe clinical outcomes associated with influenza virus infection among young children who are hospitalized and those with asthma (*26*–*28*), the effect of A(H1N1)pdm09 virus infection among hospitalized pregnant women (*10*), the effect of hospital-associated influenza on clinical outcomes (*29*), and the role of alcohol abuse as a risk factor for influenza severity (*30*). Studies have explored the association between pneumonia and influenza before and during the 2009 influenza pandemic (*31*).

Another contribution from the network was a description of the association between use of statins and death among patients hospitalized with laboratory-confirmed influenza. Using FluSurv-NET data, Vandermeer et al. reported a 41% reduction in 30-day mortality rate among patients hospitalized with laboratory-confirmed seasonal influenza who were receiving statin treatment (*32*). Much discussion has involved the use of statins to improve survival rates among hospitalized patients with infectious conditions (*33*). Findings from FluSurv-NET have generated interest in further exploring use of statins to reduce severe outcomes among those with influenza virus infection. Further analyses using FluSurv-NET data to explore the potential benefit of statin treatment among hospitalized patients with influenza are under way.

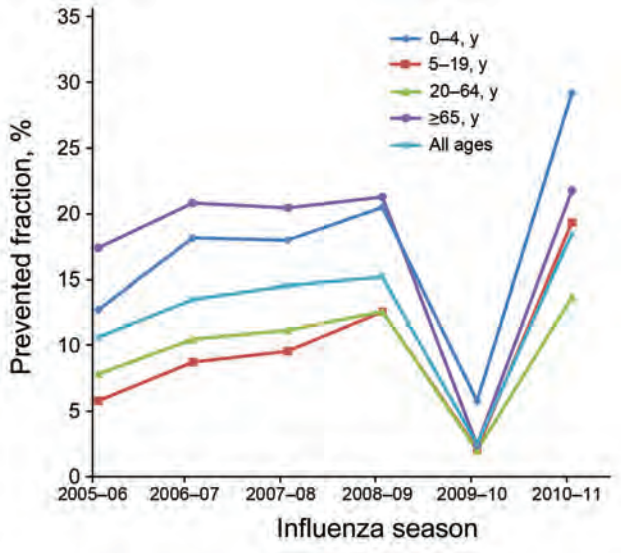

Figure 5. Prevented fraction of influenza cases as a result of vaccination, by age group and influenza season, United States, 2005–06 through 2010–11 influenza seasons. Prevented fraction was defined as the proportion of averted outcomes out of potential outcomes in the absence of vaccination (*15*).

Because FluSurv-NET data are geocoded, exploratory analyses looking at socioeconomic and other disparities among patients hospitalized with influenza have also been conducted (*34*,*35*). These analyses indicated a correlation between patient residence in impoverished or densely populated neighborhoods and incidence of influenza-associated hospitalization in Connecticut. Multisite analyses are under way to explore whether other patterns may be found in other states when considering various influenza seasons and age groups. Linking geocoded surveillance data and census information to identify geographic pockets of persons at higher risk for severe influenza or hospitalization may help local and state health departments prioritize targeted interventions among groups or neighborhoods at high risk for hospitalization for influenza.

Data from FluSurv-NET are also useful for describing differences in clinical severity of disease from season to season (*36*,*37*) and by type and subtype of influenza viruses (*38*,*39*). Since the 2009 influenza pandemic, more hospitals in the surveillance areas have access to molecular diagnostics, support from state public health laboratories with test confirmation and subtyping of influenza A viruses, or both. The data have enabled the exploration of severity and clinical presentation of influenza according to virus subtype during the 2010–11 season (*39*). Although the 2009 influenza pandemic was first thought of as a relatively mild pandemic, data from FluSurv-NET were able to demonstrate that infection with A(H1N1)pdm09 virus led to more severe disease in persons in all age groups, including older adults who were more likely to be admitted to an intensive care unit or require mechanical ventilation than were those infected with influenza (H3N2) or influenza B viruses, which co-circulated during the postpandemic influenza season (*39*).

Challenges and Opportunities

Testing for influenza viruses is often underutilized because of the low sensitivity of rapid tests, lack of prompt access to RT-PCR and other molecular assays at the hospital level, and greater reliance on clinical diagnosis for influenza. As a consequence, the number of persons identified as part of influenza hospitalization surveillance is probably lower than the true number of persons hospitalized with influenza. Nonetheless, as new and more rapid molecular assays to detect influenza viruses become available in the FluSurv-NET hospitals and laboratories, testing practices for influenza may change. It is important to keep track of changes in laboratory capacity over time and to monitor testing practices at the hospital level to aid in interpretation of results and to adjust estimates of incidence rate for hospitalization.

To identify catchment area denominators for persons in high-risk groups (e.g., those with diabetes, obesity, or chronic cardiovascular disease), FluSurv-NET will also explore data from the Behavioral Risk Factor Surveillance System, a large, worldwide, ongoing telephone health survey system. This information will enable estimation of relative risk for hospitalization, intensive care unit admission, and death among persons in specific high-risk groups, facilitating outreach messaging and justifying efforts to prioritize these groups for interventions. New molecular diagnostics can identify the presence of influenza virus RNA in specimens from the respiratory tract and can discriminate between virus type and subtype in some cases. In general, these assays yield results in 1–8 hours. Moreover, multipathogen testing platforms are becoming increasingly more common in clinical settings (*40*). These new diagnostic tools can improve ascertainment of respiratory pathogens and accuracy of detection, informing clinicians of the need for additional diagnostic testing, antibacterial or antiviral therapy, and helping with decisions regarding hospitalization and infection control measures. FluSurv-NET will need to continue to monitor testing practices in its catchment area to understand the data gathered and interpret trends on influenza hospitalization and severity of seasons over time. Furthermore, the availability of reliable data on other respiratory pathogens may enable surveillance for additional causes of hospitalization for severe acute respiratory illness.

Use of metagenomics and bioinformatics can improve our understanding of the association between respiratory microbiota and the risk for severe disease associated with various respiratory pathogens, including influenza. In preparation for the role that advanced molecular detection could have in transforming existing surveillance platforms and the way surveillance data are commonly used for public health response, the FluSurv-NET platform is in a unique position to contribute respiratory specimens for sequencing and to answer questions about influenza virus evolution, antiviral drug susceptibility, molecular determinants of severity, and whether the viral molecular profiles differ among hospitalized patients with influenza who have or have not been vaccinated.

Another area of growing interest within EIP is the use of spatial epidemiology to evaluate health disparities and geographic spread of influenza. FluSurv-NET uses geocoded surveillance data linked to census tract data to look at area-based factors influencing health inequalities (e.g., poverty) instead of race/ethnicity. FluSurv-NET will use surveillance data from influenza-associated hospitalizations to assess modifiable area-based determinants of health in the community, to generate new lines of research or promote targeted interventions for persons in identified high-risk groups, and to explore the effect of differential access to care and poverty level on rates of hospitalizations. Efforts to analyze the association between different influenza

seasons (by type and subtype) and socioeconomic status are under way, and collaborations with academic institutions with experience in this area are now being fostered.

Conclusions

The EIP network was used to establish population-based surveillance for laboratory-confirmed, influenza-related hospitalizations. This system was expanded during the 2009 influenza pandemic to include additional surveillance sites and is now known as FluSurv-NET. A powerful attribute of this surveillance is that key data are collected and submitted in near real time to CDC to provide situational awareness during an influenza season. The system was enhanced during the 2009 influenza pandemic and proved to be extremely helpful for monitoring disease burden, severity, and at-risk groups. FluSurv-NET is also expanding into measuring health disparities and pathogen genomics. FluSurv-NET has proven to be a comprehensive yet efficient system for measuring severe influenza in the United States and serves as an exceptional and nimble platform for investigating questions of public health importance with regard to severe influenza.

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Use of Pneumococcal Disease Epidemiology to Set Policy and Prevent Disease during 20 Years of the Emerging Infections Program

Matthew R. Moore, Cynthia G. Whitney

Two decades ago, the Emerging Infections Program of the US Centers for Disease Control and Prevention implemented what seemed like a simple yet novel idea: a population- and laboratory-based surveillance system designed to identify and characterize invasive bacterial infections, including those caused by *Streptococcus pneumoniae.* This system, known as Active Bacterial Core surveillance, has since served as a flexible platform for following trends in invasive pneumococcal disease and studying vaccination as the most effective method for prevention. We report the contributions of Active Bacterial Core surveillance to every pneumococcal vaccine policy decision in the United States during the past 20 years.

Streptococcus pneumoniae, or pneumococcus, is the most common bacterial vaccine-preventable cause of death in the United States; globally pneumococcus is responsible for 476,000 deaths annually among children <5 years of age (*1*). Most of these deaths occur in developing countries. However, early efforts by the Emerging Infections Programs (EIPs) to track pneumococcus in the United States grew out of concerns regarding increasing antimicrobial resistance in the early 1990s. At that time, the Centers for Disease Control and Prevention noted an increase in drug-resistant strains reported through its passive, sentinel, hospital-based surveillance system (*2*) and determined that more intensive tracking of pneumococcal disease was needed.

Surveillance for invasive pneumococcal disease (IPD) began in 1995 as part of the EIP/Active Bacterial Core surveillance (ABCs) programs in California, Connecticut, Georgia, Maryland, Minnesota, Oregon, and Tennessee. IPD, defined for this program as isolation of pneumococcus from a normally sterile site, was chosen as the syndrome to be tracked because pneumococci identified from blood or cerebrospinal fluid are indicative of disease, whereas pneumococci from the respiratory tract might not be indicative, and because clinical practices associated with severe disease were unlikely to vary dramatically in different geographic areas. Audits of clinical laboratories, which can be performed during in-person visits or by electronic queries, aimed to ensure that all cases of IPD in EIP sites were ascertained. Extensive reviews of medical records enable investigators to ascertain underlying conditions, as well as discharge status. The population under surveillance in 1996 was >19 million, but sites were added in 1997, 2000, and 2004. Population growth within each site has increased the total population under surveillance to 31 million in 2014. ABCs have reported estimates of disease burden every year since 1998 (http://www.cdc.gov/abcs). A more detailed presentation of methods used in ABCs is provided by Langley et al. elsewhere in this issue (*3*).

Since the inception of ABCs, numerous publications have drawn heavily on primary analysis of ABCs pneumococcal data, and many others have incorporated secondary analyses of data published in peer-reviewed literature. Some of the most influential outputs have focused on basic descriptive epidemiology. For example, EIP/ABCs data on antimicrobial resistance among pneumococci causing IPD helped shape treatment policy for pneumonia and meningitis (*4*,*5*). A seminal paper containing data collected during 1995–1998 highlighted the increased risk for disease among children <2 years of age and adults ≥65 years of age, as well as substantial racial disparity (greater risk for black persons vs. white persons) in every age group (*6*). In addition, the analysis showed that 59% of disease among adults 18–64 years of age occurred in persons who had an indication for receiving 23-valent pneumococcal polysaccharide vaccine (PPV23). However, vaccine coverage was and remains unacceptably low. An estimated 48,000 cases (76%) of IPD and 5,300 deaths (87%) occurred annually among persons who were eligible for pneumococcal vaccines at that time. This analysis, which was conducted as pneumococcal conjugate vaccines were undergoing clinical trials, helped to highlight the need to include the conjugate vaccine in the US pediatric vaccine schedule and to improve use of PPV23 among adults.

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Having a solid surveillance infrastructure in place has provided major opportunities for EIPs to conduct special studies. One of the earliest with key policy implications was the Preventability Study, which was designed to evaluate the extent to which addition of proposed new Advisory Committee on Immunization Practices (ACIP) indications for PPV23 might increase the proportion of IPD preventable through better immunization coverage (*7*). In 2000, the age for universal influenza vaccination was reduced from 65 to 50 years of age (*8*). This reduction raised the question of whether PPV23, which is frequently given to adults along with influenza vaccine, should also be administered to adults ≥50 years of age. In the Preventability Study, EIP investigators interviewed 1,705 adults who had recovered from IPD to identify all providers from whom they had received care. The EIPs then determined which patients had already received PPV23 and, among those who had not, which patients had at ≥1 ACIP indication for PPV23. Ultimately, the existing recommendations were proven to capture most adults with IPD, and the extant data were not sufficient to support reducing the age of universal vaccination with PPV23 (*7*).

Early EIP data served a major baseline for assessing the benefits of introduction of 7-valent pneumococcal conjugate vaccine (PCV7, Prevnar; Pfizer, Pearl River, NY, USA) in 2000. PCV7 was licensed on the basis of a randomized controlled trial in The Northern California Kaiser Permanente health care system, which demonstrated 97% efficacy against PCV7-serotype IPD when administered on a schedule of dosing at 2, 4, 6, and 12–15 months of age (*9*). The ACIP recommended use of PCV7 on that schedule (*10*), and the American Academy of Pediatrics issued similar recommendations (*11*). In 2001, a shortage of PCV7 led ACIP to recommend suspension of the booster (fourth) dose for healthy children (*12*) and, in 2003, a second shortage led to suspension of the third and fourth doses for healthy children (*13*). Although these shortages were unfortunate, they provided the EIPs with an opportunity to evaluate reduced-dose schedules, something which would have been challenging in the context of a randomized controlled trial.

The EIPs conducted a case–control study of PCV7 effectiveness during 2001–2003 and ultimately enrolled 782 case-patients and 2,512 controls (*14*). Effectiveness of ≥1 doses of PCV7 against PCV7-type IPD was 96%, and estimates of serotype-specific effectiveness were strikingly similar to those from the Kaiser trial (Table). However, because of the shortages, EIPs were able to demonstrate that virtually any PCV7 schedule with ≥2 doses in the first 6 months of life was 95% effective in preventing PCV7-type IPD. A schedule of 2 doses in the first 6 months, followed by a booster dose, was 98% effective. This 2 + 1 schedule was subsequently adopted widely in many countries. EIP/ABCs surveillance documented a 94% reduction in disease among children <5 years of age in the United States by 2003, in spite of the widespread shortages (Figure 1) (*15*).

Because the posterior nasopharynx had long been recognized as the reservoir for pneumococci, studies of asymptomatic colonization provided many insights into the dynamics of pneumococcal transmission. Multiple studies of the effects of pneumococcal conjugate vaccines on nasopharyngeal colonization demonstrated that vaccination prevents acquisition of vaccine-type pneumococci (*16*). This finding resulted in the hypothesis that widespread vaccination of children might reduce transmission to and ultimately, disease in adults. Herd protection conferred by PCV7 was far greater than predicted. Within the first 3 years of the PCV7 program in the United States, rates of PCV7-type IPD among adults began to decrease (*17*) and continued to decrease over subsequent years (Figure 2) (*18*). Whereas a primary driver of cost-effectiveness of PCV7 before introduction was the anticipated effect on otitis media visits among children, a key driver after introduction was the reduction in adult disease (*19*), something only identifiable through population-based surveillance. The cost per IPD episode averted without consideration of herd protection was $33,000, and the cost per episode averted with herd protection decreased to $5,500. This observation fundamentally changed the method for cost-effectiveness analyses of pneumococcal conjugate vaccines, not only in the United States (*20*,*21*) but also

Table. Comparison of serotype-specific effectiveness of PCV7 (EIP/ABCs case–control study) (*14*) with that of NCKP trial (*9*) against invasive pneumococcal disease*

Serotype	Vaccine effectiveness/efficacy, % (95% CI)	
	CDC/ABCs	NCKP trial 2000
All PCV7 types	Healthy: 96 (93–98); underlying illness: 81 (57–92)	94 (80–98)
4	93 (65–99)	NA
6B	94 (77–98)	86 (–11 to 100)
9V	100 (88–100)	100 (–142 to 100)
14	94 (81–98)	100 (60–100)
18C	97 (85–99)	100 (49–100)
19F	87 (65–95)	85 (32–98)
23F	98 (80–100)	100 (15–100)

*PCV7, 7-valent pneumococcal conjugate vaccine; EIP, Emerging Infections Program; ABCs, Active Bacterial Core Surveillance; NCKP, Northern California Kaiser Permanente; CDC, Centers for Disease Control and Prevention; NA, not available.

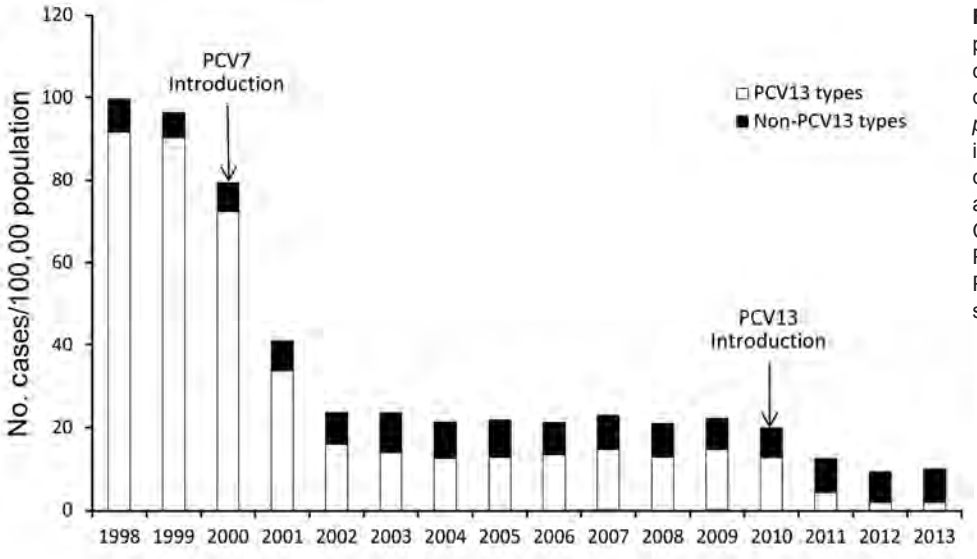

Figure 1. Incidence of invasive pneumococcal disease among children <5 years of age, caused by *Streptococcus pneumoniae* serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) and by non-PCV13 serotype, Centers for Disease Control and Prevention Emerging Infections Program/Active Bacterial Core surveillance, 1998–2013.

in other countries (*22*,*23*). A subsequent analysis, which incorporated the effect on pneumonia from non-EIP data sources, found PCV7 to be cost-saving (i.e., improved health outcomes at lower costs) (*20*).

During subsequent years, as shortages resolved, vaccine coverage increased and disease caused by PCV7 serotypes decreased, and EIPs detected an increase in rates of IPD caused by serotypes not included in PCV7. Even larger increases were described by other investigators in Alaska (*24*). A leading hypothesis was that these increases might represent serotype replacement, the process by which reductions in vaccine types open an ecologic niche for increases in nonvaccine serotypes in the nasopharynx, which ultimately lead to an increase in disease caused by nonvaccine serotypes. This phenomenon had been described in multiple randomized controlled trials of the effects of pneumococcal conjugate vaccines on nasopharyngeal colonization (*16*) but had never been described in the setting of invasive disease. Periodic increases and decreases in the incidence of invasive disease caused by certain serotypes, so-called secular trends, had been described for decades and this was the main hypothesis competing against serotype replacement in the early years after introduction of PCV7 (*25*).

Several antimicrobial drug–resistant strains were serotypes ultimately included in PCV7. Therefore, reductions in antimicrobial drug–resistant IPD were much anticipated and ultimately realized early on (*17*) and after several years of use of PCV7 (*26*). However, an observation compounding fears regarding serotype replacement was that serotype 19A was the non-PCV7 serotype with the greatest increase in incidence and that it was also associated with multidrug resistance (*27*). These findings suggested that inappropriate antimicrobial drug use was playing a role in the observed increases in non-PCV7 serotypes. Another hypothesis to explain the increase in serotype 19A after introduction of PCV7 was that genetic recombination events, whereby a PCV7 serotype could incorporate the genetic sequences of a non-PCV7 serotype, were occurring. So-called capsular switching might have contributed to increasing non-PCV7 serotype disease (*28*).

Ultimately, each of these mechanisms was shown to play a role. A systematic review of surveillance data from around the world, with EIP data being the primary contributor from North America, showed that increases in non-PCV7 serotypes were quite common in many settings and with many schedules of PCV7. However, in none of those settings did the increases in non-PCV7 IPD overshadow the reductions in PCV7-type IPD in children <5 years of age (*29*). Secular trends appeared to be a minor contributor in the United States, where epidemic serotypes 1 and 5 are relatively uncommon. Antimicrobial drug use probably influenced selection of antimicrobial drug–resistant strains among those serotypes (e.g., 19A) destined to cause replacement disease (*30*,*31*). Finally, capsular switching clearly occurred but played a minor role in the increases in non-PCV7 serotypes (*28*). In some settings, improvements in surveillance methods at or after the time of PCV7 introduction might have falsely enhanced the increase in IPD caused by nonvaccine serotypes (*32*).

Worries concerning serotype replacement were tempered to an extent by the anticipated licensure of PCV13 in 2010. PCV13 included the same serotypes as PCV7 plus 6 additional types: 1, 3, 5, 6A, 7F, and, most important, 19A, the dominant replacement serotype worldwide. The US Food and Drug Administration licensed PCV13, and ACIP voted to recommend its use for children in February 2010 (*33*). PCV13 had large and immediate effects, in part

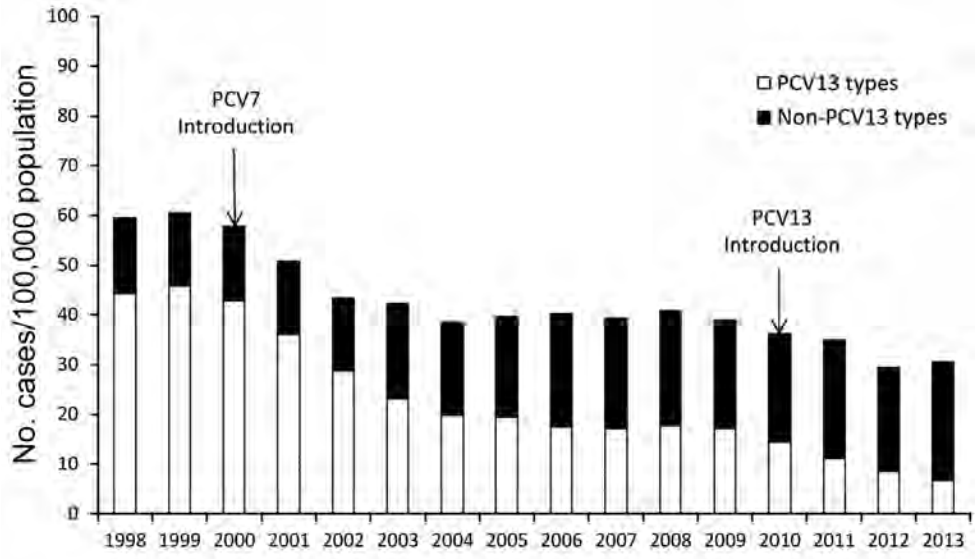

Figure 2. Incidence of invasive pneumococcal disease among adults ≥65 years of age caused by *Streptococcus pneumoniae* serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) and by non-PCV13 serotype, Centers for Disease Control and Prevention Emerging Infections Program/Active Bacterial Core surveillance, 1998–2013.

because it was licensed on the same schedule as PCV7, which enabled rapid swapping out of PCV7 for PCV13. Coverage increased rapidly, and by the end of 2011, EIPs identified reductions in PCV13-type IPD, not only among children but also among adults (*34*). In the short term, the benefits of PCV13 appeared comparable with those of PCV7 and have resulted in large reductions in serotypes that caused most replacement disease after widespread PCV7 use (19A and 7F). Nonetheless, more time is needed to determine whether remaining nonvaccine types will cause extensive replacement disease.

The PCV7 immunization program for children also benefited persons with immunocompromising conditions. After PCV7 introduction, rates of IPD caused by PCV7 serotypes among adults with HIV infection decreased substantially. When PCV13 was licensed for adults in 2011, ACIP discussed the possibility of recommending that vaccine for adults with immunocompromising conditions, including HIV (*35*). Rates of PCV7-type IPD among HIV-infected adults had remained extremely high despite having decreased from their pre-PCV7 baseline (*36*). Around the same time, a randomized controlled trial of PCV7 in HIV-infected adults in Malawi showed PCV7 to be 74% effective in preventing PCV7-type IPD. ACIP considered, among others, these 2 factors—high remaining burden of PCV7-type IPD among HIV-infected adults in the EIPs and demonstrated efficacy of PCV7—in ultimately recommending PCV13 for immunocompromised adults (*37*). On the basis of similar EIP data on disease burden among adolescent children, the ACIP ultimately recommended PCV13 for that population as well (*38*).

The most recent and perhaps widest-ranging change in ACIP recommendations came about in August 2014, when PCV13 was recommended for every adult ≥65 years of age in the United States (*39*). After initially refraining from recommending PCV13 for this group (*35*), the ACIP reviewed extensively results of a randomized controlled trial in the Netherlands, which became available in early 2014 and showed that PCV13 was 76% effective in preventing PCV13-type IPD among persons ≥65 years of age and 45% effective against non-invasive pneumonia caused by PCV13 serotypes (*40*). However, if there were no PCV13-type disease remaining, the ACIP might not have ever recommended the vaccine for this population of 44 million adults. Instead, data from the EIPs were instrumental in demonstrating that, despite major reductions in rates of PCV7- and PCV13-type IPD among adults, the remaining disease burden was sufficiently high that a universal, age-based recommendation was cost-effective in the short term (*39*).

Pneumococcal disease epidemiology has changed substantially in the United States in the past 20 years because of new prevention measures. Disease has decreased, first as a result of PCV7 introduction and, most recently, as a result of PCV13 introduction. EIPs have documented the effects of this vaccine on disease in children, disease in adults, and antimicrobial drug resistance and have provided data that helped to refine vaccine policy in the United States and elsewhere. The EIPs have elucidated the complex mechanisms at play when increases in nonvaccine-type disease are observed after reductions in vaccine-type disease and when antimicrobial drug resistance increases in response to inappropriate antimicrobial drug use and decreases in response to vaccination. In addition, the EIPs have contributed in fundamental ways to every pneumococcal vaccine recommendation in the United States since 2000. For these reasons, the EIPs have reason to celebrate their 20th anniversary.

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Monitoring Effect of Human Papillomavirus Vaccines in US Population, Emerging Infections Program, 2008–2012

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In 2007, five Emerging Infections Program (EIP) sites were funded to determine the feasibility of establishing a population-based surveillance system for monitoring the effect of human papillomavirus (HPV) vaccine on pre-invasive cervical lesions. The project involved active population-based surveillance of cervical intraepithelial neoplasia grades 2 and 3 and adenocarcinoma in situ as well as associated HPV types in women ≥18 years of age residing in defined catchment areas; collecting relevant clinical information and detailed HPV vaccination histories for women 18–39 years of age; and estimating the annual rate of cervical cancer screening among the catchment area population. The first few years of the project provided key information, including data on HPV type distribution, before expected effect of vaccine introduction. The project's success exemplifies the flexibility of EIP's network to expand core activities to include emerging surveillance needs beyond acute infectious diseases. Project results contribute key information regarding the impact of HPV vaccination in the United States.

Human papillomavirus (HPV) vaccines are primarily designed to prevent HPV-associated cancers that typically occur years to decades after exposure to HPV-16 and -18. Three prophylactic HPV vaccines are available in the United States: bivalent, quadrivalent, and 9-valent vaccines. The bivalent vaccine protects against HPV-16 and -18, the most common oncogenic HPV types, which are responsible for ≈70% of HPV-associated cervical cancers and a large proportion of other HPV-related cancers (*1*). The quadrivalent vaccine also protects against HPV-16 and -18 and against HPV-6 and -11, two nononcogenic HPV types that cause genital warts and respiratory papillomatosis (*2*). The 9-valent vaccine also protects against HPV-6, -11, -16, and -18 and against 5 other oncogenic types: HPV-31, -33, -45, -52, and -58 (*3*).

Since June 2006, the Advisory Committee on Immunization Practices (ACIP) has recommended routine HPV vaccination of girls 11–26 or 12–26 years of age who have not previously been administered the quadrivalent vaccine (*4*). After licensure of the bivalent vaccine against HPV-16 and -18 in 2009, the ACIP guidelines for vaccination of women and girls were expanded to recommend quadrivalent or bivalent vaccine for protection against HPV types that can cause cancer. The 9-valent vaccine was licensed in 2014, and in February 2015, ACIP included it as one of 3 recommended HPV vaccines (*5*). To date, the quadrivalent vaccine accounts for almost all HPV vaccines distributed (*6*).

Postlicensure surveillance activities include a range of early, mid, and late biological outcomes for the timely monitoring of the effects of the vaccines in the population (*7*). In the United States, type-specific HPV infection and genital warts are being monitored in a variety of settings to evaluate the earliest evidence of vaccine effect, and HPV-associated cancers are monitored through the National Cancer Institute's Surveillance, Epidemiology, and End Results program and the Centers for Disease Control and Prevention (CDC)–administered National Program of Cancer Registries, which cover the entire US population (*8*,*9*).

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Because of the slow natural history of HPV oncogenesis, the effect of vaccination on invasive cancers will not be evident for decades. Preinvasive cervical intraepithelial neoplasia 2 and 3 and adenocarcinoma in situ (together referred to as CIN2+), which are detected through routine screening, take less time to develop and were used as a surrogate for cervical cancer in vaccine trials. Real-world reductions in CIN2+ have been shown in countries with high vaccination coverage and catch-up programs for older persons and where it is possible to link data across population-based disease, screening, and vaccination registries (*10*–*13*).

In the United States, population-level CIN2+ declines that are attributable to vaccination are more challenging to measure because of a lack of national screening registries and because CIN2+ diagnosis is affected by changes in screening recommendations that have been implemented since vaccine introduction. Historically, cervical cancer screening guidelines in the United States differed across organizations in regard to the age for initial screening and the frequency of screening; many organizations (e.g., the American Cancer Society) recommended screening begin at age 18 or the age of onset of sexual intercourse, whichever was first (*14*). However, over the past decade, screening guidelines have evolved to recommend cervical cancer screening begin at older ages. Currently, all guidelines recommend beginning screening at 21 years of age and that the intervals between screenings be longer than previously recommended, particularly if HPV-based co-testing is used (*15*). Furthermore, CIN2+ lesions are not reportable to public health authorities, except in New Mexico, nor monitored through most existing cancer registries. Therefore, precise determination of the number of women screened is difficult, which, together with changes in and gradual implementation of cervical cancer screening recommendations, makes it difficult to determine whether declines in CIN2+ diagnoses are attributable to vaccination or changes in screening utilization. Given these limitations, additional measures, such as characterizing HPV types associated with CIN2+ lesions and obtaining vaccination histories, are needed to evaluate vaccine-attributable reductions in CIN2+ incidence among the US population.

In 2007, five sites within the Emerging Infections Program (EIP) received funding to determine the feasibility of establishing a population-based surveillance system that could, in addition to monitoring overall CIN2+ trends, enable monitoring of trends in HPV type distribution in CIN2+ lesions among vaccinated and unvaccinated women with a diagnosis of CIN2+. Although the EIP network has traditionally focused on acute infectious diseases with typically short incubation periods, their extensive expertise and proficiency for enhanced surveillance and demonstrated ability to develop local infrastructure to support complex surveillance activities made the EIP network an ideal candidate for collaboration on developing this new system.

The 5 EIP US sites selected to participate in the pilot HPV-IMPACT project were in California, Connecticut, New York, Oregon, and Tennessee. Catchment areas comprised 8 contiguous cities in northwest Alameda County, California; New Haven County, Connecticut; Monroe County, New York; a contiguous region including Portland and most of Washington and Multnomah Counties, Oregon; and Davidson County, Tennessee. On the basis of the 2010 US census, the population of women (≥18 years of age) ranged from ≈260,000 to 350,000 for the 5 catchment areas. The size of each catchment area was selected to maximize successful implementation of all elements of the system while allowing adequate precision for measuring trends over time. The objectives of the HPV-IMPACT project were to 1) conduct active population- and laboratory-based surveillance of CIN2+ diagnoses in women ≥18 years of age residing in defined catchment areas, 2) determine HPV types in CIN2+ lesions among women 18–39 years of age, 3) collect relevant clinical information and detailed HPV vaccination history for women 18–39 years of age, and 4) estimate annual rates of cervical cancer screening among the catchment area population.

Initial activities included establishment of advisory committees comprising key community members, such as health practitioners, anatomic pathologists, and public health authorities, to assist with the development and implementation of the new surveillance system. A variety of methods were used to systematically identify all local and remote histopathology laboratories that serve residents of the catchment areas: conducting surveys of family practitioners, gynecologists, and laboratories; contacting local cancer registries; and using telephone and other directories. The number of laboratories identified in each catchment area varied widely, from 4 local laboratories in New York to 29 laboratories within and outside the catchment area in Connecticut. Although some of the same large national reference laboratories served multiple catchment areas, EIP sites had to work with different regional offices and staff to establish reporting.

This project was reviewed by the following agencies and determined to be exempt from institutional review board approval because the activity constitutes routine disease surveillance activity for disease control program and policy purposes: CDC; Public Health Division, Oregon Health Authority; Tennessee Department of Health; and the institutional review boards of Yale University; University of California, Berkeley; University of California, San Francisco; Vanderbilt University; Alameda County Medical Center; Kaiser Permanente; Unity Health System; University of Rochester Research Subjects Review Board; and Health Clinical Investigation Committee. The project was approved by the State of California Committee for

Protection of Human Subjects. Informed consent was not required by any reviewing or approving institution.

Because CIN2+ reporting was not legally required or routinely performed in any of the participating sites and the legal authority to mandate disease reporting rests with the state, each EIP site investigated the possibility of mandated reporting in their jurisdiction. Connecticut was the first to make the necessary changes to enable statewide CIN2+ reporting through the EIP in 2008 (*16*), Tennessee followed with mandated reporting through the state cancer registry in 2009, Oregon made CIN2+ reportable statewide in 2013 (with retroactive reporting starting in 2008), and California worked with the Alameda County health officer to mandate prospective reporting as of 2013. New York did not pursue reporting mandates because of legislative restrictions and because the established strong support and good working relationships with each laboratory ensured completeness of voluntary reporting.

A protocol and case report forms were developed to standardize methodology for case ascertainment, specimen and data collection, and DNA typing methods. A centralized electronic case management system was created for data collection and maintenance. Each EIP site's unique characteristics required use of different strategies to achieve project objectives, so the system was designed to maintain standards while accommodating site-specific requirements. Because classification systems and nomenclature for preinvasive cervical neoplasia are not standardized in the United States, a master list of possible diagnostic codes, terminology, and synonymic search terms was developed and provided to all reporting laboratories to standardize case finding. Reporting laboratories were asked to provide demographic information for patients (age, race/ethnicity, and health insurance status), along with histopathologic findings. Reports were deduplicated, anonymized, and entered into the project database.

Additional information was obtained for women 18–39 years of age who received a diagnosis of CIN2+. Reporting laboratories were requested to provide samples of archived specimens. At most sites, 1 laboratory agreed to process all specimens according to standard procedures, and prepared specimens were sent to CDC (Atlanta, GA, USA) for HPV DNA typing. Laboratory methods have been previously described (*17*). In brief, a representative block of the diagnostic tissue was provided by the laboratory and presence of a lesion was histologically verified at CDC. DNA was extracted and tested by using the Linear Array HPV Genotyping Assay (Roche Diagnostics, Indianapolis, IN, USA), which detects 37 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 7273, 81, 82, 83,84, 89, IS39). Samples with inadequate or HPV-negative assay results were retested by using the INNO-LiPA HPV Genotying Extra Assay (Innogenetics, Gent, Belgium). Samples negative for the genomic control probe and HPV by both assays were considered inadequate and omitted. HPV vaccination history was investigated by using a variety of sources and methods, as appropriate for each site. Information was collected regarding the number, date, and type of each vaccine dose received. Identified sources for vaccination history comprised state immunization registries, outpatient provider medical records, and administrative and Medicaid claims databases. One site contacted case-patients directly if a vaccination history was not found through an existing data source; self-reported vaccination histories were verified by contacting the vaccine provider, when possible.

Site-appropriate methods for obtaining screening rates in the catchment areas' populations were investigated. Self-reported cervical cancer screening is subject to misclassification (especially overestimation); thus, novel methods to determine screening rates were explored at each EIP site, and methods using existing resources were developed to obtain screening estimates in 3 sites: California, New York, and Oregon. In California and Oregon, weighted estimates of screening were calculated by using available data from national and state-based surveys and administrative databases. National survey data indicated differences in screening rates between insured and uninsured women, so women in the catchment areas were divided into 2 groups on the basis of insurance status (insured or uninsured), and annual screening rates were obtained for each group by using data from the American Community Survey (http://www.census.gov/acs/www/) and the Behavioral Risk Factor Surveillance Survey (http://www.cdc.gov/brfss/data_|documentation/index.htm) to estimate the relative proportion and the difference in screening rates between the groups. The insured and uninsured groups were then combined to estimate overall annual screening rates by age group (18–20, 21–29, and 30–39 years of age) adjusted for insurance status. New York obtained deidentified cervical cancer screening reports from cytopathology laboratories serving the catchment area. The reports, which were deduplicated within the laboratory, included patient age and results of the first screening in a given calendar year and combined and categorized into specified age groups. Screening rates were estimated by using data from the 2010 US census.

During 2008–2012, a total of 13,089 CIN2+ cases were reported among women ≥18 years of age. Almost half of reported cases (48.1%) were in women 21–29 years of age. Women in the youngest (18–20 years of age) and oldest (≥50 years of age) age groups represented only 3.9% and 7.2%, respectively, of all cases (Table). HPV vaccination status was investigated for all women 18–39 years of age with CIN2+. Among those 18–30 years of age at the time of diagnosis who were eligible for vaccination before or during 2008–2012 (n = 7,344), a total of 3,621 (49.3%)

Table. Selected characteristics among women with a diagnosis of CIN2+, Emerging Infections Program HPV-IMPACT project, United States, 2008–2012*

Characteristic	No. (%)
Diagnosis age, y, N = 13,089	
18–20	507 (4)
21–29	6,294 (48)
30–39	3,774 (29)
40–49	1,575 (12)
≥50	939 (7)
Race/ethnicity, N = 10,932	
White, non-Hispanic	6,629 (61)
Black, non-Hispanic	1,857 (17)
Hispanic	1,540 (14)
Asian	551 (5)
Other	355 (3)
Missing	2,157
Vaccination status, N = 7,344	
Vaccinated	1,811 (25)
Not vaccinated	1,812 (25)
Unknown	3,721 (51)
Not age-eligible	5,745
Diagnosis, N = 13,089	
CIN2	6,275 (48)
CIN2/3	2,149 (16)
CIN3/AIS	4,665 (36)
Site location, N = 13,089	
California	2,286 (17)
Connecticut	3,729 (28)
New York	2,813 (21)
Oregon	2,557 (20)
Tennessee	1,704 (13)

*AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; CIN+, CIN grade 2 or 3 or adenocarcinoma in situ; HPV, human papillomavirus.

had documented vaccination status in the medical chart or by self-report, and 894 (24.7%) of those women had initiated the vaccination series.

Archived specimens were retrieved for 7,693 (72.2%) of 18- to 39-year-old women with a diagnosis of CIN2+ during 2008–2012. Of these specimens, 6,745 (87.7%) were histologically adequate and underwent DNA testing; HPV DNA was detected in 6,721 (99.6%) of the specimens. The prevalence of HPV types in CIN2+ lesions is shown in the Figure. Our findings confirmed that HPV-16 and -18 (i.e., types targeted by current vaccines) accounted for over half of all lesions in this population-based sample of women with CIN2+. DNA typing data from the project have also been helpful in predicting the effect of the new 9-valent HPV vaccine in the United States.

Vaccination and screening history data were used to demonstrate that proportions of HPV-16– and HPV-18–attributable CIN2+ in women who initiated vaccination at least 24 months before receiving an abnormal screening test result were statistically significantly lower than proportions in unvaccinated women (*18*). Recent data indicate substantial declines in CIN2+ among women <25 years of age since HPV vaccine was introduced; not all of these declines can be explained by concurrent decreases in the use of screening (*19*). Investigation is ongoing to determine the extent to which the observed decreases may be attributable to vaccine effect and to further quantify vaccine effectiveness on type-specific lesions.

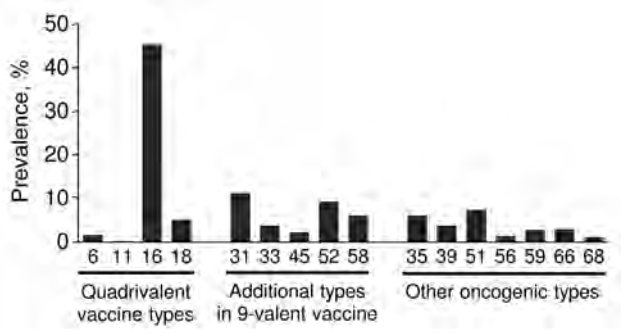

Figure. Prevalence of human papillomavirus (HPV) types among women with a diagnosis of cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ, Emerging Infections Program HPV-IMPACT project, 2008–2012. HPV-16 and -18 are the most common oncogenic HPV types; HPV-6 and -11 are nononcogenic HPV types that cause genital warts and respiratory papillomatosis.

The HPV-IMPACT project has provided valuable information for monitoring the effect of HPV vaccine among the US population, including data on the type distribution of HPV before widespread introduction of the vaccine. A variety of challenges to developing a sustainable population-based system for monitoring CIN2+ and associated HPV types were identified and addressed during the project's pilot phase. Since 2011, active surveillance has been ongoing at all 5 EIP sites, and the systems have been periodically evaluated. Laboratories serving the catchment areas are monitored through routine contact with health care providers, regional and local surveys, and other means to ensure completeness of reporting is maintained over time for all women in the catchment areas. Case ascertainment methods are continually updated and refined as the recommended diagnostic terminology evolves. New mechanisms for obtaining complete vaccination histories, such as interviewing case-patients and contacting vaccine providers to verify self-reported vaccination, are being explored. Efforts are ongoing to improve methods for measuring cervical cancer screening rates.

The success of the HPV-IMPACT project exemplifies the flexibility of the EIP network to expand core activities to include emerging surveillance needs beyond acute infectious diseases. Results from this project contribute key information on the effect of HPV vaccination among the US population.

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Encephalitis Surveillance through the Emerging Infections Program, 1997–2010

Karen C. Bloch, Carol A. Glaser

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Evaluate clinical profiles associated with different etiologic agents of encephalitis
- Assess challenges in diagnosing the etiology of encephalitis
- Distinguish the most common etiology of sporadic encephalitis in the United States
- Determine the epidemiology of the anti-N-methyl-D-aspartate receptor in encephalitis

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Encephalitis is a devastating illness that commonly causes neurologic disability and has a case fatality rate >5% in the United States. An etiologic agent is identified in <50% of cases, making diagnosis challenging. The Centers for Disease Control and Prevention Emerging Infections Program (EIP) Encephalitis Project established syndromic surveillance for encephalitis in New York, California, and Tennessee, with the primary goal of increased identification of causative agents and secondary goals of improvements in treatment and outcome. The project represents the largest cohort of patients with encephalitis studied to date and has influenced case definition and diagnostic evaluation of this condition. Results of this project have provided insight into well-established causal pathogens and identified newer causes of infectious and autoimmune encephalitis. The recognition of a possible relationship between enterovirus D68 and acute flaccid paralysis with myelitis underscores the need for ongoing vigilance for emerging causes of neurologic disease.

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Encephalitis is a potentially devastating illness: the related case-fatality rate in the United States is >5% (*1*), and substantial neurologic disability is common among survivors. Historically, this syndromic illness has been difficult to diagnose: an etiologic agent was identified in <50% of encephalitis cases in the United States diagnosed during 1987–1998 (*2*). A major barrier to diagnosis during that period was the lack of sensitive, noninvasive laboratory techniques to identify central nervous system pathogens. However, by the early 1990s, PCR was proven to be comparable to brain biopsy for the diagnosis of herpes simplex virus (HSV) encephalitis, without the need for an invasive surgical procedure (*3*). There was optimism that application of PCR could also improve microbiologic diagnoses of encephalitis infections caused by other pathogens and, by extension, the outcome of the illnesses. The Emerging Infections Program (EIP), which is funded by the Centers for Disease Control and Prevention, initiated the Encephalitis Project, a syndromic surveillance program for encephalitis in existing EIP sites beginning in New York in 1997, California in 1998, and Tennessee in 2000, and all ending by 2010.

Materials and Methods

Researchers from the 3 sites collaborated to develop shared inclusion criteria that captured both infectious and post-infectious syndromes such as acute disseminated encephalomyelitis (ADEM), using a case definition adapted from previous studies (Table 1). The case definition was constructed to maximize sensitivity, acknowledging that a proportion of cases meeting the EIP standardized definition may have had other conditions known to mimic encephalitis. Common exclusion criteria included patient age <6 months, immunocompromised status (HIV/AIDS or transplantation), and outpatient status. The California and Tennessee EIP sites collected comparable demographic, epidemiologic, and clinical information that was able to be aggregated for combined data analysis (*5*). The New York site focused on development of molecular diagnostic assays (*6–8*).

A major goal of the EIP Encephalitis Project was the implementation of a standardized diagnostic algorithm to be used at all 3 sites. However, early in the course of the project, it was recognized that there were substantial regional differences in the frequency of specific pathogens, such as arboviral and rickettsial infections. The concept of a standardized testing algorithm thus evolved to include a site-specific core set of routinely performed laboratory tests to capture the most common and most treatable etiologies, supplemented by targeted testing on the basis of season, exposures, clinical features, and geography (Table 2) (*9*). For instance, Powassan virus, a tickborne pathogen endemic to the northern United States and Canada and therefore not included in the core algorithm of the Tennessee Unexplained Encephalitis Project, was diagnosed in a patient from New York who became ill during a trip to Tennessee, underscoring the importance of a thorough travel history to guide laboratory evaluation (*10*). This concept of tiered or individualized testing has subsequently been endorsed in management guidelines by the Infectious Diseases Society of America (*11*) and in a consensus statement of the International Encephalitis Consortium, an ad hoc group of subject matter experts and patient representatives (*4*).

Table 1. Case definition for encephalitis in the Emerging Infections Program Encephalitis Project, 1997–2010*

Criteria
Major criterion (required): Altered mental status lasting ≥24 h
Plus ≥1 of 6 minor criteria:
1. Fever ≥38°C occurring ≤72 h before or after hospital admission
2. Seizures
3. Focal neurologic deficits not previously present on examination
4. Cerebrospinal fluid pleocytosis (≥5 leukocytes/mm^3)
5. Abnormal electroencephalogram
6. Abnormal neuroimaging (computed tomography or magnetic resonance imaging) representing an acute process

*International Encephalitis Consortium case definition requires the presence of the major criteria plus ≥3 minor criteria for confirmed/probable; ≥2 for probable encephalitis (*4*).

A final unique feature of the EIP Encephalitis Project was the development of defined a priori pathogen-specific criteria to establish causality. Cases were classified as having a possible, probable, or confirmed etiology constructed on the basis of whether the identified pathogen was a well-established cause of encephalitis and whether there was direct evidence of central nervous system infection (*12*). For example, mycoplasma infection was the single most common infectious etiology identified in the California Encephalitis Project; however, in most cases, the diagnosis was based on serologic test results with no corroborating evidence of neuroinvasive disease; therefore, these cases were classified as having a "possible" diagnosis (*13*).

Encephalitis Profiles

Although the findings for all patients enrolled in the study met the encephalitis case definition, there was tremendous heterogeneity in the clinical characteristics and outcomes of the cases. The large numbers of patients in these projects facilitated recognition of discrete clinical patterns. For example, temporal lobe abnormalities were predictive of HSV encephalitis. It was hypothesized that similar patterns might represent clinical clues to other infectious causes; ultimately, several subsets that had particular characteristics, referred to as encephalitis profiles, were identified (Table 3) (*14*). Although none of these profiles were found to be pathognomonic for a single

Table 2. Core diagnostic testing algorithm for the Emerging Infections Program Encephalitis Project, 1997–2010*

Pathogen	Specimen type	Test type	Seasonality
Viruses			
Adenovirus	NP swab	PCR	Year-round
Arbovirus panel†	Serum	Serology	May–October
Enteroviruses	CSF	PCR	Year-round
	NP swab	PCR	Year-round
	Rectal swab	PCR	Year-round
Epstein-Barr virus	CSF	PCR	Year-round
	Serum	Serology	Year-round
Herpes simplex virus 1 and 2	CSF	PCR	Year-round
Human herpesvirus 6	CSF	PCR	Year-round
Influenza virus A and B	NP swab	PCR	November–April
Parainfluenza virus 1–3	NP swab	PCR	November–April
Rotavirus	Rectal swab	Antigen	November–April
Varicella zoster virus	CSF	PCR	Year-round
West Nile virus	CSF	Serology	May–October
	Serum	Serology	May–October
Bacteria			
Bartonella spp.	Serum	Serology	Year-round
Chlamydia pneumoniae	NP swab	PCR	Year-round
Ehrlichia spp.	Whole blood	PCR	May–October
	Serum	Serology	May–October
Mycoplasma pneumoniae	NP swab	PCR	Year-round
	Serum	Serology	Year-round
Rickettsia spp.	Serum	Serology	May–October
Treponema pallidum	CSF	VDRL	Year-round
	Serum	RPR	Year-round

*Diagnostic testing algorithm at the Tennessee site; regional differences and testing availability associated with minor variations in core testing at the California site. Additional supplementary testing was performed when indicated based on individualized epidemiologic, demographic, clinical, or radiographic features. CSF, cerebrospinal fluid; NP, nasopharyngeal; VDRL, venereal disease research laboratory test; RPR, rapid plasma reagin.
†Arbovirus panel included Lacrosse virus, St. Louis encephalitis virus, Western equine encephalitis virus, and Eastern equine encephalitis virus.

pathogen, this schema has yielded new insights into the epidemiology and potentially to the treatment of subsets of patients who have encephalitis. For instance, the California Encephalitis Project identified a group of patients with profound refractory seizures, accounting for 5% of all cases enrolled at this site (*15*). This profile, subsequently characterized as idiopathic catastrophic epileptic encephalopathy or febrile infection-related epilepsy syndrome, is now widely acknowledged as a particularly severe form of encephalitis. Although the cause of this syndrome remains unknown, by identifying this unique phenotype, promising therapies such as initiation of a ketogenic diet have been identified (*16*).

Unexplained Cases

The EIP Encephalitis Project represents the largest cohort of patients (>5,000) with encephalitis studied to date: >4,000 case-patients were enrolled in the California Encephalitis Project and >700 in the Tennessee Unexplained Encephalitis Project. (Cases at the New York site were enrolled for diagnostic testing only.) Despite the rigorous diagnostic testing algorithm, in approximately half of all cases, no underlying cause for encephalitis was identified. Several factors likely contribute to the frustratingly high proportion of cases that had unidentified pathogens. Foremost is that, for many pathogens other than HSV, PCR of cerebrospinal fluid (CSF) was not an optimal diagnostic test. The high sensitivity of PCR in some instances lead to detection of reactivated viruses in CSF of questionable significance, such as Epstein-Barr virus (*17*) and human herpesvirus 6 (*18*). Also, for many organisms, serologic testing was superior to PCR, but antibodies were often not detectable until several weeks after the acute infection, and serum samples from the convalescent period was not always available. Issues related to specimen integrity such as volume, storage, and timing of collection likely contributed to inability to identify a cause in some cases. Finally, it has become increasingly clear that >5% of case-patients in whom encephalitis was presumed to have been caused by an infectious organism actually had autoimmune encephalitis. Retrospective testing of specimens from case-patients with undiagnosed disease in the California Encephalitis Project identified a newly described autoimmune syndrome, termed anti–N-methyl-D-asparate receptor (NMDAR) encephalitis, as the leading cause of encephalitis among patients ≤30 years of age (*19*). Our initial supposition that the large proportion of undiagnosed cases might be caused by the presence of undiscovered pathogens does not appear to be the case; independent testing of numerous samples at several research laboratories using multiple different techniques, including next-generation sequencing, did not identify any novel infectious agents.

Results

Established Causes of Encephalitis

A confirmed or probable cause of encephalitis was identified in approximately one third of cases studied. HSV, the most frequent cause of sporadic encephalitis in the United States (*1*), was underrepresented in this cohort, reflecting a referral bias toward more diagnostically challenging cases. In fact, clinician referral to one of the EIP encephalitis projects was often deferred until a commercially available HSV PCR test returned negative results, which led to the recognition that HSV PCR analysis early in the disease course could represent a false-negative result (*20*). On the basis of this observation, the recommendation for repeat HSV PCR on a subsequent CSF specimen for patients whose symptoms indicate a high clinical suspicion for HSV encephalitis has been incorporated into national management guidelines (*11*).

The substantial number of patients with encephalitis identified through this project enabled robust pathogen-specific case series of well-established but relatively rare causes of encephalitis. These included large series of patients with enteroviral encephalitis (*21*), tuberculosis meningoencephalitis (*22*), and amebic granulomatous encephalitis (*23*). Furthermore, the project was able to explore the putative association of several organisms for which a causal relationship with encephalitis remains tenuous, such as rotavirus (*24*), human metapneumovirus (*25*), and *Mycoplasma pneumoniae* (*13*). Although the latter organism remains a controversial cause of encephalitis because of the difficulty in demonstrating neuroinvasion, the frequency with which it is detected, particularly in children, has led to the inclusion of *Mycoplasma* serologic testing as part of the recommended pediatric testing algorithm (*4*).

Autoimmune Cases of Encephalitis

Before the start of the EIP Encephalitis Project, it was well recognized that paraneoplastic syndromes could cause limbic encephalitis, albeit infrequently. In 2007, Josep Dalmau and colleagues described anti-NMDAR encephalitis, a novel form of autoimmune encephalitis (*26*). This syndrome was initially reported in women with ovarian teratomas and was believed to represent a paraneoplastic phenomenon. Testing of residual samples from the California Encephalitis Project confirmed that anti-NMDAR encephalitis affects a much broader spectrum of patients, including male and pediatric patients without a neoplastic antigenic stimulus (*27*). Among patients ≤30 years of age, anti-NMDAR encephalitis accounted for more cases than HSV, West Nile virus (WNV), and varicella zoster virus combined (*19*). A recent study showed that HSV encephalitis may serve as an antigenic trigger for subsequent development of anti-NMDAR encephalitis (*28*).

Vaccine-Preventable Cases of Encephalitis

The widespread implementation of the varicella vaccine in the 1990s has essentially eliminated varicella zoster virus as a cause of pediatric encephalitis (*29*). Although various immunizations have been linked to encephalitis (*30*), a large review of pediatric cases showed no temporal relationship between vaccination and subsequent encephalitis, confirming the rarity of vaccine-associated neurologic complications (*31*). This finding, coupled with the identification of encephalitis as a potentially fatal complication of vaccine-preventable infections such as measles (*32*) and influenza virus (*33*), highlights the critical importance of universal immunization.

Emerging Pathogens and Syndromes

When the EIP Encephalitis Project was initiated, it was unforeseeable that a virus never before identified in the Western Hemisphere would cause an encephalitis epidemic in the United States. Yet, during 1999–2013, more than 17,000 cases of West Nile neuroinvasive disease were diagnosed; the case-fatality rate was 9% (*34*). After the emergence of WNV in 1999, the New York site was uniquely

Table 3. Emerging Infections Program Encephalitis Project clinical profiles, 1997–2010*

Clinical profile	Patient description	Comments
Focal		
Temporal lobe	Temporal lobe enhancement on imaging or activity on EEG	HSV accounted for approximately one third of cases
Extrapyramidal	Movement disorder	Measles (SSPE), autoimmune encephalitides
Cerebellar	Ataxia or gait disorder, or focal cerebellar lesion on imaging	Acute EBV infection seen in a minority of cases
Generalized		
Cerebral edema	Neuroimaging showing diffuse brain edema	Deaths exceed 70%
Intractable seizures	Seizures requiring anesthetic coma for management	Majority of case-patients: pediatric patients with prolonged hospitalization
Seizure with rapid recovery	Onset with seizure and return to baseline mental status in <96 h	CSF typically bland; *Bartonella* spp. most common cause (cat-scratch encephalopathy)
Psychosis	New onset of prominent psychiatric symptoms	Anti-NMDAR antibodies common in this syndrome

*EEG, electroencephalogram; HSV, herpes simplex virus; SSPE, subacute sclerosing panencephalitis; EBV, Epstein-Barr virus; NMDAR, anti-N-methyl-D-asparate receptor.

positioned to assist with the identification of this unexpected pathogen, and to perform surveillance for additional cases (*35*). As the virus spread throughout the continental United States, the large numbers of patients referred to California Enchephalitis Project enabled analysis of WNV encephalitis among pediatric patients (*36*) and identification of risk factors predisposing to neuroinvasive disease (*37*).

The infrastructure that proved invaluable in enabling a rapid response to the WNV epidemic also was instrumental in identifying an emerging neurologic syndrome characterized by acute flaccid paralysis. In 2012, several physicians familiar with the California Encephalitis Project contacted the project, reporting cases of previously healthy patients with acute onset of a polio-like illness. Routine testing for organisms associated with acute flaccid paralysis returned negative results, raising concern for a novel agent or pathogen causing this syndrome. These sporadic cases occurred at geographically disparate sites and likely would not have been recognized without an existing surveillance mechanism. Ultimately, more than 23 cases were identified in California (*38*). The sentinel cluster of cases in California triggered national surveillance, resulting in 88 cases identified to date in 32 states (*39*). Investigation is ongoing, and although no causative pathogen has been identified, enterovirus D68 has been implicated in several cases (*40*).

Discussion

The EIP Encephalitis Project has demonstrated the value of syndromic surveillance in a constantly changing environment. Globally, this project represents the largest known cohort of patients with encephalitis. The robust sample size provided sufficient power to investigate recognized pathogens and to identify newer causes of encephalitis, both infectious and autoimmune. Syndromic surveillance confirmed that previously common causes of pediatric encephalitis such as VZV have been all but eliminated by vaccination, and conversely, that childhood immunization is not substantially associated with development of encephalitis. The recognition of an emerging syndrome of acute flaccid paralysis with myelitis, possibly caused by enterovirus D68, underscores the need for ongoing vigilance for emerging causes of neurologic disease.

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Tracking Pertussis and Evaluating Control Measures through Enhanced Pertussis Surveillance, Emerging Infections Program, United States

Tami H. Skoff, Joan Baumbach, Paul R. Cieslak

Despite high coverage with pertussis-containing vaccines, pertussis remains endemic to the United States. There have been increases in reported cases in recent years, punctuated by striking epidemics and shifting epidemiology, both of which raise questions about current policies regarding its prevention and control. Limited data on pertussis reported through the National Notifiable Disease Surveillance System have proved insufficient to answer these questions. To address shortcomings of national pertussis data, the Emerging Infections Program at the US Centers for Disease Control and Prevention launched Enhanced Pertussis Surveillance (EPS), which is characterized by systematic case ascertainment, augmented data collection, and collection of *Bordetella pertussis* isolates. Data collected through EPS have been instrumental in understanding the rapidly evolving epidemiology and molecular epidemiology of pertussis and have contributed essential information regarding pertussis vaccines. EPS also serves as a platform for conducting critical and timely evaluations of pertussis prevention and control strategies, including targeting of vaccinations and antimicrobial prophylaxis.

Pertussis (whooping cough) has proven to be a frustratingly persistent public health problem. Although annual numbers of reported cases decreased >99% in the United States after introduction of whole-cell pertussis vaccines in the 1940s, this highly contagious respiratory illness has refused to go the way of other vaccine-preventable diseases of childhood, such as polio, *Haemophilus influenzae* type b infection, and diphtheria. Pertussis remains endemic to the United States, and the number of reported cases has been increasing steadily since the late 1980s, with notable epidemic peaks in recent years (Figure 1). In 2012, more than 48,000 cases were reported nationally, the largest number since 1955. Possible reasons for the observed increase include changes in diagnostic testing and reporting, increased provider and public awareness, mismatch of vaccine antigens and circulating strains, and reduced duration of immunity from acellular pertussis (aP) vaccines that replaced whole-cell vaccines in the United States during the 1990s.

The cough illness associated with pertussis can be quite severe and the disease debilitating in persons of all ages, but illness and death rates remain highest among young infants, especially those too young to be directly protected by vaccination. Recently, the epidemiology of pertussis has indicated an increasing burden of disease among school-age children and adolescents, most of whom are up-to-date on pertussis vaccinations (*1*,*2*). Changes have also been identified in *Bordetella pertussis* at the molecular level, such as loss of pertactin, a key aP vaccine antigen (*3*).

Pertussis has been a reportable disease in the United States since 1922. Case-based surveillance data are captured through the National Notifiable Diseases Surveillance System (NNDSS) from 57 public health jurisdictions (50 states; 5 US territories; New York, NY; and Washington, DC) (*4*). NNDSS is a passive system that relies on reports from health care providers and laboratories, probably resulting in underreporting of cases. In addition, because case investigation requires the effort and resources of disparate local and state public health agencies, the quantity and quality of pertussis case reports vary, and data elements fundamental to the understanding of pertussis, including case demographics, clinical symptoms and pertussis vaccination history, are often incomplete. NNDSS is a relatively inflexible system that cannot readily accommodate newly desired data elements, and complex data transmission processes and challenges might compromise the quality of data received at the Centers for Disease Control and Prevention (CDC).

Although NNDSS has been essential for monitoring the national burden of pertussis and age-related trends in disease

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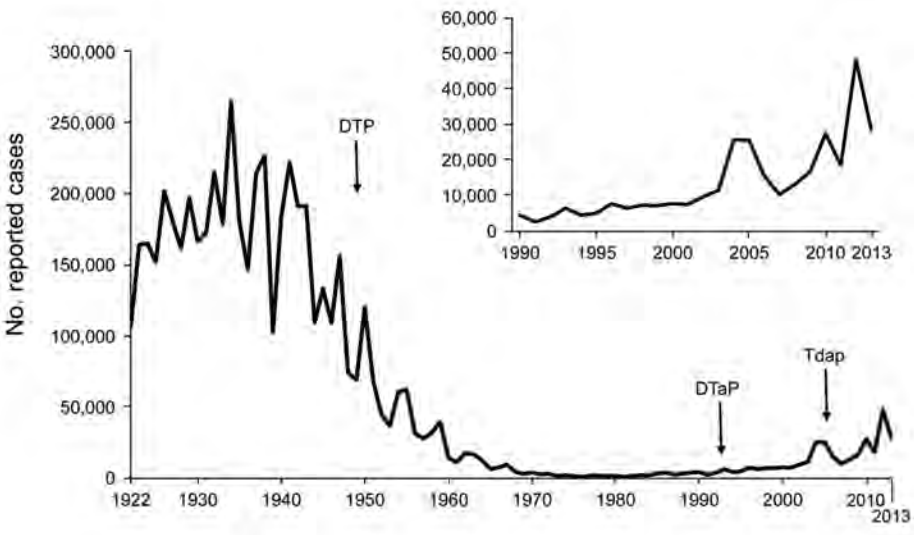

Figure 1. Reported pertussis cases from the National Notifiable Diseases Surveillance System, United States, 1922–2013. Inset show cases during 1990–2013. Data for 1950–2013 were obtained from the Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System. Data for 1922–1949 were obtained from passive reports to the US Public Health Service. DTP, diphtheria and tetanus toxoids combined with whole-cell pertussis vaccine; DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; Tdap, reduced-dose acellular pertussis vaccine combined with tetanus and diphtheria toxoids.

over time, data are of insufficient detail and consistency to answer reliably the many urgent questions relevant to public health. Are current pertussis prevention and control strategies effective, specifically, vaccination and postexposure antimicrobial chemoprophylaxis (PEP)? Has the spectrum of clinical illness changed, and does it differ by factors such as age and vaccination status? In the setting of waning aP-induced immunity, should additional doses of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) be recommended, and if so, for which populations? Is *B. pertussis* evolving in key ways at the molecular level, and what, if any, is the clinical and epidemiologic relevance of identified changes? What are the disease burden and epidemiologic and molecular characteristics of other *Bordetella* species, and how might these species be contributing to the resurgence of pertussis-like cough illness?

Enhanced Pertussis Surveillance System

In 2011, Enhanced Pertussis Surveillance (EPS) was undertaken by 6 states within the Emerging Infections Program (EIP), a collaborative network between CDC and state and local health departments, academic institutions and laboratories that serves as a national resource for surveillance, prevention, and control of emerging infectious diseases (*5*). EPS was initiated in EIP sites that had varying levels of *B. pertussis* incidence and existing pertussis surveillance infrastructure. The principal objectives of EPS are to determine overall and age-specific incidence and epidemiologic characteristics of pertussis, to characterize the molecular epidemiology of circulating *B. pertussis* strains, to monitor the effects of pertussis vaccines, and to provide a platform for conducting special studies, including critical and timely evaluations of pertussis prevention and control strategies. As a secondary objective, the system collects data to describe the epidemiology and molecular characteristics of other *Bordetella* species, including *B. holmseii*, *B. parapertussis*, and *B. bronchiseptica*.

For efficiency, EPS was built upon the NNDSS pertussis surveillance infrastructure within participating states, leveraging and enhancing existing efforts; within the same catchment area, cases reported through EPS are also reported through NNDSS. As with NNDSS, case investigations are triggered by a positive pertussis laboratory result or report from a diagnosing health care provider, and follow-up is initiated by the local public health system. EPS cases are classified according to the NNDSS/Council of State and Territorial Epidemiologists (CSTE) pertussis case definition, and all modifications made to the case definition at the national level are adopted by EPS (*6*). Similar to NNDSS, EPS is population-based, thereby maximizing the generalizability of its findings.

Although NNDSS serves as a foundation for EPS, a substantial investment of resources is made to EPS states annually, and additional personnel are employed to conduct a higher-level of pertussis surveillance that is sustainable in the longer term. The specific enhancements of EPS involve the following items.

Optimizing Case Detection and Reporting and Ensuring Consistency across Sites

As resources permit, EPS sites educate and encourage area health care providers, including pediatricians, internists, and family practitioners, to consider pertussis as part of the differential diagnosis and to test for it properly. In some EPS sites, state public health laboratories offer pertussis testing (e.g., culture and real-time PCR) at no cost to catchment-area health care providers or to patients without access to health care to ensure testing whenever *B. pertussis* is suspected as a cause of illness.

Expansion of Variables Collected

The standardized EPS case report form mirrors the NNDSS form, but collects several supplemental demographic, clinical, and epidemiologic variables. The EPS case report form is revised annually, maintaining the flexibility to address key public health questions in a timely manner.

Aggressive Attempts to Capture Complete Case Report Form Data

Local investigators and surveillance personnel work to interview each case-patient or parent proxy and the case-patient's diagnosing health care provider and complete follow-up interviews when necessary. Multiple procedures are used to obtain accurate vaccination histories, including routine review of state immunization information systems and school immunization records, and occasionally contacting additional health care providers of a case-patient.

Site-Specific Strategies to Maximize Acquisition of Isolates from Case-Patients

This feature is an arduous task, given the increasing reliance on non–culture-based methods for diagnosis of infection with *B. pertussis*. Approaches range from promoting centralized testing at a state public health laboratory, to identification of sentinel site providers for specimen collection, to recovering isolates from PCR-positive specimens. Once collected, *B. pertussis* isolates are sent to CDC, where they undergo susceptibility testing to erythromycin and azithromycin and a full panel of molecular characterization, including pulsed-field gel electrophoresis, multilocus variable number tandem repeat analysis, and multilocus sequence typing. More recently, laboratory testing has evolved to include phenotypic and genotypic assays for detection of pertactin-deficient isolates, as well as whole-genome sequencing of *B. pertussis*.

Expansion of Activities to Include Collection of *B. pertussis* Clinical Specimens

In response to advancements made in molecular characterization, EPS has positioned itself to monitor characteristics of a larger population of circulating strains and to follow the molecular epidemiology of pertussis. As of 2014, EPS is conducted in the 5-county Denver metropolitan area of Colorado; 8 counties in metropolitan Atlanta, Georgia (added at the beginning of 2014); the 15-county Rochester and Albany areas of New York; the 3-county Portland area of Oregon; and statewide in Connecticut, Minnesota, and New Mexico. Although EPS is conducted in ≈5% of the US population, the demographic composition of the EPS catchment area is similar to the whole United States in terms of racial, ethnic, and age distributions, which enables characterization of the epidemiology of *B. pertussis* among select population groups.

Accomplishments

Since its inception, data collected through the EPS system have maintained a higher level of completeness than surveillance data reported through NNDSS. A comparison of data collected from both systems during 2011–2012 found significantly more complete data from EPS on race (91% vs. 76%; p<0.001) and ethnicity (93% vs. 72%; p<0.001) (*7*). Dramatic differences i n completeness have also been observed for key variables, such as cough onset date, duration of cough, hospitalization status, and pertussis vaccination history (Table). High-quality race and ethnicity data enabled an analysis of EPS data from Oregon that found higher rates of disease among Hispanic infants than non-Hispanic infants, and identified that household size, regardless of ethnicity, might be a key marker of increased exposure to pertussis (*8*). In addition, complete vaccination history served as the foundation of EPS analyses that have further demonstrated the correlation between severe disease and lack of vaccination, comparisons that would

Table. Completeness of pertussis surveillance data collected from the NNDSS and EPS, United States, 2011–2012*

Characteristic	Complete, %†		Difference, %
	NNDSS‡	EPS	
Race	76	91	15
Ethnicity	72	93	11
Any cough	79	100	21
Paroxysms	78	100	22
Whoop	74	97	23
Post-tussive vomiting	75	99	24
Primary symptoms known§	72	96	24
Cough onset date	66	100	34
Duration of cough	71	100	29
Hospitalized	73	99	26
≥1 vaccine date and type, age range 3 mo–7 y	71	99	28

*Data were obtained from Kamiya et al. (7). NNDSS, National Notifiable Disease Surveillance System; EPS, Enhanced Pertussis Surveillance. All p values for comparisons were <0.0001.
†Unknown or missing responses were considered incomplete.
‡NNDSS completeness calculation excludes data from EPS area.
§Cough, paroxysms, whoop, and post-tussive vomiting

have been difficult to make with a high proportion of missing data (*9*).

Overall and age-specific incidence rates have tracked 1.5–3.3 times as high among EPS sites as national NNDSS rates (Figure 2). State-specific differences in pertussis incidence are recognized nationally, and states experience peaks at different times. Although differences between EPS and NNDSS certainly reflect variations in state-specific pertussis cycles and burden of disease, enhanced case ascertainment and awareness of the EPS program among diagnosing providers and local public health investigators also likely translates to increased case recognition and reporting within the EPS catchment area.

More than 20 EPS-specific data elements have been added to the case report form, many of which are intended to inform policy or help monitor the impact of new vaccine recommendations. As we await potential licensure of the expanded use of >1 dose of Tdap, and the Advisory Committee on Immunization Practices (ACIP) considers additional doses for special populations, EPS is tracking the burden of pertussis among health care personnel, a target group for which few data are available on the burden of pertussis. To protect young infants at highest risk for severe illness and death from pertussis, the ACIP recommended Tdap vaccination of pregnant women in October 2011 and expanded the recommendation in 2012 to include a dose during every pregnancy (*10*). Maternal Tdap vaccination history is being captured for all infant pertussis cases identified through EPS, along with timing of Tdap receipt in relation to pregnancy and reasons for not getting vaccinated during pregnancy. This information is being collected to determine the uptake of the recent vaccination recommendation and to identify any epidemiologic changes in infant disease.

Since 2011, EPS has been ascertaining pregnancy status for female case-patients; during 2011–2013, a total of 3.5% of case-patients 15–44 years of age were identified as being pregnant at the time of their pertussis infection (EPS, unpub. data). Little is known about the course of illness and complications of pertussis among pregnant women, a group for which pertussis vaccination is currently recommended as a means of protecting young infants. EPS has also been documenting the source of infant infection and has identified a shift from mothers to siblings as the most commonly identified source of disease transmission to infants (*11*). This finding is in contrast to those of previously published studies (*12*,*13*) in the United States and is crucial in the context of increasing burden of disease among school-age children.

EPS now serves as a key source of *B. pertussis* isolates for CDC, accounting for >50% of isolates received annually during 2011–2013. To date, >400 isolates have been collected from case-patients across the age spectrum; >80% of isolates have been obtained from case-patients >1 year of age. The availability of isolates linked to corresponding epidemiologic case data positions EPS to monitor the evolving molecular epidemiology of pertussis and quickly detect changes in the *B. pertussis* genome. EPS isolates were crucial to a recent analysis that identified emergence and rapid proliferation of pertactin-deficient strains in the United States (*3*). Isolates from EPS states conducting population-based surveillance over time helped illustrate the emergence of pertactin deficiency across the general population. Because of highly complete case report data, EPS data were also key to understanding the clinical and epidemiologic relevance of pertactin deficiency. Clinical symptom profiles were similar by pertactin status; however, vaccinated case-patients were more than 3 times as likely as unvaccinated case-patients to have pertactin-deficient isolates, suggesting a selective pressure of vaccination (*14*).

Another unique feature of the EPS system is its ability to influence national pertussis surveillance practices. Through the collection of ruled-out cases (i.e., PCR-confirmed

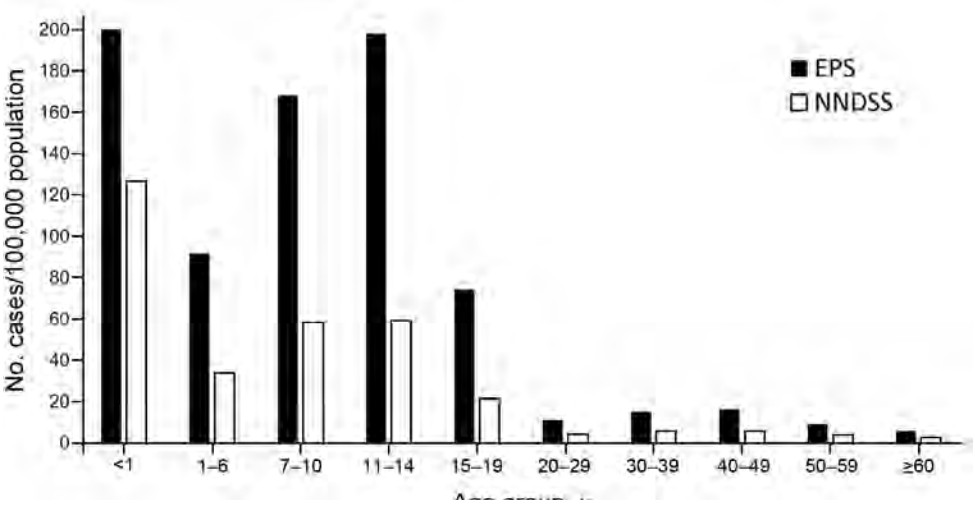

Figure 2. Overall and age-specific pertussis incidences, United States, 2012, from the National Notifiable Diseases Surveillance System (NNDSS) and Enhanced Pertussis Surveillance (EPS). Overall incidence for 2012. NNDSS: 15.4 cases/100,000 population (Centers for Disease Control and Prevention, NNDSS and Supplemental Pertussis Surveillance System, and 1922–1949 passive reports to the US Public Health Service). EPS: 42.0 cases/100,000 population (Emerging Infection Program, EPS for Colorado, Connecticut, Minnesota, New Mexico, New York, and Oregon).

cases that did not meet the 14-day cough requirement of the CSTE case definition), EPS gathered data that helped guide revisions to the national CSTE pertussis case definition for infants <1 year of age, which included removing the required 14-day cough for PCR-confirmed or epidemiologically linked cases (*6*). In addition, although serologic results are currently not considered confirmatory in the national case definition and the lack of standardization among the >40 commercially available assays in the United States makes interpretation of serologic results challenging, EPS has begun to investigate serologically confirmed cases to ensure consistency in identification of clinically compatible disease across sites. This activity should help to measure the additional burden of disease and workload resulting from routine investigation of serologically confirmed cases and lay the groundwork for future inclusion of serologic results into the CSTE case definition. EPS will also serve as a platform for piloting a revised case definition before it is implemented on a national level, a key step in this era of increased disease burden and limited resources.

Special Studies Using the EPS Platform

One of the hallmarks of the EIP infrastructure is the flexibility to add special studies. The EPS platform has served as a foundation for several key pertussis projects ranging from resource-intensive, case–control evaluations to activities considered "low-hanging fruit." Through EPS, it has been observed that ≈30% of pertussis hospitalizations are occurring in age groups other than infants and the elderly (EPS, unpub. data), prompting the question, why are older children and adults being hospitalized for pertussis? EPS investigators conduct expanded reviews of medical records of all hospitalized EPS case-patients. Data gathered enable characterization of the severity of infections in hospitalized patients across age groups, determination of reasons for hospital admission, documentation of underlying health conditions associated with severe illness, assessment of current practices in treatment, and outcomes of severe pertussis infection.

Although data suggested that maternal antibody transfer resulting from Tdap vaccination during pregnancy would probably confer protection and modify the severity of pertussis among infants, at the time the ACIP recommendation was made for women to receive a dose of Tdap during pregnancy, there was no direct evidence demonstrating effectiveness of the strategy in preventing infant disease (*15*–*17*). EIP has initiated a timely case–control evaluation of the new recommendation and will provide urgently needed data on the usefulness of the strategy in the United States, adding to the data available from the United Kingdom (*18*,*19*). In addition, the evaluation will include an assessment of older infants to identify any negative effects of maternally transferred pertussis antibodies on protection provided by the primary pertussis immunization series, a theoretical consequence and potential concern of vaccination during pregnancy.

In the setting of increasing pertussis burden and waning aP-induced immunity after pertussis vaccination, it is crucial to ensure the effectiveness of other strategies, such as administration of PEP to close contacts to support current prevention and control efforts. Secondary attack rates of pertussis are high within household settings, and data are limited on the effectiveness of newer macrolide antimicrobial drugs currently recommended for PEP after pertussis exposure. Selected EPS sites are embarking on a study to assess secondary transmission of *B. pertussis* among household contacts after a 5-day course of azithromycin PEP. This labor-intensive study requires identification of case-patient household contacts and follow-up and specimen collection at multiple time points. Results from this evaluation will aid in determining whether current PEP recommendations for household contacts are useful for preventing secondary transmission of disease and, being mindful of judicious antimicrobial drug use policies, will determine whether or not alternate PEP guidelines should be considered. In addition, the study will provide information on nasopharyngeal carriage of *B. pertussis* among asymptomatic household contacts before PEP, an area for which few data are available.

Before official establishment of EPS, the EIP infrastructure was used to evaluate the clinical accuracy of available pertussis diagnostics. Because PCR and serologic assays were being used more frequently to diagnose pertussis in the United States, a study looking at the clinical accuracy of current pertussis diagnostics was needed. Data collected from EIP sites during 2007–2011 are currently being used to estimate the clinical sensitivity, specificity, and predictive values of a CDC multiplex real-time PCR and a serologic assay (ELISA) developed by CDC and the Food and Drug Administration. In addition, the EIP sites are assessing the clinical utility of the tests as they relate to stage of pertussis illness, age of patient, antimicrobial drug use, and vaccination status. Data from the evaluation will ensure that validated, standardized laboratory assays are available to help improve the diagnosis and reporting of pertussis, which will ultimately facilitate prevention and control efforts.

Future Opportunities for EIP

Current evidence indicates that the resurgence of pertussis in the United States is real and not simply an artifact of improved surveillance. Furthermore, current vaccination strategies are not expected to reduce further the growing burden of disease in the United States. Because pertussis remains a notable public health challenge, EPS is well-positioned to monitor the changing epidemiology of this

disease and provide timely, reliable surveillance data to help answer key questions. The flexibility and expertise of the EIP network can be relied on to tackle challenging public health issues and to make direct recommendations to advance the prevention and control of pertussis in the United States and can serve as a model for collaborators abroad hoping to implement standardized surveillance for pertussis in the international setting.

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TickNET—A Collaborative Public Health Approach to Tickborne Disease Surveillance and Research

Paul Mead, Alison Hinckley, Sarah Hook, C. Ben Beard

TickNET, a public health network, was created in 2007 to foster greater collaboration between state health departments, academic centers, and the Centers for Disease Control and Prevention on surveillance and prevention of tickborne diseases. Research activities are conducted through the Emerging Infections Program and include laboratory surveys, high-quality prevention trials, and pathogen discovery.

Through their bites, ticks expose humans to a remarkable array of pathologic agents, including neurotoxins, allergens, bacteria, parasites, and viruses. The clinical features of tickborne illness range from mild to life-threatening, and collectively, tickborne diseases constitute a substantial and growing public health problem in the United States. New agents of tickborne disease are described regularly, and known agents are spreading to new areas.

The most common tickborne disease in the United States is Lyme disease, caused by the spirochete *Borrelia burgdorferi*. With >37,000 cases reported to the Centers for Disease Control and Prevention (CDC) during 2013, Lyme disease ranks fifth among all nationally notifiable conditions (*1*,*2*). Less common but potentially serious tickborne infections include anaplasmosis, babesiosis, ehrlichiosis, spotted fever group rickettsioses, and Powassan virus disease (*3*). Recent reports of US patients infected with *Borrelia miyamotoi* (*4*), an *Ehrlichia muris*–like agent (*5*), a novel bunyavirus (*6*), and a putative new genospecies of *Borrelia burgdorferi* (B. Pritt, pers.com.) all serve to highlight the potential for discovery of novel tickborne pathogens. In addition, several tickborne diseases of unknown etiology have also been described, most notably STARI (southern tick–associated rash illness). Easily confused with early Lyme disease, STARI is a distinct, idiopathic entity associated with bite of the lone star tick, *Amblyomma americanum* (*7*,*8*). This tick species has also been implicated recently as a cause of IgE-mediated hypersensitivity to red meat and certain chemotherapeutic agents (*9*).

Tickborne diseases pose special challenges for clinicians and public health agencies alike. Although tickborne diseases occur throughout the United States, the distribution of any given disease can be highly focal (Figure 1), and this information must be known and considered by health care providers when assessing patients. In addition, laboratory testing is often limited to serologic assays that require paired samples drawn several weeks apart to confirm recent infection, which complicates the use of laboratory testing for both patient management and public health surveillance. With regard to prevention, tick checks, repellent use, and other personal protective measures, although generally benign and inexpensive, are not especially effective (*10*). Despite decades of education about these measures, case reports for the more common tickborne diseases continue to increase (Figure 2). Pesticide use can reduce tick abundance (*11*–*13*) but has not been proven to reduce tickborne disease in humans (*14*,*15*). Lymerix, developed to prevent Lyme disease, is the only vaccine ever licensed in the United States to prevent a tickborne disease in humans, but it was removed from the market during 2003 amidst poor sales and unsubstantiated reports of increased adverse events (*16*,*17*).

The Network

To foster greater coordination on surveillance, research, education, and prevention of tickborne diseases, CDC established TickNET during 2007. TickNET is a public health network that includes partners from state health departments and academic institutions collaborating through the Emerging Infections Program (EIP), staff of state and local health departments collaborating through the Epidemiology and Laboratory Capacity (ELC) cooperative agreement, and CDC staff in the Division of Vector-Borne Diseases and the Division of Parasitic Diseases and Malaria. We will briefly describe key TickNET projects completed or currently underway.

TickNET provides funding to state and local health departments through the ELC cooperative agreement to help sustain and enhance routine surveillance for tickborne diseases. Approximately 18 state and local health departments are funded annually for Lyme disease surveillance, with priority given to states with a reported incidence of Lyme disease greater than the national average and to bordering states where the disease may be spreading. During 2014, an

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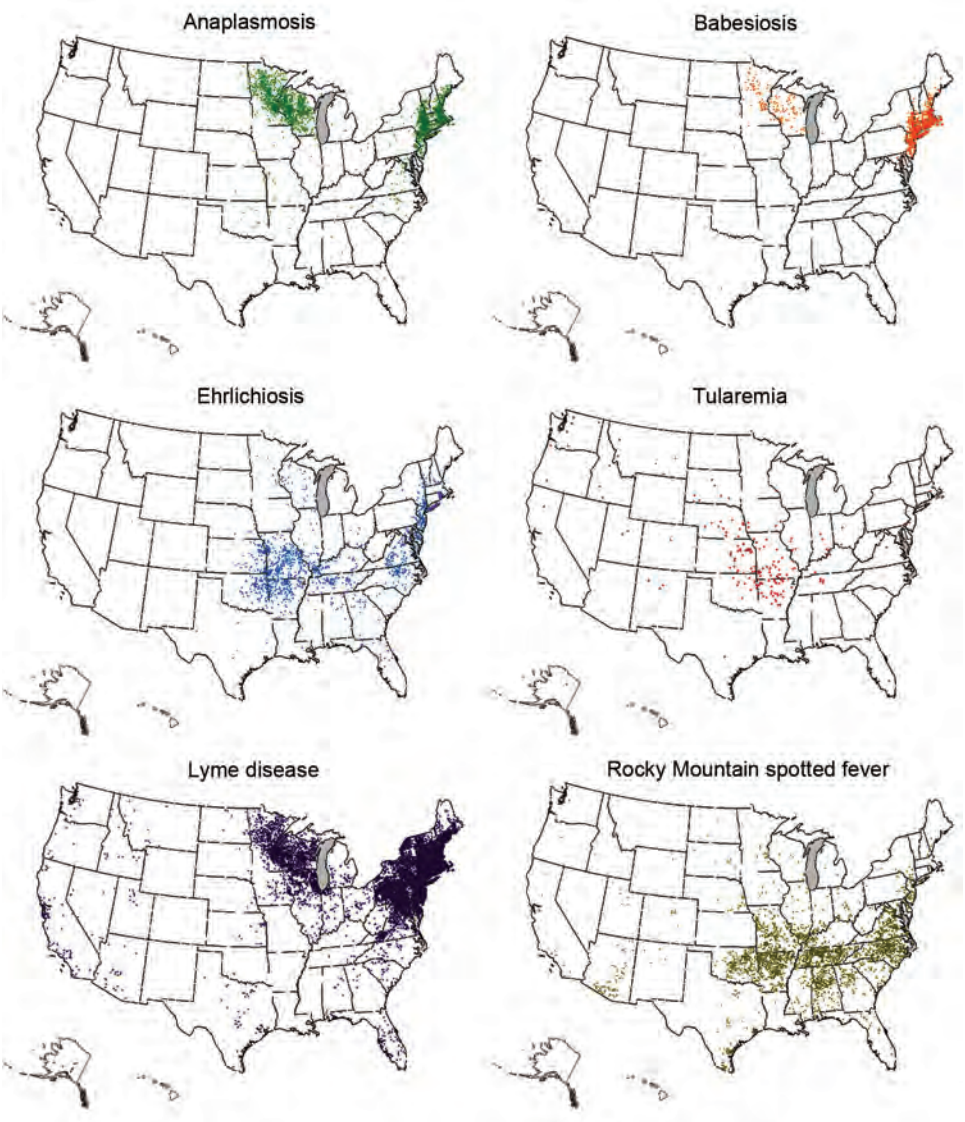

Figure 1. Geographic distribution of leading tickborne diseases among humans, United States, 2013. Each dot represents 1 case, based on patient residence; exposure location may be different.

additional 7 state and local health departments received ELC funding to support surveillance for other tickborne diseases.

Together with ELC funding for program support, funding through EIP has allowed TickNET partners in Maryland, Minnesota, and New York to undertake special studies to quantify underreported tickborne diseases. These studies include a review of patient charts and codes from the International Classification of Diseases, Ninth Edition, and provide insights into the use of electronic medical records for public health surveillance. Other studies in Massachusetts, Minnesota, and New York are examining ways to streamline the evaluation of positive laboratory reports by using random sampling methods. Results from these and related studies will become available in 2015.

During 2008, TickNET partners at EIP sites in Connecticut, Maryland, Minnesota, and New York conducted a survey of commercial, clinical, and state laboratories to evaluate practices and volume of testing for 5 leading tickborne diseases. Collectively, 7 large commercial laboratories reported testing ≈2.4 million patient specimens for evidence of *B. burgdorferi* infection during 2008, at an estimated cost of $492 million. After correcting for test sensitivity, specificity, and stage of illness, the overall frequency of infection among patients for whom samples were tested was estimated at ≈12%. Applied to the total number of specimens, this percentage yielded an estimated 288,000 true *B. burgdorferi* infections (range 240,000–444,000) among source patients during 2008 (*18*). Results of this study will be compared with results of other ongoing CDC studies to estimate the overall frequency of Lyme disease and other tickborne infections in the United States.

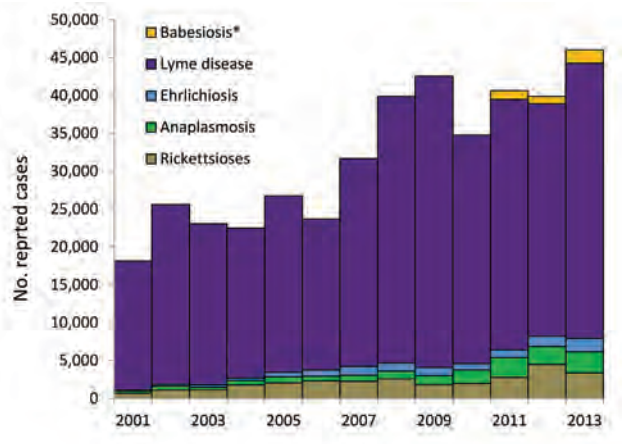

Figure 2. US cases of Lyme disease, ehrlichiosis, anaplasmosis, babesiosis, and spotted-fever group rickettsioses reported to the Centers for Disease Control and Prevention, 2001–2013. Counts include confirmed and probable cases, according to the case definition in effect in each year. Anaplasmosis cases were reported as human granulocytic ehrlichiosis before 2008. Ehrlichiosis refers to infections caused by *Ehrlichia chaffeensis*, *E. ewingii*, and undetermined species. *Babesiosis was first designated a nationally notifiable condition during 2011.

Frequency is but one measure of the public health importance of a disease. To better quantify the public health burden of tickborne diseases, TickNET EIP partners in Connecticut, Maryland, Minnesota, and New York have undertaken a study to quantify current costs associated with individual cases of Lyme disease. Begun during 2014, the Cost of Lyme Disease study uses a prospective survey design to capture individual and societal costs of Lyme disease, including out-of-pocket medical costs, nonmedical costs, and productivity losses, as well as total direct medical costs to society by using billing codes from enrolled patients' providers. This estimate will be used to guide impact assessments of current and future prevention methods.

As an adjunct to personal protective measures such as use of insect repellents, several yard-based interventions have been proposed to reduce tick abundance in the home environment. To assess the efficacy of such interventions in preventing human illness, TickNET sites have instituted a series of studies to evaluate the efficacy of novel and commercially available prevention strategies. One study, a randomized, blinded, placebo-controlled, multistate trial assessing the effectiveness of acaricide barrier sprays, involved ≈2,700 households in 3 states, with outcomes measures including tick density on acaricide-treated properties, the number of tick–human encounters, and the number of tickborne diseases in humans. (Study results are forthcoming.) A second study, begun in Connecticut during 2012, uses a similar design to evaluate the effectiveness of bait boxes that apply fipronil to rodents that are the reservoirs of *B. burgdorferi*. Used by veterinarians to prevent flea and tick infestations on dogs, fipronil kills ticks on the rodents for several weeks and may potentially interrupt the local transmission cycle of *B. burgdorferi*. This study of 625 enrolled households will be completed during 2016.

Recent experience indicates that additional tickborne pathogens are waiting to be discovered. In collaboration with the Tennessee and Minnesota health departments, the Mayo Clinic, and Vanderbilt University, TickNET has recently initiated a study to identify novel agents of tickborne disease. Over the next 3 years, >30,000 clinical specimens from US patients with suspected tickborne diseases will be screened by using high-throughput molecular methods designed to detect bacteria, followed by use of genomic sequencing to characterize detected pathogens. The ultimate goal is to better describe the epidemiologic and laboratory features associated with recognized and novel tickborne pathogens and to guide the development of new diagnostic methods.

Conclusions

Although sometimes overlooked, tickborne diseases pose an increasing threat to public health. Factors driving the emergence of tickborne diseases are poorly defined, but current prevention methods are clearly inadequate. Addressing this problem requires a multidisciplinary approach with input of entomologists, epidemiologists, educators, and infectious disease and communications specialists. Built on the pillars of the EIP and the ELC cooperative agreements, TickNET provides a collaborative network that brings together these resources at the federal and state levels to enhance surveillance, improve prevention, and identify new tickborne diseases.

Dr. Mead is a medical epidemiologist with CDC in Fort Collins, CO. His research interests include medical and public health aspects of Lyme disease, plague, tularemia, and other vectorborne diseases.

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Emerging Infections Program as Surveillance for Antimicrobial Drug Resistance

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Across the United States, antimicrobial drug–resistant infections affect a diverse population, and effective interventions require concerted efforts across various public health and clinical programs. Since its onset in 1994, the Centers for Disease Control and Prevention Emerging Infections Program has provided robust and timely data on antimicrobial drug–resistant infections that have been used to inform public health action across a spectrum of partners with regard to many highly visible antimicrobial drug–resistance threats. These data span several activities within the Program, including respiratory bacterial infections, health care–associated infections, and some aspects of foodborne diseases. These data have contributed to estimates of national burden, identified populations at risk, and determined microbiological causes of infection and their outcomes, all of which have been used to inform national policy and guidelines to prevent antimicrobial drug–resistant infections.

The 1992 Institute of Medicine report Emerging Infections: Microbial Threats to Health in the United States describes the ability of microbes to adapt, the development of antimicrobial drug resistance, and the importance of recognizing and monitoring emerging microbial threats to human health (*1*). In response, because of the recognized need for more accurate surveillance to detect and address emerging microbial health threats, in 1994 the Centers for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) was established as a collaboration of CDC and state health departments and academic partners. EIP works collaboratively across different programs and disease areas at CDC to deliver critical data that the program is well suited to obtain (*2*).

EIP as an Antimicrobial Drug Resistance Surveillance System

EIP is grounded in performing active population-based and laboratory-based surveillance. EIP staff regularly query laboratories serving the populations under surveillance (i.e., they perform active case finding) to ensure the reporting of all cases of the selected diseases occurring in the residents of the population under surveillance. EIP investigators then abstract clinical and demographic data from medical records of many patients. To minimize underreporting and ensure complete case ascertainment, they also audit laboratories. For many of the diseases, isolate characterization, including typing and antimicrobial drug susceptibility testing, is done at a central laboratory. Although it is resource intensive, EIP antimicrobial drug resistance surveillance has 4 key attributes: flexibility to adapt to new antimicrobial drug resistance threats, design that enables estimates of the burden of disease (representing large diverse metropolitan areas), collection and delineation of resistant strains, and the ability to follow trends over time. In addition, EIP provides a platform for studies to determine risk factors for antimicrobial drug–resistant disease or to evaluate the effectiveness of public health interventions aimed at preventing antimicrobial drug–resistant infections. Because these data from the EIP have greatly advanced the public health knowledge base of a wide spectrum of antimicrobial drug–resistant infections, the EIP is considered a key antimicrobial drug resistance surveillance platform. For example, EIP contributed data that allowed for national estimates of 10 of the 18 urgent, serious, and concerning pathogens highlighted in the CDC report Antibiotic Resistance Threats in the United States, 2013 (*3*).

Examples of Antimicrobial Drug Resistance Surveillance and Research in EIP

The Active Bacterial Core surveillance system (ABCs) was one of the initial core areas of the EIP. ABCs tracks invasive (defined as occurring in a sterile site) bacterial infections. During the 1990s in the United States, concern about *Streptococcus pneumoniae* resistance to penicillin increased. From the beginning of ABCs, *S. pneumoniae* isolates were tested by broth microdilution and serotyped at 1 of 3 reference laboratories (CDC, University of Texas Health Science Center, or Minnesota Department of Health). In 2000, nonsusceptibility of *S. pneumoniae* to penicillin peaked (http://www.cdc.gov/abcs/reports-findings/survreports/spneu00.html), coincident with the introduction of the

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7-valent pneumococcal conjugate vaccine (PCV7) for routine use in young children. Mathematical modeling with ABCs data predicted that, by 2004, in the absence of an intervention, 41% of invasive pneumococcal isolates would be dually nonsusceptible to penicillin and erythromycin (*4*). Notably, in 1998, of the penicillin-nonsusceptible isolates, 78% were serotypes included in PCV7, and because the vaccine eliminated nasopharyngeal colonization with vaccine serotypes, invasive disease caused by vaccine serotypes declined not only among vaccinated children but also among persons in other age groups (*5*,*6*). However, after widespread use of PCV7, serotype 19A (absent from PCV7 vaccine) became more prominent and more frequently resistant, resulting in increased resistant invasive disease; these results were shared in real time with the Advisory Council for Immunization Practices to help inform the vaccine industry about relevant changes in serotypes. In 2010, the 13-valent pneumococcal conjugate vaccine, which included this serotype, was licensed, and resistance once again declined, as measured by EIP (http://www.cdc.gov/abcs/reports-findings/survreports/spneu13.pdf).

Other community invasive bacterial infections evaluated by EIP include those caused by group A *Streptococcus*, group B *Streptococcus*, and *Neisseria meningitidis*. Program highlights have included demonstration of a plasmid carrying the *erm*T methylase gene that conferred macrolide and inducible clindamycin resistance in group A *Streptococcus* (*7*); demonstration of macrolide and inducible clindamycin resistance in group B *Streptococcus*, leading to changes in recommendations for intrapartum antimicrobial drug prophylaxis for penicillin-allergic women, by CDC and professional organizations (*8*); and the finding of ciprofloxacin-resistant *N. meningitidis* in Minnesota and North Dakota (*9*), prompting a local change in prophylaxis recommendations.

In a similar fashion, through routine collection and evaluation of isolates, the EIP Healthcare Associated Infections–Community Interface activity (*10*) has produced critical knowledge for informing approaches to clinical management of candidemia. Data collected from Georgia and Maryland EIP sites during 2008–2011 showed that, during a period of general adopton of fluconazole prophylaxis in infants of extremely low birthweight to prevent neonatal candidemia, rates of candidemia in infants markedly declined (*11*) and levels of fluconazole resistance among *Candida* spp. bloodstream isolates remained relatively stable (*12*). However, subsequent analyses identified increases in echinocandin-resistant and multidrug-resistant *Candida* infections during 2008–2012 (*13*); evaluation of the emergence of echinocandin resistance in *C. glabrata* and development of molecular testing to detect resistance could be accomplished because of the systematic collection of such isolates in EIP (*14*).

As carbapenem-resistant *Enterobacteriaceae* (CRE) emerged rapidly in the United States and elsewhere, there was no clear method or mechanism in place for hospitals or health departments to develop an accurate assessment of CRE in their area. Susceptibility definitions were evolving, laboratory methods differed, and different resistance mechanisms had been associated with carbapenem resistance. In 2010, as part of the Healthcare Associated Infections-Community Interface portfolio of EIP projects (*10*), the Georgia and Minnesota EIP sites piloted methods for CRE surveillance. A review of epidemiologically defined CRE-case isolates characterized at CDC for carbapenemase genes enabled analysis of different case definitions to maximize specificity or sensitivity to most likely predict the presence of a carbapenemase gene. This information is helping to inform a national case definition for CRE (*15*) to be used by state health departments and hospital infection control staff for reporting and responding to CRE infections.

Several attributes of EIP are clear in the success of the methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance activity. First, in the late 1990s, after the deaths of 4 children in Minnesota and North Dakota who did not have traditional health care–associated risk factors for MRSA were reported (*16*), EIP demonstrated flexibility by modifying operations to expand case ascertainment to include nonsterile sites (in addition to the more typical approach of sterile sites) and to characterize the epidemiology of community-associated MRSA through work at 4 EIP sites. In 2001, the Georgia, Maryland, and Minnesota EIP sites (*17*) reported that infections were more likely among young children and black persons and that only 6% of infections were invasive (compared with 77% reported as skin and soft tissue infections). Notably, almost three quarters of community-associated MRSA infections were treated with antimicrobial drugs to which the strains were resistant. Second, EIP contributed to a more standardized surveillance approach by providing definitions for case types: community-associated (no health care risk factors), health care–associated community-onset (within 3 days of hospital admission), and hospital-onset (*18*). Most (58%) invasive disease was health care–associated community-onset, 27% was hospital-onset, and only 14% was community-associated. Third, population-based surveillance enabled extrapolation to the US population. In 2005, invasive MRSA was estimated to have caused 94,000 infections and 18,600 deaths, a number that was >2-fold higher than cases and deaths caused by invasive pneumococcal disease. Fourth, EIP comprehensive case finding and ability to categorize characteristics of patients brought underappreciated populations at risk to attention; the largest burden of disease requiring the next wave of prevention activity is among patients recently discharged from the hospital (*19*).

In several ways, the EIP system provides a platform for work on antimicrobial drug resistance among infections transmitted commonly by food. CDC conducts the human side of the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) (*20*) in collaboration with the Food and Drug Administration and the US Department of Agriculture.

FoodNet sites also participate in NARMS surveillance for antimicrobial resistance in *Campylobacter* spp. and, along with health departments in all other states, in *Salmonella* spp., *Shigella* spp., and *Vibrio* spp. (*21*). The FoodNet sites also collaborate with the Food and Drug Administration retail meat sampling for NARMS. Its purpose is to monitor the prevalence of selected bacteria, including *Salmonella* and *Campylobacter* spp., in meat and poultry and to track resistance in these bacteria. FoodNet has also collaborated with NARMS on studies of human illnesses. FoodNet conducted studies of *Campylobacter* infections, which showed that eating poultry was a risk factor for quinolone-resistant infections and that diarrhea persisted longer in patients with these resistant infections; this finding contributed to the withdrawal of approval for use of fluoroquinolones in poultry (*22*,*23*). All of these data have helped inform ongoing approaches taken by the Department of Health and Human Services to eliminate the use of antimicrobial drugs for growth promotion in food animals and to bring all therapeutic uses under veterinary oversight (*24*).

Conclusions

As an antimicrobial drug resistance surveillance system, EIP is unique because it takes advantage of a design to enable much more useful analyses and public health assessments than simply defining the proportion of clinical isolates processed by a laboratory that are resistant to a specified antimicrobial drug. Data from EIP provide the clinical and epidemiologic context needed to quantify and compare clinically relevant infections and relative burden of disease with other public health priorities. Because EIP surveillance is population based, robust national estimates can be made, and these have been proven very useful for informing national policy. Also, the systematic collection and study of isolates have informed surveillance definitions and methods for routine public health activities, as well as direction for industry to develop pharmacologic and nonpharmacologic interventions. The infrastructure provides the flexibility needed to respond to new resistance problems by having a committed and experienced collaboration among federal, state, and local public health institutions with clinical laboratories and academic institutions.

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Effect of Culture-Independent Diagnostic Tests on Future Emerging Infections Program Surveillance

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The Centers for Disease Control and Prevention Emerging Infections Program (EIP) network conducts population-based surveillance for pathogens of public health importance. Central to obtaining estimates of disease burden and tracking microbiological characteristics of these infections is accurate laboratory detection of pathogens. The use of culture-independent diagnostic tests (CIDTs) in clinical settings presents both opportunities and challenges to EIP surveillance. Because CIDTs offer better sensitivity than culture and are relatively easy to perform, their use could potentially improve estimates of disease burden. However, changes in clinical testing practices, use of tests with different sensitivities and specificities, and changes to case definitions make it challenging to monitor trends. Isolates are still needed for performing strain typing, antimicrobial resistance testing, and identifying other molecular characteristics of organisms. In this article, we outline current and future EIP activities to address issues associated with adoption of CIDTs, which may apply to other public health surveillance.

The Centers for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) network conducts population- and laboratory-based surveillance for foodborne, health care–associated, respiratory, and invasive bacterial pathogens of public health importance. The main objectives of surveillance are to 1) measure disease burden and monitor disease trends over time, 2) evaluate the impact of public health interventions, 3) track microbiological and molecular characteristics of pathogens, and 4) detect emerging infectious disease threats. EIP data are used for national projections of disease incidence and formulation of national public health policy for prevention and control of disease. Central to accomplishing these objectives is accurate laboratory detection of the pathogens under surveillance.

In the field of microbiology, culture remains the standard for detection of most organisms, but in clinical settings, detection of pathogens is increasingly reliant on culture-independent diagnostic tests (CIDTs). CIDTs include antigen-based tests and molecular tests. The most commonly used molecular tests are the nucleic acid amplification tests, which include PCR. In clinical settings, most CIDTs have several advantages over culture. Foremost, CIDT results can be obtained more rapidly than culture, a feature that can be critical for clinical decision-making. Additionally, CIDTs may require less technical expertise to perform. Although initial adoption of these newer technologies can be expensive, costs generally decline over time, particularly those associated with labor.

CIDTs have the potential to improve estimates of disease burden because 1) they may be more sensitive than culture, 2) their relative ease of use may increase the number of patients tested, 3) they may enable detection of organisms for which there are currently no practical laboratory tests, and 4) they may increase the ability to detect polymicrobial infections. However, incorporating CIDTs into public health surveillance presents several challenges. Interpreting trends in disease incidence can be difficult because of changes to testing practices and surveillance case definitions. Although also true for culture, detection of molecular material may not reflect the presence of a living microbe and true disease, especially when detected from nonsterile body sites. At least for now, it is generally more difficult to assess microbiological and molecular characteristics, such as pathogen subtypes and antimicrobial drug resistance and genotypes, without bacterial isolates. Addressing these and other factors that affect estimates of disease burden and the characterization of infectious pathogens is critical for public health surveillance systems and clinical decision-making. EIP sites have a long history of close collaboration between CDC, state and local public health departments, academia, and clinical laboratories, making them uniquely positioned to help chart the course in addressing these concerns. Because many infections are already being

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diagnosed by use of CIDTs and more CIDTs will probably be developed and used in the near future, a path for addressing these issues is urgently needed. This article provides an overview of current testing practices for pathogens under EIP surveillance and addresses how EIPs plan to advance their core objectives in the face of this dynamic diagnostic environment.

Current Status of CIDTs in the EIP Network

CIDTs are either singleplex (i.e., they test for a single organism) or multiplex (i.e., they simultaneously test for multiple organisms). There has been rapid development of multiplex molecular tests that detect pathogens commonly associated with particular syndromes (e.g., respiratory, enteric, and bloodstream infections). CIDTs can be classified into commercial test kits that receive Food and Drug Administration (FDA) clearance or laboratory-developed tests (LDTs). FDA-cleared CIDTs undergo various levels of validation before they are made available for purchase in the United States, but postmarketing evaluations are generally not required (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm). FDA defines LDTs as "in vitro diagnostic tests that are designed, manufactured, and used within a single laboratory." Laboratories are required to establish test characteristics for LDTs, including accuracy and precision. Historically, FDA has not generally enforced premarket review and other applicable requirements because LDTs were relatively simple and available on a limited basis. Many LDTs are now more complex and are used nationwide. FDA guidance on additional oversight of LDTs is pending. (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm).

Many EIPs regularly conduct systematic surveys of clinical, commercial, and public health laboratories to monitor the use of CIDTs in laboratories that provide services to the population under surveillance. These surveys show that the availability and type of CIDTs used varies by pathogen (Table 1, http://wwwnc.cdc.gov/EID/article/21/9/15-0570-T1.htm). All or nearly all cases of influenza, *Clostridium difficile, Legionella* spp., and *Bordetella pertussis* infection reported through EIP are diagnosed by CIDTs. The percentage diagnosed by a particular type of CIDT has varied over the years. For instance, rapid antigen tests for influenza have been increasingly replaced by FDA-cleared molecular assays (*1*), including multiplex assays to detect viruses and bacteria from respiratory specimens (*2*). Molecular tests are increasingly being used to detect *C. difficile* infection. During 2011, ≈50% of *C. difficile* infections were diagnosed by molecular assays performed at laboratories that serve the EIP population (*3*). Also in 2011, for surveillance of *Legionella* infections, 95% of cases were diagnosed by detection of urine antigen for *L. pneumophila* serogroup 1 (http://www.cdc.gov/abcs/reports-findings/survreports/leg12.pdf). During the early 1990s, culture and direct fluorescent antibody testing were the primary diagnostic methods used to identify *B. pertussis* cases reported through the National Notifiable Disease Surveillance System (*4*). PCR, either alone or in combination with other diagnostic tests, diagnosed 89% of laboratory-confirmed pertussis cases reported through the EIP Enhanced Pertussis Surveillance system during 2011–2014 (CDC, unpub. data).

Culture remains the mainstay for diagnosis of invasive bacterial and fungal infections that cause predominantly bloodstream infections and meningitis, which are covered under EIP Active Bacterial Core surveillance (ABCs) and Healthcare-Associated Infections Community Interface programs (Table 1). For these pathogens, fulfillment of the surveillance case definition still requires their isolation from a sterile site. Some FDA-cleared multiplex molecular tests for bacterial and fungal bloodstream pathogens are not truly culture independent because they require a positive blood culture from which an organism is identified by PCR (*5*,*6*). In 2014, ≈10% of laboratories that participate in ABCs used one of these platforms to identify species from positive blood cultures (CDC, unpub. data). There are no FDA-cleared molecular tests for directly detecting bacteria from sterile site specimens (e.g., whole blood, cerebrospinal fluid [CSF]), but there are molecular LDTs that are used to directly detect bacterial pathogens from sterile sites. Less than 1% of ABCs laboratories offer these tests for at least 1 of the ABCs pathogens (CDC, unpub. data). There is an FDA-cleared molecular test to detect *Candida* spp. directly from whole blood (*7*), but this test does not seem to be widely used by clinical laboratories (CDC Mycotic Diseases Laboratory, pers. comm.). Nonetheless, multiplex PCR-based tests that detect organisms directly from blood and CSF are under development and may soon become more widely available in clinical settings (*8*,*9*).

For most pathogens covered under the surveillance system for foodborne pathogens (FoodNet, http://www.cdc.gov/foodnet/index.html), culture remains the primary means of diagnosis, but this predominance is changing (*10*,*11*). Antigen-based tests and molecular tests for *Campylobacter* and Shiga toxin–producing *Escherichia coli* have been increasingly adopted by EIP laboratories. Adding positive reports from CIDTs for *Campylobacter* and Shiga-producing *E. coli* results that are not culture confirmed could add an additional ≈13% and ≈8% cases to FoodNet surveillance, respectively (Table 1). FDA recently cleared several molecular enteric syndrome panels (*12*), which are being rapidly adopted (*13*).

Measuring Disease Burden Trends and Evaluating Public Health Interventions

To assess trends and the effect of population-based interventions over time, methods for measuring disease burden should remain relatively stable or adjustments should be made to account for changes in the use of diagnostic tests. The stability of disease burden estimates will be affected by differences in the performance characteristics of tests used, changes in clinical testing practices, and changes to case definitions.

Performance Characteristics and Use of Diagnostic Tests

Accurate tests give positive results when infection is present (i.e., the tests are sensitive) and negative results when infection is absent (i.e., the tests are specific). The predictive value of tests depends, in part, on the prevalence of infection in the population and on whether the organism may be present in the absence of disease (i.e., colonizing body sites). Molecular tests for influenza viruses, *C. difficile*, and *B. pertussis* have been found to be highly sensitive in clinical settings (*14*–*16*). The sensitivity of molecular tests for bacteria may be better than that for culture, particularly when antimicrobial drugs have been administered before specimen collection (*17*–*19*). Highly sensitive molecular tests may produce false-positive results, however, as has been shown in pseudo outbreaks of *B. pertussis* (*20*). Molecular mutations in the organism may result in decreased sensitivity for antigen-based tests (*21*) and molecular tests (*22*). The specificity of CIDTs may be lower than that of culture because molecular targets may be nonspecific for the species of interest (*23*). The influenza and *C. difficile* infection surveillance systems collect data on test method used and adjust national disease estimates on the basis of the sensitivity of the different test types (*3*,*24*).

The availability of tests; their speed, cost, and ease of use; and other factors (e.g., changes in testing guidelines) may result in changes to clinical testing practices, which may affect disease burden trends. These changes may especially be true for pathogens detected by multiplex panels for which clinical suspicion for an organism does not have to be as high as that for a specific organism. If more persons are tested for multiple organisms, more pathogens might be detected. To account for these potential changes, EIP influenza surveillance periodically collects data on the proportion of patients who are tested for influenza if they have an influenza-like illness and adjusts disease burden estimates on the basis of this information (*25*).

Case Definitions

The case definitions for EIP pathogens include specific requirements for the laboratory methods used and, for some pathogens, the site from which specimens were obtained (Table 1). One consideration is whether clinical symptoms should be included in case definitions because detection of an organism may indicate asymptomatic carriage and not true disease (*26*). This consideration may especially be relevant for organisms that are detected after sample collection from nonsterile sites and that are known to colonize body sites. In EIP, the only activity that includes clinical symptoms as part of the surveillance case definition is Enhanced Pertussis Surveillance. Another consideration may be collection of specimens from negative controls to determine the likelihood of true infection.

In general, EIP case definitions have been characterized by high specificity and high positive clinical predictive value because most rely on culture from a normally sterile body site. Culturing of samples collected from nonsterile sites (e.g., stool samples) may also be more specific than testing for molecular material. EIP decisions about when and how to change case definitions will probably be specific for each pathogen. Advances in the quality of PCR diagnostics led the Council of State and Territorial Epidemiologists to include validated PCR results obtained from sterile site specimens in the Nationally Notifiable Disease Surveillance System for *Haemophilus influenzae* (http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/2014PS/14_ID_05.pdf) and *Neisseria meningitidis* starting in 2015 (http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/2014PS/14_ID_06.pdf). Similarly, campylobacteriosis became nationally notifiable in 2015, and detection of *Campylobacter* spp. by use of any CIDT would be classified as a "probable" case (http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/2014PS/14_ID_09upd.pdf). Like the Council of State and Territorial Epidemiologists, EIP will need to consider what constitutes a valid test. FDA clearance may be a consideration, but FDA-cleared tests may not perform well in real-world clinical settings. LDTs may undergo rigorous validation that may justify including results from those tests. Presenting incidence data stratified by laboratory method (culture-confirmed and positive CIDT reports), as has been done for FoodNet, may be one way to highlight changes to case definitions (*13*).

Detecting Other Emerging Pathogens

Increased availability and use of CIDTs may increase detection of certain pathogens that were previously hard to identify by culture (particularly those that are part of multiplex panels) or of bacterial pathogens that would otherwise be suppressed by antimicrobial drugs. This increased use may provide the opportunity to conduct surveillance for organisms for which the burden of disease may not have been measured or recognized as emerging infections (e.g.,

Mycoplasma pneumoniae, respiratory syncytial virus, human metapneumovirus, enteroviruses, enterotoxigenic *E. coli*). Additionally, the detection of multiple infectious organisms by multiplex panels could provide insight into polymicrobial interactions and their effect on disease manifestations and severity.

Analyzing Microbiological and Molecular Characteristics

One of the characteristics that has made EIP surveillance so useful for public health action has been the systematic collection of isolates that enable microbiological and molecular characterization. Serotyping and serogrouping data have been used for developing and evaluating vaccines and for measuring the effectiveness of prevention programs (*27–31*). Isolates collected through EIP have been used to identify outbreaks (*32*), monitor and raise awareness of the problem of antimicrobial drug resistance (*33–35*), identify mechanisms of resistance (*36*), detect the emergence of new strains (*34*) or mutations that may reduce vaccine effectiveness (*37*), and identify virulence factors (*38*). These isolates have been deposited in national repositories, and streptococcal isolates are widely available to the research communities (http://www.cdc.gov/abcs/pathogens/isolatebank/index.html).

Collection of isolates has been critical for strain characterization by serologic techniques and for in vitro determination of antimicrobial drug susceptibility in EIP reference laboratories. Over time, there has been a shift toward using molecular techniques for strain typing, but both typing and susceptibility testing still rely heavily on the availability of isolates. Although molecular techniques can identify genetic mutations that correlate with phenotypic antimicrobial drug resistance, new mutations may convey the emergence of phenotypes that are not apparent today. Through the CDC Advanced Molecular Detection initiative, EIPs have recently started whole-genome sequencing of EIP isolates (http://www.cdc.gov/amd/project-summaries/emerging-infections.html). Whole-genome sequencing will be used for pathogen characterization for general surveillance and outbreak detection and for exploring genetic determinants of antimicrobial drug resistance, disease severity, and vaccine failure. Some molecular characterization has been performed directly for *N. meningitis* in blood and CSF specimens and for *B. pertussis* in respiratory tract specimens. For better characterization of strains without the use of culture, clinical specimens are now collected thorough EIP Enhanced Pertussis Surveillance, as will probably be done for other EIP pathogens in the future. However, much additional research is needed to determine whether and which molecular characteristics can be identified directly from clinical specimens. In the interim, collection of isolates remains essential, as demonstrated by the experience with the *C. difficile* epidemic in the early 2000s, when CIDT use was widespread for this infection and the emergence of the NAP1 strain was not detected until 5 years after steady increases in *C. difficile* incidence and severity (*39*).

Future Considerations and Directions

To continue to impact public health programs and policies, EIPs will have to be forward-thinking in how disease burden trends are measured in light of the continued development and uptake of CIDTs (Table 2). First, EIPs need to continue to systematically monitor the availability and use of these tests through periodic laboratory surveys, either within the EIP network or through coordination with outside organizations and to measure their use in clinical settings. Understanding the use of tests outside of EIP laboratories may also be relevant because some EIPs project estimates of national disease burden. EIPs will also need to develop and regularly evaluate criteria for incorporating CIDTs into case definitions, which will probably vary by pathogen. EIPs can and should contribute to the national discussion about changing case definitions for reportable diseases. Confirmatory testing at public health laboratories

Table 2. Plans for measuring disease burden and analyzing microbiological and molecular characteristics in the era of culture independent diagnostics, Emerging Infections Program*

Plan steps
• Conduct periodic laboratory surveys to monitor uptake of tests both within and outside Emerging Infections Program
• Develop and continuously evaluate criteria for accepting CIDTs into surveillance case definitions
• Consider whether results should be confirmed on all or a subset of detections
• Advocate for post-marketing evaluations of CIDTs
• Collect individual test types to account for the sensitivity and specificity of CIDTs
• Adopt methods to account for changes in testing practices that result from use of CIDTs
• Develop an interim strategy for collecting isolates until techniques for serotyping and antimicrobial drug testing on direct patient specimens are available
• Assist in the development and provide specimens to collaborators for the development of microbiological and molecular characterization directly from patient specimens
• Prepare for use of more advanced techniques, like whole-genome sequencing and metagenomics
• Consider performing surveillance for other organisms of public health importance contained in multiplex panels
• Contribute to the understanding of when detection equates with true infection

*CIDT, culture-independent diagnostic test.

may also be necessary for pathogens detected by CIDTs that have questionable performance in real-world settings; however, doing so would require additional public health resources. Performance characteristics need to be determined on an ongoing basis because new variants of organisms that are not detected by the tests may arise. As is already being done for some EIP pathogens, data collection at EIP sites would need to expand to capture information on specific test types and to allow for the reporting of multiple test results. In the era of electronic laboratory reporting, the use of standard test codes that can be transmitted electronically will be essential, and data systems must be able to accommodate more complex data. It will also be critical to perform system checks to avoid counting cases multiple times because >1 testing method may be used for 1 patient. The type of test and the sensitivity and specificity of individual tests and adjustments for changes in testing practices could potentially be incorporated into incidence calculations. After CIDTs have been incorporated into case definitions, EIPs will need to highlight these changes and may consider reporting disease burden by testing method (e.g., cases by culture and molecular testing).

Because CIDTs may obviate the need for culture for making a clinical diagnosis, EIPs must consider short- and long-term strategies for assuring the continued availability of isolates. Isolates remain critical for molecular characterization and antimicrobial drug resistance testing. Resources or legal/regulatory approaches may be needed to give clinical or public health laboratories incentives to continue culturing specimens. It is unlikely that clinical laboratories will be paid by insurers for culture in addition to CIDTs. If providing resources to all laboratories is not possible, the EIP network may have a role in providing sentinel sites for collection of isolates. EIP may also have a role in the development and validation of culture-independent methods for serotyping, subtyping, virulence profiling, and antimicrobial drug resistance testing. EIPs have started using banked isolates for developing whole-genome sequence libraries, which will better characterize pathogens at the molecular level and may make characterization from patient specimens (e.g., whole blood, CSF) easier. In the clinical diagnostic setting, metagenomics (the study of genomes from mixed communities of organisms) may eventually replace organism identification, virulence profiling, and some resistance testing, and it may be possible to use this data stream for a variety of public health purposes, including surveillance. Although whole-genome sequencing and metagenomics hold great promise for characterizing pathogens for surveillance, outbreak detection, and detection of emergence of new pathogens, they also pose challenges for processing, analyzing, and interpreting large amounts of data. Resources are needed to develop and sustain the bioinformatics infrastructure and to make sequences available to genomics reference banks so that EIPs can play a broader role in advancing public health practice.

Perhaps the most challenges and opportunities for surveillance systems are presented by use of multiplex tests. They may enable better tracking organisms that are currently underrecognized because culturing is difficult or because they would not otherwise be considered in the differential diagnosis. It may also enable better tracking of polymicrobial infections. However, understanding when detection equates with true infection is a challenge. The EIP may play a unique role in helping to decipher true infections from mere detection of organisms and in describing true polymicrobial infections because laboratory results can be matched with epidemiologic and clinical data.

Conclusions

The availability and use of CIDTs in clinical medicine present opportunities to rapidly characterize diseases currently covered under the EIP surveillance umbrella and to detect and monitor other emerging infectious diseases. Their use also presents challenges for maintaining the EIP ability to accurately describe disease burdens, the effect of interventions, and microbiological and molecular characteristics of pathogens over time. Because of the long-standing collaboration between the EIP, laboratories, and disease reporters and resources devoted to collecting highly detailed and comprehensive surveillance data, the EIP infrastructure lends itself to close examination of the effect of CIDTs. EIP hopes to work with other domestic and international public health entities, regulatory bodies, diagnostic manufacturers, and academic and clinical groups to chart an evidence-based course for continuing to incorporate CIDTs into public health surveillance.

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Emerging Infections Program Efforts to Address Health Equity

James L. Hadler, Duc J. Vugia, Nancy M. Bennett, Matthew R. Moore

The Emerging Infections Program (EIP), a collaboration between (currently) 10 state health departments, their academic center partners, and the Centers for Disease Control and Prevention, was established in 1995. The EIP performs active, population-based surveillance for important infectious diseases, addresses new problems as they arise, emphasizes projects that lead to prevention, and develops and evaluates public health practices. The EIP has increasingly addressed the health equity challenges posed by Healthy People 2020. These challenges include objectives to increase the proportion of Healthy People–specified conditions for which national data are available by race/ethnicity and socioeconomic status as a step toward first recognizing and subsequently eliminating health inequities. EIP has made substantial progress in moving from an initial focus on monitoring social determinants exclusively through collecting and analyzing data by race/ethnicity to identifying and piloting ways to conduct population-based surveillance by using area-based socioeconomic status measures.

Describing health disparities and achieving health equity have been priorities of the national public health agenda for the past 20 years. One of the 2 goals of Healthy People (HP) 2010, the public health agenda for 2000–2010, was to "eliminate health disparities among different segments of the population, including differences that occur by gender, race or ethnicity, education or income, disability, geographic location, or sexual orientation" (*1*). In addition, HP 2010 included a related public health infrastructure objective (23.4), to track HP 2010 objectives by each population group. HP 2020, the agenda for 2010–2020, specifically added mention of social determinants of health. It reframed the goal and the related infrastructure objective, the former as "Achieve health equity, eliminate disparities, and improve the health of all groups," and the latter, now Public Health Infrastructure Objective (7.1), as "Increase the proportion of population-based Healthy People 2020 objectives for which national data are available for all population groups" with a specific subobjective (7.3) "by socioeconomic status" (*2*).The World Health Organization, in a similar vein, recently recognized that addressing the social determinants of health was a key priority to eventually achieving health equity (*3*).

The Emerging Infections Program (EIP), established by the Centers for Disease Control and Prevention (CDC) in 1995, is a network that now includes 10 state health departments and their collaborators in local health departments, academic institutions, other federal agencies, and public health and clinical laboratories, with a catchment area of ≈44 million persons (*4*–*7*). In addition to performing active, population-based surveillance for important infectious diseases, EIP activities are intended to be flexible and address new problems as they arise, answer critical public health questions, emphasize projects that lead to prevention, and develop and evaluate public health practices. In this context, the EIP has increasingly taken on the challenges posed by HP 2010 and HP 2020, moving from a focus on monitoring social determinants exclusively through collecting and analyzing data by race/ethnicity to identifying and piloting ways to conduct population-based surveillance by using socioeconomic status (SES) measures with an ultimate focus on working toward health equity.

Most data collected by EIP sites comes from laboratory-based surveillance for bacterial, parasitic, and viral diseases, which does not include individual-level SES information. Missing data, especially ethnicity, is a consistent challenge. However, because residency in an EIP catchment area is a requirement for inclusion in surveillance, and to enable deduplication of multiple reports, addresses of residence for individual case-patients are collected at the time of diagnosis, making it possible to link cases to specific census tracts. With linkage to census tract, a wealth of data on census tract–level SES status indicators (e.g., poverty, education level, crowding) becomes available. Seminal work done by Nancy Krieger and colleagues in the Public Health Disparities Geocoding Project found that these census tract–level SES measures, especially low SES status (usually the lowest quartile or quintile of each measure), often predict disease incidence and mortality rates (*8*,*9*) and do so within and across groups defined by race/ethnicity. These authors recommended routine use of area-based SES

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measures in disease surveillance to describe and monitor, over time, disparities by SES, particularly poverty as measured by the percentage of persons in a census tract who lived below the federal poverty level.

In this article, we describe the evolution of EIP involvement in monitoring health disparities and in working toward health equity. These efforts began with a focus on race/ethnicity and, more recently, have included the piloting use of area-based SES measures under the guidance of a Health Equity Working Group.

EIP and Health Disparities

To date, EIP population-based surveillance data (from single or multiple sites) have been used to describe racial and socioeconomic disparities for invasive pneumococcal disease (IPD), invasive group B *Streptococcus* (GBS) disease, invasive group A *Streptococcus* (GAS) disease, influenza-associated hospitalizations, and several other diseases (*10*–*32*).

IPD (*Streptococcus pneumoniae*)

Racial disparities in the incidence of IPD have long been described (*10*). Before the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States in 2000, IPD rates among blacks had been documented by the EIP to be approximately twice that of whites, and this disparity was seen in all age groups (*11*). After PCV7 was introduced, the racial disparity in IPD, caused by bacterial serotypes included in PCV7, was eliminated for children <5 years of age, and rates among white children decreased below the HP 2010 target of 46 cases per 100,000 population by 2001 (*12*–*14*). Rates for black children met this goal a year later. However, incidence rates for those ≥5 years of age remained higher among blacks.

The most recent analysis of national EIP IPD data tracked the effects of trends in PCV7-type and non–PCV7-type IPD rates on racial disparities (*15*). Although incidence of IPD caused by PCV7-types was nearly eliminated in blacks and whites after PCV7 was introduced, rates of non–PCV7-type IPD increased in both races so that, by 2009, non–PCV7-type IPD incidence among blacks was still much higher than that among whites, in all age groups (*15*). Research has suggested that these findings may be due to a higher prevalence of underlying conditions among blacks (e.g., asthma, diabetes, HIV/AIDS) and lower SES (*16*–*18*).

The first analysis of IPD data that controlled for SES by using census tract measures was a study of 1994–1997 rates in San Francisco County, published by the California EIP (*19*). In a Poisson model, black race and living in census tracts with low median household income were both highly significantly associated with higher IPD rates. In an analysis of 2003–2004 bacteremic pneumonia (caused by *S. pneumoniae*, *Haemophilus influenzae*, GAS, and GBS), data from 9 EIP sites showed that the rates were highest among US adults living in the poorest census tracts (with ≥20% of persons living below federal poverty level) and among blacks (*20*). In models that controlled for age, census tract poverty level, and EIP site, "racial disparities in incidence were reduced but remained significant." This article was notable for using geocoded EIP surveillance data and linking such data to the 2000 US census tract data for the analyses, following the method of the Public Health Disparities Geocoding Project (*8*).

The Connecticut EIP also used this method to analyze and describe the changing disparities in IPD incidence rates in Connecticut during 1998–2008 by SES and by race/ethnicity (*21*). The authors found that before the introduction of PCV7, persons living in high-poverty census tracts had a much higher incidence of IPD than their counterparts in low-poverty census tracts. After PCV7 was introduced, these differences nearly disappeared for those infected with PCV7 serotypes but increased for those infected with non-PCV7 serotypes.

Invasive GBS Disease

Racial disparities have also been described for invasive GBS disease. In the late 1980s, black infants in metropolitan Atlanta were found to have a higher risk for early- and late-onset GBS disease than white infants (*22*), and black adults had higher rates of invasive GBS infections than white adults (*23*).

Coincident with active efforts in the mid-1990s to provide antimicrobial prophylaxis to pregnant women at risk of transmitting GBS to their newborns, EIP data documented that early-onset invasive GBS disease had decreased substantially by 1998 for both white and black neonates, but the incidence in black neonates remained higher than that in whites (*24*). The 2010 national health objective of 0.5 cases per 1,000 live births has been reached among white neonates since 1998; although the incidence for black neonates has been approaching this goal, it had not been achieved by 2003 (*25*). Indeed, through 2006, EIP surveillance data showed that the rate of early-onset invasive GBS disease had increased for black infants, particularly preterm black infants, widening the gap between black and white infants (*26*,*27*). During 1990–2005, the incidence of late-onset neonatal GBS disease, which intrapartum antibiotic prophylaxis does not prevent, was also higher among black infants than among white infants (*28*).

In addition to disparities for GBS disease, disparities are found for other causes of neonatal sepsis. During 2005–2008, EIP surveillance documented that rates of early-onset neonatal sepsis (caused by GBS, *Escherichia coli*, viridans streptococci, and other bacteria) among black preterm infants were >10 times those of nonblack term infants

(5.14 vs. 0.4 cases/1,000 live births) (*29*). The authors of this study commented that race is likely a surrogate for social determinants of health that contribute more broadly to disease disparities.

Invasive GAS Disease

The epidemiology of invasive GAS disease in the United States was described by using 1995–1999 population-based surveillance data from several EIP sites (*30*). The incidence of invasive GAS disease among blacks was 1.6 times higher than incidence among other racial groups. The higher incidence of invasive GAS disease among blacks was confirmed in another analysis of 1989–1999 surveillance data from the California EIP (*31*). The authors suggested that race may be a surrogate marker for other, unmeasured, factors such as access to health care.

Influenza

The Connecticut EIP analyzed influenza-associated hospitalizations and census tract SES following the process used by the Public Health Disparities Geocoding Project (*8*). In one analysis, 2003–2010 influenza-associated hospitalization cases among children <18 years of age were geocoded and linked to 2000 census tract SES data (*32*). The mean annual incidence of influenza–associated hospitalizations for children in high-poverty and high-crowding census tracts was at least 3 times greater than that in low-poverty and low-crowding tracts. This disparity could not be fully explained by prevalence of underlying conditions or receipt of influenza vaccination. Incidences of influenza-associated hospitalization among black and Latino children were 3.4 and 3.0 times higher, respectively, than among white children.

In another analysis, 2007–2011 influenza-related hospitalization cases of adults ≥18 years old were geocoded and linked to 2006–2010 American Community Survey data for census tract SES measures (*33*). Again, a statistically significant trend was found: the incidence of influenza-related hospitalizations increased as SES decreased (or poverty increased), for each influenza season and within each racial/ethnic group. Black and Latino adults had higher influenza hospitalization rates than white adults within each SES group, and rates for women were higher than those for men for each age group. The study authors noted that systematic efforts are needed to achieve higher influenza vaccination rates in low SES neighborhoods and among women.

Campylobacteriosis

The Connecticut EIP geocoded 1999–2009 cases of campylobacteriosis and linked them to 2000 census tract data to analyze for case-patient SES (*34*). For children <10 years of age, campylobacteriosis rates increased as census tract poverty level increased, but for children ≥10 years of age and for adults, rates decreased as census tract poverty level increased. The authors stated that children living in poorer census tracts could conceivably have a higher rate of exposure to *Campylobacter* spp. in the home, although this possibility needed to be verified.

Cervical Cancer Precursors

Again using methods of the Public Health Disparities Geocoding Project, the Connecticut EIP linked 2008–2009 Connecticut cases of cervical intraepithelial neoplasia grade 2 or higher and adenocarcinoma in situ (CIN2+/AIS), cervical cancer precursors, with poverty level as determined from 2000 census tract data (*35*). The authors found that, overall, higher rates of CIN2+/AIS were associated with higher levels of poverty and that the association of higher proportions of African American residents with poverty was the strongest and most consistently associated measure. Among women 20–24 years of age, however, CIN2+/AIS rates were inversely associated with poverty, a finding suggesting that screening rates are higher among those living in SES census tracts where income level is higher.

EIP population-based surveillance data analyses have contributed to identification or confirmation of race- and SES-based health disparities for several diseases under EIP surveillance. Linking geocoded surveillance data to census tract SES measures has shed further light on the influence of neighborhood poverty on some of these diseases. Notably, when interventions have decreased infection rates of IPD and invasive GBS significantly, some racial disparities remained. Although the underlying reasons for racial disparities associated with these diseases await further investigation, identifying such disparities on the basis of SES provides opportunities for focusing prevention efforts to populations defined by SES rather than solely by race/ethnicity.

EIP Health Equity Working Group

In 2012, the EIP commissioned an external review to seek advice about future directions and strategies. Among other issues, the external review panel was asked specifically to identify areas for increased emphasis considering the extant portfolio of work, the strengths and composition of the network, and key public health issues involving infectious diseases. The panel responded: "EIP should develop and implement a plan for studying the role and [causal] pathways of underlying determinants of health in creating infectious disease disparities, and the extent to which these pathways are similar or different across diseases" (EIP External Review Report, 2012). This recommendation was discussed extensively at the 2013 meeting of the EIP Steering Committee and, as a result, the EIP Health Equity Working Group was formed. Members of the Working Group include interested collaborators from the EIP sites

as well as CDC staff. The goals of the working group are to describe disparities and the contributions of various social determinants of health, to target and evaluate the effects of interventions aimed at reducing disparities, and, to the extent possible, to develop and test hypotheses regarding the causal pathways that lead to disparities in conditions studied by the EIP.

To focus on the social determinants of health, the working group determined that it was critical to move beyond an analysis exclusively based on race/ethnicity and to take advantage of having the residence address of case-patients. The addresses can be geocoded routinely and linked to census tract-level socioeconomic data as described (*8*). An approach using area-based SES data to describe health disparities provides certain advantages over EIP's previous approach based on race/ethnicity (*12*). Although race/ethnicity and SES are associated in the United States, use of race/ethnicity as a proxy for SES has distinct limitations. Race and especially ethnicity are often missing from inpatient medical records, requiring the use of complex methods to impute unknown values (*8*). In addition, unlike income or educational level, race/ethnicity is not modifiable, and it has been biologically causally linked to disparities only for certain conditions (e.g., sickle cell disease) (*36*). Further, SES is a determinant of health within groups defined by race/ethnicity, something not measured when race/ethnic group is the variable of analysis (*8*). Finally, using race/ethnicity as a proxy for SES in the absence of other measures fails to capture the full spectrum of social determinants of disease and makes it difficult to accurately target interventions.

One of the strengths of the EIP is that methods are standardized among the 10 geographically distributed sites. The first order of business for the Health Equity Working Group was to develop a standardized protocol for geocoding cases to the census tract level. Case-patients that are college students or residents of long-term care facilities, for example, often have at least 2 addresses to which they could be geocoded, and this protocol ensures they are geocoded in the same way by all EIP sites. A variety of geocoding software is now available, and it varies in its ability to geocode cases to the rooftop level, a method which is necessary to accurately assign addresses to census tracts (*37*). Although individual EIP sites are not required to use the same software, the protocol does require the use of software capable of geocoding to the rooftop level. Privacy concerns have been addressed by limiting retention of address information to the local EIP sites. For activities that might involve small numbers of potentially identifiable case-patients, additional methods are available to protect confidentiality (*38*). In addition, the EIP affords investigators an opportunity to use the best possible analytic approaches to better define the influence of a variety of social determinants.

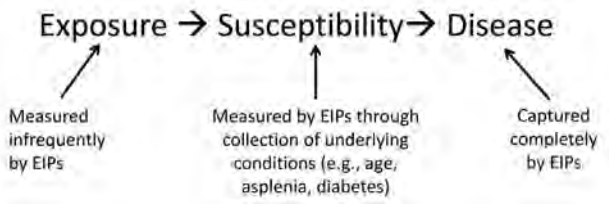

Figure 1. Simplified causal pathway previously accessible by using Emerging Infections Program (EIP) data.

Future Directions

Although the EIP has substantial experience in evaluating the effects of public health interventions, including some that have reduced racial disparities, the EIP has less

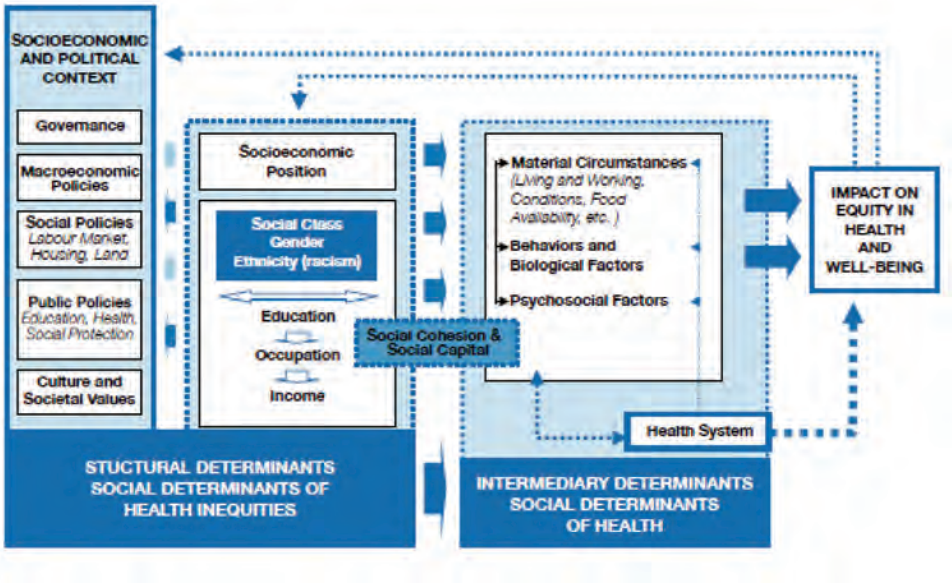

Figure 2. Framework for considering social disparities of health determined by the Commission on Social Determinants of Health, World Health Organization (*3*).

experience developing and testing hypotheses regarding the causal pathways that lead to health disparities in the first place. Instead, the EIP has historically collected basic demographic data (age, sex, race/ethnicity) and clinical data available from the inpatient medical record (date of hospitalization and presence of underlying conditions such as diabetes and heart disease). These limited data lend themselves to only a simple causal pathway (Figure 1). The causal pathway to direct exposure to infections monitored by the EIPs, such as exposure to respiratory pathogens, is extremely difficult to determine in nonoutbreak settings. On the other hand, assessing individual-level susceptibility, such as that conferred by certain underlying conditions, is relatively straightforward to measure through review of medical records. But this simplistic model misses separate but important dimensions of risk of disease.

In contrast, the World Health Organization's Commission on Social Determinants of Health has adopted a more complex framework for considering the nature of health disparities (Figure 2) (*3*). Under this framework, interventions are aimed at the circumstances of daily life and the structural drivers of disparities. The former includes differential exposure to disease, such as those that occur early in life, those that affect social and physical environments, and work, all of which are associated with differences in social strata. The structural drivers of disparities include the nature and degree of social stratification; biases, norms, and values within societies; global and national economic and social policy; and processes of governance at global, national, and local levels.

The commission also made several recommendations, including one to "measure the problem, evaluate action, expand the knowledge base, develop a workforce that is trained in the social determinants of health, and raise public awareness about the social determinants of health." To respond to that recommendation, the EIP will need to broaden its scope of expertise and collaborate with new partners. These partners could include, for example, academic investigators who are advancing our understanding of the biologic basis for the effects of social position on risk of disease (*39*) and professional organizations that support new ways of thinking about health disparities (*40*). Such collaborations could shed light on ways in which the EIP could design new studies aimed at understanding the causal pathways leading to health disparities, and they could assist the EIP in becoming a vocal advocate for health equity.

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Improving Accuracy of Influenza-Associated Hospitalization Rate Estimates

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Diagnostic test sensitivity affects rate estimates for laboratory-confirmed influenza–associated hospitalizations. We used data from FluSurv-NET, a national population-based surveillance system for laboratory-confirmed influenza hospitalizations, to capture diagnostic test type by patient age and influenza season. We calculated observed rates by age group and adjusted rates by test sensitivity. Test sensitivity was lowest in adults ≥65 years of age. For all ages, reverse transcription PCR was the most sensitive test, and use increased from <10% during 2003–2008 to ≈70% during 2009–2013. Observed hospitalization rates per 100,000 persons varied by season: 7.3–50.5 for children <18 years of age, 3.0–30.3 for adults 18–64 years, and 13.6–181.8 for adults ≥65 years. After 2009, hospitalization rates adjusted by test sensitivity were ≈15% higher for children <18 years, ≈20% higher for adults 18–64 years, and ≈55% for adults ≥65 years of age. Test sensitivity adjustments improve the accuracy of hospitalization rate estimates.

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In the United States, surveillance for influenza-associated hospitalizations relies on laboratory-confirmed diagnostic testing (*1*–*3*). Influenza testing modalities have expanded from traditional viral culture to include rapid influenza diagnostic tests (RIDTs) and molecular assays, such as reverse transcription PCR (RT-PCR) (*4*,*5*). RIDTs are point-of-care tests that provide results within 30 minutes; however, with reported sensitivities of 10%–80%, negative test results can be unreliable (*6*–*9*). RT-PCR exceeds viral culture in sensitivity for detecting influenza, but its widespread use is limited by cost and complexity of the assay (*10*,*11*).

Researchers have examined rates of influenza-associated hospitalization during different influenza seasons (*1*,*2*,*12*,*13*). However, comparing rates between seasons can be inaccurate without accounting for changes in the sensitivity of diagnostic testing used. In particular, after the 2009 influenza A(H1N1) pandemic, hospitals and state public health laboratories expanded diagnostic capabilities with high-sensitivity molecular assays to better detect influenza viruses and other respiratory pathogens (*5*). Particularly for nationally based surveillance, the use of different testing platforms by health care facilities and the variability in sensitivity of these diagnostic tests could lead to underestimation of rates of influenza-associated hospitalization and limit comparisons of severity across influenza seasons (*3*,*4*,*6*,*7*).

Methods

Study Setting

We used data from the Centers for Disease Control and Prevention (CDC) Influenza Hospital Surveillance Network (FluSurv-NET) from the 2003–2013 influenza seasons (*3*,*14*). FluSurv-NET conducts population-based surveillance for laboratory-confirmed influenza-associated hospitalizations among children <18 years of age (since the 2003–04 influenza season) and adults (since the 2005–06 influenza season). The FluSurv-NET system and protocol have been described previously (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/9/14-1665-Techapp1.pdf) (*1*,*3*,*15*).

CDC determined that data collected through FluSurv-NET were for routine public health surveillance and not subject to institutional review board approval for human research protections. Participating sites submitted the surveillance protocol to their state and local institutional review boards for review.

Case Definition and Data Collection

A case of influenza-associated hospitalization was defined as hospitalization of a catchment-area resident who was hospitalized in a catchment-area hospital during a designated influenza season (October 1–April 30) with a laboratory-confirmed influenza test within 14 days before or 3 days after hospital admission. Laboratory-confirmed influenza was defined as a positive result from RT-PCR, viral culture, direct fluorescent antibody staining (DFA), or RIDT or a positive result for an unspecified laboratory test documented in the medical chart. RT-PCR could be performed at the participating hospital or at the state public health laboratory depending on test availability in the hospital laboratory. The frequency of identified cases by diagnostic test type (observed case count) by patient age and by influenza season was evaluated. When an identified case had >1 type of positive influenza test, we used the test type with the highest sensitivity—RT-PCR, viral culture, DFA, RIDT (ordered from highest to lowest sensitivity)—for the analysis. If an identified case had no other test type and a positive result from an unspecified laboratory test documented in the medical chart, we assumed 100% sensitivity for that test.

Diagnostic Test Sensitivity

We reviewed the literature to obtain sensitivity ranges for influenza diagnostic tests. We searched PubMed with a strategy containing search terms for influenza disease or virus combined with search terms for RT-PCR, viral culture, DFA, and RIDTs and search terms for sensitivity. Search terms for influenza were as follows: "influenza, human" [Medical Subject Heading (MeSh)] OR "influenza A virus" [MeSh] OR "influenza B virus" [MeSh] OR "influenza" or "flu." Search terms for the tests included "RT-PCR," "reverse transcription polymerase chain reaction," "culture," direct florescent antibody," "DFA," "rapid diagnostic test." Search terms for clinical sensitivity included "sensitivity," "test characteristics," "diagnostic test characteristics," and "test performance characteristics." We hand-searched bibliographies of included studies and recent narrative reviews of influenza diagnostic tests for additional relevant studies. We included only studies describing the clinical performance of the different diagnostic test types and did not use the manufacturer's package insert or subtype-specific assessments. We identified studies describing the clinical sensitivities of different diagnostic test types in the system and focused on the periods before and after the 2009 influenza pandemic. The diagnostic reference standard used in the studies was either viral culture or RT-PCR. The sensitivity of influenza diagnostic tests varies by age because of factors, such as differences in viral shedding (*16*–*19*); therefore, we collected characteristics on each test type by age group (children <18 years, adults 18–64 years, and adults ≥65 years). Because we categorized the influenza diagnostic test type by method, we preferentially selected studies, such as meta-analyses, that could evaluate multiple brands of a particular influenza diagnostic test. We attempted to select studies based in hospitalized or emergency department settings when available.

We abstracted sensitivity values from the literature by age group as a range of minimum to maximum values or as a point estimate with a 95% CI, depending on how the data were reported (online Technical Appendix Table 1). To create a summary empirical distribution across all included studies for each age group and test type, we applied bootstrap techniques (*20*). All ranges were evaluated as a single observation and equally weighted in the analysis. We resampled 1,000 times from each reported distribution of test sensitivity (uniform distribution when only a minimum and maximum sensitivity were reported or a normal distribution when the midpoint and 95% CI were reported). To summarize the resulting empirical distribution, we calculated a median estimate and 95% CI for each diagnostic test type by age group.

Rate Calculations

We calculated rates of influenza-associated hospitalization per 100,000 population using the National Center for Health Statistics (NCHS) population estimates for the counties in the surveillance catchment area. We calculated observed rates per 100,000 population by age group for each season using the observed case count and dividing it by the NCHS population estimate for that age group and influenza season. To adjust the observed hospitalization rates for test sensitivity, we used the following formula to estimate an adjusted case count by age group for each diagnostic test:

$$(\text{adjusted case count})_{\text{test}} = (\text{observed case count})_{\text{test}} \times (1/\text{sensitivity}_{\text{test}})$$

We calculated the total adjusted case count for a season and age group by summing the test-specific adjusted case counts. Finally, we calculated adjusted rates per 100,000 population by dividing the total adjusted case counts by the NCHS population estimate for that age group and season.

To reflect the previously described distribution of test sensitivity, this series of calculations was performed within the previously described bootstrap for each resampled value of test sensitivity. Reported here are the median estimate and 95% CI for each season and age group. All analyses were performed in SAS version 9.3 (SAS Institute, Cary, NC, USA).

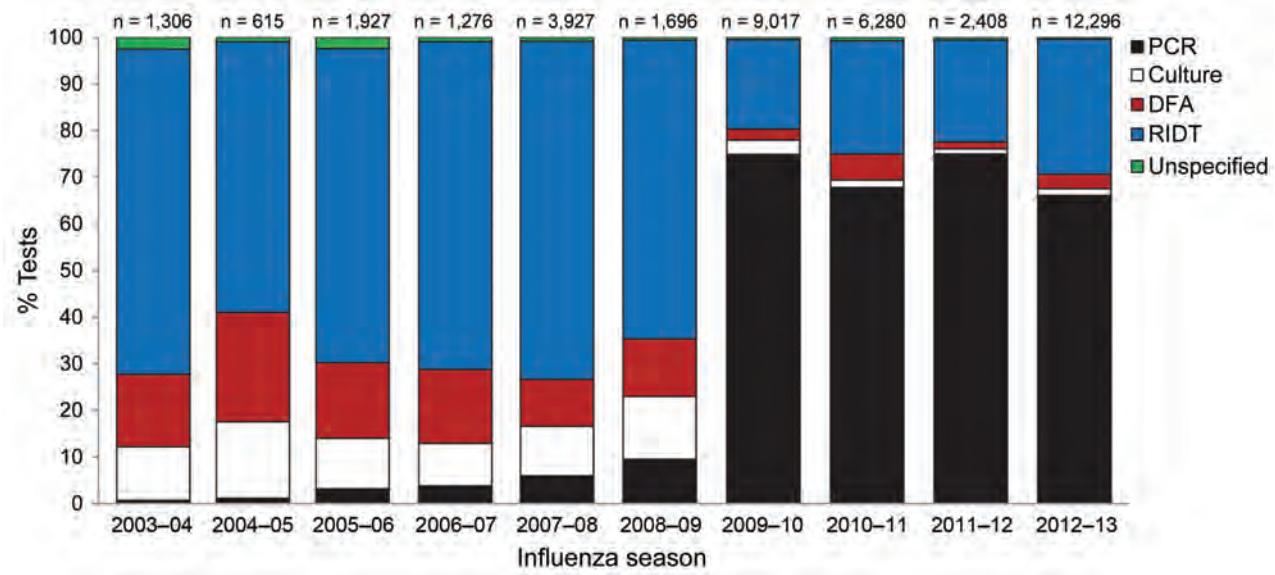

Figure 1. Distribution of influenza diagnostic tests among identified cases in the Centers for Disease Control and Prevention Influenza Hospital Surveillance Network (FluSurv-NET), 2003–2013. RT-PCR, reverse transcription PCR; DFA, direct fluorescent antibody test; RIDT, rapid influenza diagnostic test.

Results

During 2003–2013, the distribution of influenza diagnostic tests among identified cases changed, particularly after the 2009 pandemic (Figure 1). Before 2009, RIDTs were the most common test type, accounting for ≈70% of cases identified in FluSurv-NET. After the 2009 pandemic, RT-PCR became the most frequent test type for all age groups (online Technical Appendix Figure). The proportion of RT-PCRs among identified cases increased from <10% before 2009 to ≈70% after 2009.

The Table summarizes the diagnostic test performance characteristics by age group obtained from the literature review and the bootstrap analysis. Influenza diagnostic tests are generally most sensitive when performed on specimens from children <18 years; RT-PCR has the highest sensitivity in this age group (sensitivity estimate 95%, 95% CI 82%–98.7%). The sensitivity of influenza diagnostic tests in adults 18–64 years is similar to that in children <18 years except for RIDTs, which are less sensitive in this age group. Overall, influenza diagnostic tests have poor sensitivity in adults ≥65 years. RIDTs have the lowest sensitivity in this age group (sensitivity estimate 20.1%, 95% CI 8.8%–41.4%), and although RT-PCR is more sensitive in this age group than are other test types, the midpoint sensitivity estimate for RT-PCR is still <90%. DFA sensitivity appears higher than that of culture and RIDTs in this age group; however, these results were extrapolated from studies that primarily included a younger population (*27*,*28*).

Table. Influenza diagnostic test sensitivity range, by patient age group (years), FluSurv-NET, 2003–2013*

Diagnostic test/patient age group, y	Range from literature review, %	References	Bootstrap estimate (95% CI)
RT-PCR			
0–17	79.2–100	(*19*,*21*–*24*)	95.0 (82–98.7)
18–64	79.2–100	(*19*,*21*–*23*)	94.1 (81.1–98.7)
≥65	79.2–93	(*19*,*21*,*25*)	86.1 (79.6–92.7)
Culture			
0–17	45–100	(*4*,*19*,*24*,*26*)	69.3 (48.3–95.9)
18–64	45–100	(*4*,*19*,*26*)	72.8 (47.2–96.3)
≥65	19.4–53.8	(*8*,*25*)	36.2 (20.3–52.1)
DFA			
0–17	45–90	(*24*,*27*–*30*)	70.9 (46.8–86.6)
18–64	53–84.2	(*27*,*28*)	68.0 (53.8–83.4)
≥65	53–84.2	(*27*,*28*)	68.0 (53.8–83.4)
RIDT			
0–17	61.6–71.7	(*7*)	66.7 (61.3–71.7)
18–64	47.7–59.8	(*7*)	53.9 (47.8–59.8)
≥65	8–43	(*8*,*17*,*25*,*31*)	20.1 (8.8–41.4)

*DFA, direct fluorescent antibody; FluSurv-NET, Centers for Disease Control and Prevention Influenza Hospital Surveillance Network; RIDT, rapid influenza diagnostic test; RT-PCR, reverse transcription PCR.

Additionally, DFA was seldom performed in this age group (online Technical Appendix Table 1).

Observed and adjusted rates of influenza-associated hospitalization per 100,000 population varied by season for all age groups, indicating a particular influenza season's severity (Figure 2; online Technical Appendix Table 2). Observed hospitalization rates ranged from 7.3 during 2011–12 to 50.5 during 2009–10 for children <18 years of age, 3.0 during 2006–07 to 30.3 during 2009–10 for adults 18–64 years, and 13.6 during 2008–09 to 181.8 during 2012–13 for adults ≥65 years. Hospitalization rates were highest for adults ≥65 years of age and lowest for adults 18– 64 years of age.

Adjusting for test sensitivity increased hospitalization rates across all age categories (Figure 2). Adjusted rates showed that the number of hospitalizations was higher than previously reported in all seasons for all age groups, regardless of the severity of the season; however, rates increased more in earlier seasons. The magnitude of hospitalizations during severe influenza seasons during earlier surveillance years (2003–04 for children <18 years and 2007–08 for adults ≥65 years) increased substantially after the adjustments, better highlighting the morbidity associated with influenza infections during those earlier seasons (online Technical Appendix Table 3). The wide CIs in the adjusted rates for adults ≥65 years in all seasons reflects the poor sensitivity of influenza diagnostic tests in this age group.

When adjusted for test sensitivity, observed rates of hospitalization underestimated influenza-associated hospitalization rates for all age groups but especially for adults ≥65 years (Figure 3). Observed hospitalization rates underestimated adjusted rates by ≈30% during 2003–2008 versus 15% during 2009–2013 for children <18 years; by 40% during 2005–2008 versus 20% during 2009–2013 for adults 18–64 years; and by 75% during 2005–2008 versus 55% during 2009–2013 for adults ≥65 years.

Discussion

Adjusting for influenza diagnostic test sensitivity reveals that observed rates of influenza-associated hospitalization currently reported from surveillance data underestimate influenza-associated hospitalizations, particularly for adults ≥65 years. The increased use of high sensitivity tests, such as RT-PCR, after 2009 for all age groups has substantially reduced the degree of underestimation for children <18 years and adults 18–64 years of age. However, FluSurv-NET surveillance data still underestimate rates of influenza-associated hospitalization by 55% for adults ≥65 years without adjustments for influenza test sensitivity. Accurate influenza diagnostic testing can have a major impact on monitoring and guiding public health interventions for the control, prevention, and treatment of influenza.

Studies relying on administrative data alone to estimate rates of influenza-associated hospitalization may underestimate rates because influenza is seldom listed as a discharge diagnosis without laboratory-confirmed testing (*32*–*35*). The best way to ascertain influenza-associated hospitalization incidence rates in real time is to perform prospective surveillance that uses the most sensitive testing

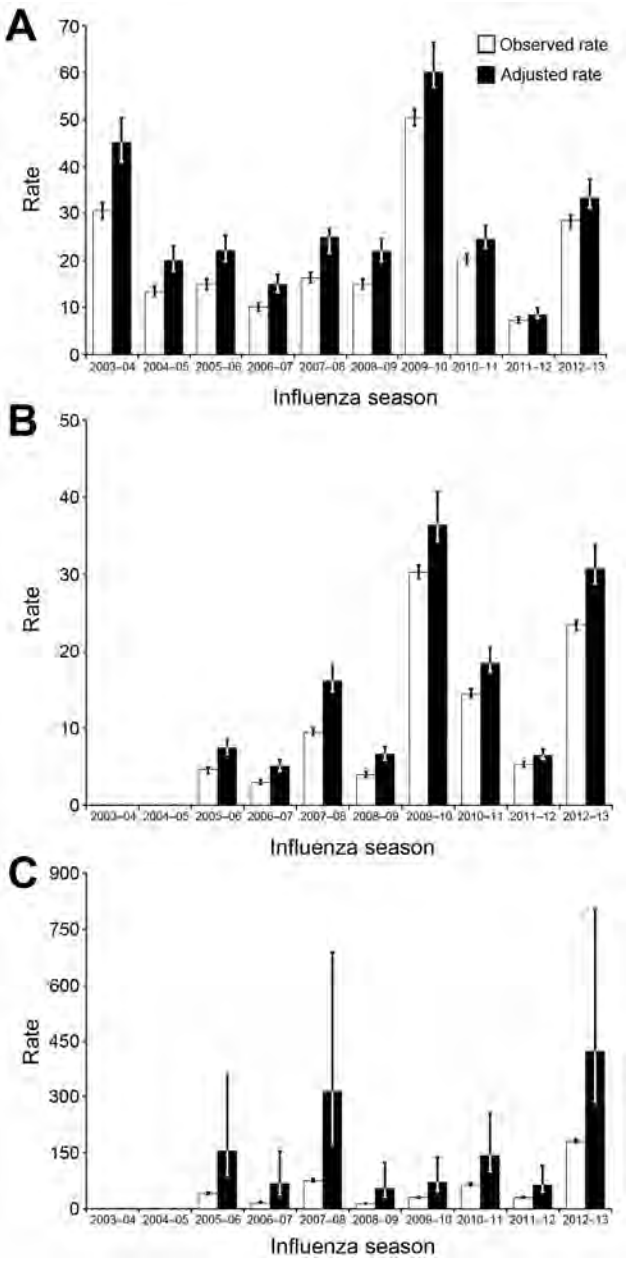

Figure 2. Observed and adjusted rates of influenza-associated hospitalizations per 100,000 population identified in the Centers for Disease Control and Prevention Influenza Hospital Surveillance Network (FluSurv-NET), 2003–2013. A) Children <18 years of age. B) Adults 18–64 years of age. C) Adults ≥65 years of age. Scale on the y-axis changes for each age group. Error bars indicate 95% CIs.

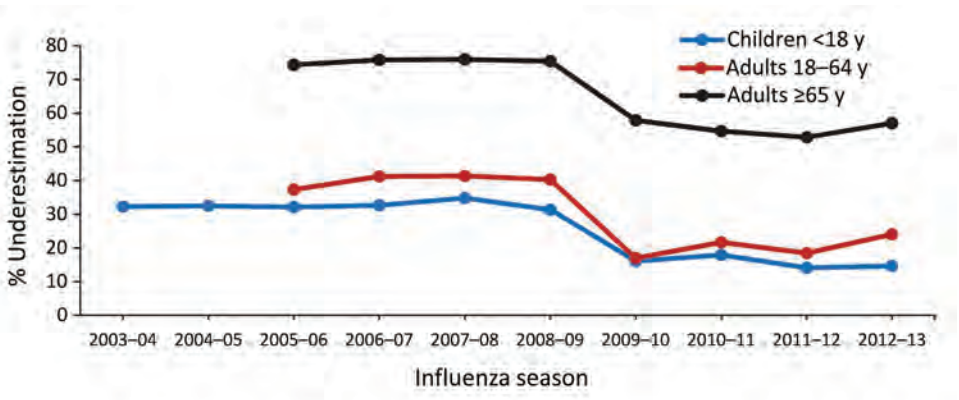

Figure 3. Underestimation of rates of influenza-associated hospitalization after adjustment for test sensitivity, by patient age group, Centers for Disease Control and Prevention Influenza Hospital Surveillance Network (FluSurv-NET), 2003–2013.

criteria (i.e., RT-PCR). Indeed, studies that have relied on active surveillance and testing, most often with RT-PCR, can improve estimates of influenza-associated hospitalization rates (*32*,*34*–*38*); however, as our study shows, failing to account for diagnostic test sensitivity can result in continued underestimation of influenza-associated hospitalizations, especially among older adults. Influenza diagnostic tests, regardless of test type, have poorer sensitivity in older adults than in younger persons. The methods used in our study account for case underascertainment resulting from varying testing sensitivity and provide opportunities to better compare the severity among different influenza seasons and age groups.

Although the degree of underestimation for the hospitalization rates reported here may seem high, the adjusted rates per 100,000 population for adults ≥65 years of age of 155.2 during 2005–06, 67.3 during 2006–07, and 314.4 during 2007–08 are still lower than the rates estimated in the literature using models of administrative data (rates per 100,000 for adults ≥65 years were 291.9 during 2005–06, 136.9 during 2006–07, and 380.9 during 2007–08) (*13*). This difference may be due to patients who had an influenza-associated hospitalization but were missed by our system because they were not tested. Nevertheless, sensitivity adjustments enable us to further improve the accuracy of estimated rates of influenza-associated hospitalization and provide timely results that account for changes in diagnostic test sensitivity over time.

Our analysis has limitations. First, our sensitivity adjustments do not reflect differences in detection by type or subtype of influenza viruses. Although this is a limitation of our analysis because diagnostic test sensitivity can vary on the basis of type or subtype of influenza viruses (*7*,*21*,*23*), differences in sensitivity based on type or subtype would have been difficult to assess, especially before the 2009 pandemic, when those data were not routinely available because of lack of RT-PCR or viral culture data in our network. Second, we did not adjust for any further variation in sensitivity measures by individual diagnostic test, but sensitivity measurements obtained from the literature enabled more generalizable estimates across the entire surveillance system. Third, we did not account for diagnostic test specificity. Influenza diagnostics tests generally have high specificities ranging from 96% to 100% regardless of age group (*7*,*10*,*11*), and the specificities of the tests used in the surveillance system have remained relatively constant over the study period, unlike test sensitivity. Although accounting for false-positive test results might decrease our estimates, the impact on overall rates would be minimal because test sensitivity covered much wider ranges. Fourth, although we conducted an extensive literature review, we did not conduct a formal systematic literature review. Additionally, published data on test sensitivity in adults ≥65 years of age are sparse; however, most studies demonstrate the poor sensitivity of influenza diagnostic tests in this particular population. Studies with larger sample sizes that focus on adults ≥65 years of age would improve understanding of diagnostic test sensitivity in this population with greater precision than is currently known. Finally, diagnostic testing in FluSurv-NET depends on a health care provider's decision to order diagnostic testing on an individual patient. Therefore, we were unable to account for patients with influenza who were not tested. Multipliers based on the probability of an influenza-infected patient's being tested have been estimated from the 2010–11 and 2011–12 seasons to correct for underascertainment (*39*; online Technical Appendix). Rates were adjusted for diagnostic test sensitivity and frequency of influenza testing (online Technical Appendix Table 3); however, because these results derive from estimates from 2 influenza seasons after the 2009 pandemic, our ability to determine whether the propensity to test has truly changed over time remains limited.

In conclusion, despite the increased use of highly sensitive molecular assays, current FluSurv-NET data still underestimate rates of influenza-associated hospitalization, particularly in adults ≥65 years of age. The primary reason for this underestimation is that diagnostic test sensitivity is

imperfect, so true cases of influenza are missed. Furthermore, test sensitivity varies with patient age, and all types of influenza diagnostic tests, but especially RIDTs, have comparatively poor sensitivity in older persons. Adjusting hospitalization rates on the basis of diagnostic test sensitivity enables more accurate and timely comparisons of associated disease activity in hospitalized patients over time.

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Socioeconomic Disparities and Influenza Hospitalizations, Tennessee, USA

Chantel Sloan, Rameela Chandrasekhar, Edward Mitchel, William Schaffner, Mary Lou Lindegren

We examined population-based surveillance data from the Tennessee Emerging Infections Program to determine whether neighborhood socioeconomic status was associated with influenza hospitalization rates. Hospitalization data collected during October 2007–April 2014 were geocoded (N = 1,743) and linked to neighborhood socioeconomic data. We calculated age-standardized annual incidence rates, relative index of inequality, and concentration curves for socioeconomic variables. Influenza hospitalizations increased with increased percentages of persons who lived in poverty, had female-headed households, lived in crowded households, and lived in population-dense areas. Influenza hospitalizations decreased with increased percentages of persons who were college educated, were employed, and had health insurance. Higher incidence of influenza hospitalization was also associated with lower neighborhood socioeconomic status when data were stratified by race.

Influenza causes annual outbreaks that result in >200,000 hospitalizations and 3,300–49,000 deaths annually in the United States (*1*). Children <2 years of age, persons >65 years of age, pregnant women, and those with underlying health conditions are at greater risk for developing serious complications (e.g., pneumonia) from influenza and are at greater risk for hospitalization and death. Despite continuing vaccine and treatment interventions, the public health effects of annual influenza epidemics remain substantial.

Although patient-level risk factors for severity of influenza have long been identified, attention is being directed towards reporting neighborhoods and contextual and environmental characteristics that increase risk for adverse health outcomes and that are independent of patient-level attributes (*2*). Geographic-based measures include physical, social, and economic characteristics of neighborhoods, such as poverty level, education, residential segregation, psychosocial stress, unemployment, inadequate transportation, social networks, distance to medical facilities, access to prevention and treatment services, insurance status, environmental exposures, and housing and density characteristics. Disparities in health outcomes likely result from a combination of factors that influence an individual's exposures, risk behaviors, susceptibility, treatment options, and social contextual factors (*3*–*5*). However, rarely are these measures collected through population-based surveillance systems. Previous work investigating influenza disparities showed a strong positive correlation between influenza hospitalization rates and geographic areas of high poverty and household crowding (*6*,*7*).

We analyzed population-based influenza hospitalization surveillance data from the Tennessee Emerging Infections Program (EIP) (*8*,*9*) to identify potential disparities in influenza hospitalization rates in Middle Tennessee according to neighborhood-level measures of socioeconomic status (SES). Understanding disparities in influenza hospitalization rates is a priority for the EIP as necessary to reduce illness and death from annual influenza epidemics.

Methods

The Study Setting and Population

Using the Tennessee EIP Influenza Hospitalization Surveillance Network, we analyzed data collected during the 2007–08 through 2013–14 influenza seasons. As part of the Influenza Hospitalization Surveillance Network, the Tennessee EIP conducts population-based surveillance for laboratory-confirmed influenza hospitalizations in 8 counties located in Middle Tennessee, which includes the city of Nashville, located in Davidson County, and its bordering suburban and rural counties: Wilson, Rutherford, Williamson, Dickson, Cheatham, Robertson, and Sumner (Figure 1). The population size of the catchment area is ≈1,557,000 persons.

Laboratory confirmation for influenza virus infection was determined by reverse transcription PCR, viral culture, direct or indirect fluorescent antibody staining, or rapid antigen testing. Influenza testing was ordered at the discretion of the treating clinicians. Those hospitals without onsite PCR capacity were encouraged to send specimens to the Tennessee Department of Health Laboratory Services for reverse transcription PCR confirmation. Surveillance for laboratory-confirmed influenza hospitalization

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was reviewed and determined to be exempt by the Human Subjects Review Board at the Centers for Disease Control and Prevention and by the Human Research Protection Program at the Vanderbilt University School of Medicine.

Information about demographic characteristics, underlying conditions, clinical outcomes, and antiviral treatment was collected from medical record review by trained reviewers who used a standard questionnaire. Surveillance was conducted annually during the influenza season (October–April). During the influenza A(H1N1) pandemic of 2009–10, surveillance continued throughout the summer. We included race in the analysis but did not stratify by ethnicity because of low numbers identified as Hispanic ethnicity.

Each participant's home address was geocoded to a latitude and longitude point by using ArcMap version 10.0 (*10*). Most (94%) addresses were geocoded successfully; those that could not be geocoded to rooftop accuracy were excluded. Each home address was assigned to a Tennessee census tract on the basis of location.

Census Data

We used the assigned census tracts to extract data from the 2010 US Census and from the 2007–2011 American Community Survey. For each tract, census data included tract population, percent below poverty, health insurance status, education, employment, and percentages of female head of household and household crowding. We also calculated population density per square mile by using census population totals and areas calculated within ArcMap. When possible, we categorized sociodemographic variables according to previously published standards by the Harvard Geocoding Project (*11*). Table 1 shows the categorization of the major sociodemographic factors from the American Community Survey.

Overall population density was calculated by dividing the total number of persons by the number of square miles in each census tract (*12*). We further categorized population densities into 3 categories: ≤200 persons/square mile, 201–700 persons/square mile, and ≥700 persons/square mile. These categories were selected because they differentiated geographic areas that were predominantly rural, suburban, or urban in our population (online Technical Appendix Figure 1, http://wwwnc.cdc.gov/EID/article/21/9/14-1861-Techapp.pdf)

Statistical Analysis

The data were analyzed by using R version 3.0.1 (http://www.r-project.org/) and SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). We calculated the Spearman's rank correlation coefficient (r_s) between each variable to determine which ones were likely to provide redundant results. The most highly correlated variables were single-parent household and female head of household (r_s = 0.96), percentage below poverty and single-parent household (r_s = 0.76), and overall population density and population density of children <5 years of age (r_s = 0.96; online Technical Appendix Figure 2). Percentage of white residents and population density were negatively correlated (r_s = -0.66), as were percentage below poverty and median income (r_s = -0.89). Percentage of single-parent households, median income, and population density of children are not presented in the results because of the high correlation among these variables. Percentage below poverty was selected instead of median income because Krieger et al., in a comparison of different SES measures, found percentage below poverty to be the most robust indicator of neighborhood poverty (*11*).

We calculated the average annual incidence of influenza hospitalizations per 100,000 person-years during the 7-year period as the proportion of persons hospitalized in the catchment area per 100,000 persons per year. We also calculated the age-standardized rate ratio (RR), rate difference (RD), relative index of inequality (RII), concentration curve (CC), and its associated concentration index (CIndex) for each census variable. The RII is used as a measure of the strength of the influence of SES on health inequality. RII is calculated as the exponent of the slope of a Poisson regression model by using incidence rate as the outcome variable and the proportion of the population in a socioeconomic group as the predictor variable. The RII can be interpreted similarly to an incidence RR by comparing those in the quantitatively highest category with those in the lowest category. For example, an RII of 2.9 would indicate a 190% increase in risk if those in the highest categorization are compared with those in the lowest. CCs were used to discern whether results were biased because of cutoffs used for variable categorization. The CC is a graph of the

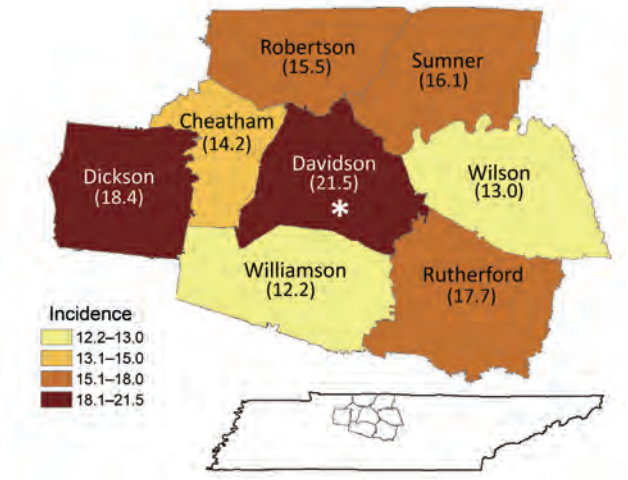

Figure 1. Average annual incidence of influenza hospitalizations, by county, Middle Tennessee, USA, October 2007–April 2014. Asterisk indicates location of the city of Nashville.

Table 1. Average annual crude and age-standardized incidence rates and relative rates of influenza hospitalization by demographic and neighborhood measures, Middle Tennessee, USA, October 2007–April 2014*

Characteristic	Hospitalizations, no. (%), N = 1,743	Crude incidence (95% CI)	Age-standardized incidence (95% CI)	Rate ratio (95% CI)	Rate difference (95% CI)	RII†
Individual-level data‡						
Sex						NA
M	775 (44.5)	15.1 (14.0–16.2)	16 (14.9–17.2)	NA	NA	
F	968 (55.5)	18.0 (16.8–19.1)	17.8 (16.7–19.0)	1.1 (1.0–1.2)	1.8 (0.2–3.4)	
Race§						NA
White	1,242 (73.4)	15.3 (14.5–16.2)	15.2 (14.4–16.1)	NA	NA	
African	418 (24.7)	24.7 (22.4–27.1)	27.4 (24.8 30.3)	1.8 (1.6–2.0)	12.2 (9.4–15.0)	
American						
Other	31 (1.8)	4.4 (2.8–5.9)	4.0 (2.5–6.5)	0.3 (0.2–0.4)	−11.2 (−13.1 to −9.3)	
Age, y						NA
<5	207 (11.9)	28.3 (24.4–32.2)	NA	NA	NA	
5–17	98 (5.6)	5.3 (4.3–6.4)	NA	NA	NA	
18–49	470 (27.0)	9.6 (8.7–10.4)	NA	NA	NA	
50–64	398 (22.8)	20.7 (18.7–22.8)	NA	NA	NA	
≥65	570 (32.7)	51.7 (47.4–55.9)	NA	NA	NA	
Neighborhood-level data‡						
% Below poverty						
<5.0	266 (15.3)	11.4 (10.0–12.8)	11.5 (10.1–13.0)	NA	NA	2.9 (2.5–3.5)
5.0–9.9	374 (21.5)	14.2 (12.8–15.6)	13.9 (12.5–15.4)	1.2 (1.1–1.4)	2.4 (0.5–4.4)	
10.0–19.9	475 (27.3)	17.3 (15.7–18.8)	16.8 (15.3–18.4)	1.5 (1.3–1.7)	5.3 (3.3–7.4)	
≥20.0	628 (36)	24.9 (22.9–26.8)	25.7 (23.7–27.8)	2.2 (2.0–2.5)	14.2 (11.8–16.7)	
% College education						
15.0–24.9	16 (0.9)	38.8 (19.8–57.7)	47.3 (23.9–92.1)	NA	NA	0.5 (0.4–0.7)
25.0–39.9	326 (18.7)	21.5 (19.2–23.9)	21.4 (19.1–23.9)	0.5 (0.1–1.7)	−25.9 (−53.7 to 1.8)	
≥40.0	1,401 (80.4)	16.1 (15.3–17)	16.1 (15.2–16.9)	0.3 (0.1–1.9)	−31.3 (−58.9 to −3.6)	
% Employed						
<50.0	1,122 (64.4)	19.3 (18.2–20.4)	18.9 (17.8–20.1)	NA	NA	0.6 (0.5–0.7)
50.0–65.9	605 (34.7)	14.1 (12.9–15.2)	14.4 (13.3–15.6)	0.8 (0.7–0.9)	−4.5 (−6.1 to −2.9)	
≥66.0–74.9	16 (0.9)	12.6 (6.4–18.8)	15.8 (8.4–27.7)	0.8 (0.5–1.4)	−3.2 (−11.9–5.5)	
% Female HH						
<20.0	637 (36.5)	12.7 (11.8–13.7)	12.7 (11.7–13.7)	NA	NA	3.2 (2.7–3.8)
20.0–39.9	531 (30.5)	17.2 (15.7–18.6)	17.2 (15.7–18.7)	1.4 (1.2–1.5)	4.5 (2.7–6.3)	
40.0–59.9	340 (19.5)	23.0 (20.6–25.4)	22.7 (20.3–25.3)	1.8 (1.6–2.0)	10.0 (7.4–12.6)	
≥60.0	235 (13.5)	34.9 (30.5–39.4)	36.0 (31.5–41.0)	2.8 (2.5–3.2)	23.3 (18.6–28.1)	
Household crowding, persons/room)						
<5.0	1,514 (86.9)	16.5 (15.7–17.3)	16.4 (15.5–17.2)	NA	NA	1.9 (1.5–2.5)
5.0–9.9	176 (10.1)	20.0 (17.0–23.0)	21.6 (18.4–25.1)	1.3 (1.1–1.5)	5.2 (1.9–8.6)	
≥10.0	53 (3.0)	27.5 (20.1–34.9)	26.9 (20.0–35.6)	1.6 (1.2–2.2)	10.5 (3.1–17.9)	
Population density, persons/mi^2						
0–<200	259 (14.9)	14.8 (13.0–16.6)	14.0 (12.3–15.8)	NA	NA	1.8 (1.5–2.2)
200–700	273 (15.7)	13.8 (12.2–15.5)	13.7 (12.1–15.5)	1.0 (0.8– 1.2)	−0.3 (−2.6– 2.1)	
≥700	1,211 (69.5)	18.6 (17.5– 19.6)	18.7 (17.7– 19.8)	1.3 (1.2–1.5)	4.7 (2.7–6.8)	
% Medical insurance						
50–74.9	200 (11.5)	22.5 (19.4–25.6)	24.1 (20.8–27.8)			0.5 (0.3–0.6)
≥75.0	1,543 (88.5)	16.5 (15.7–17.3)	16.4 (15.6–17.2)	0.7 (0.5–0.8)	−7.8 (−11.3 to −4.3)	

*HH, head of household; RII, relative indexes of inequality; NA, not applicable.
†RII is calculated as the exponent of the slope of a Poisson regression model by using incidence rate as the outcome variable and the proportion of the population in that socioeconomic group as the predictor variable. The RII can be interpreted similarly to an incidence rate ratio that compares those in the quantitatively highest category with those in the lowest categorization. For example, an RII of 2.5 would indicate a 150% increase in risk when those in the quantitatively highest category are compared with those in the lowest (such as the <49.9% category being compared with the ≥66.0–74.9 category for patients employed). A low RII (with CIs) <1 would indicate decreased risk. An RII was not calculated for variables marked NA because they do not have a readily available ordinal variable by which to compare lowest and highest socioeconomic status.
‡Sex, race, and age characteristics use individual-level data from surveillance; neighborhood-level characteristics use data from the American Community Survey §The number of patients with available race data was 1,691.

cumulative percentage of cases versus the cumulative percentage of the population distribution of the census tract variable. If no health disparities are present, the curve will fall on the diagonal. A curve above the diagonal indicates that patients are concentrated in the highest risk category. What is shown qualitatively by the CC can be summarized quantitatively by the CIndex. It is computed as twice the area between the curve and the diagonal line. A negative CIndex shows a disparity in influenza hospitalizations regarding levels of the census variable that indicate low SES (*13*). If no census variable-related inequality is present, the CIndex is 0.

Results

During the influenza seasons from 2007–08 through 2013–14, a total of 1,743 persons were hospitalized with confirmed influenza in the Middle Tennessee catchment area. The number of persons hospitalized ranged from 61 during the 2011–12 season to 590 during the 2013–14 season. The observed frequency of influenza hospitalizations was in accordance with those reported by other surveillance sites. Low rates were observed nationally during the 2011–12 season (*14*).

Women had a higher age-standardized incidence rate of hospitalizations (17.8/100,000 population; 95% CI 16.7–19.0) compared with that for men (16.0/100,000 population; 95% CI 14.9–17.2; Table 1). This finding was consistent over the study period. The highest incidence by age group was for those ≥65 years of age (51.7/100,000 population; 95% CI 47.4–55.9), compared with an incidence rate of 5.3/100,000 population (95% CI 4.3–6.4) for those 5–17 years of age, the group with the lowest rate (Table 1). Children <5 years of age had incidence rates of 28.3/100,000 population (95% CI 24.4–32.2). African Americans had an age-standardized incidence rate of 27.4/100,000 population (95% CI 24.8–30.3), compared with a rate for whites of 15.2/100,000 population (95% CI 14.4 –16.1). African Americans had higher rates than whites for all 7 seasons investigated (online Technical Appendix Figure 3).

Crude and adjusted rates of influenza hospitalization for each variable studied are shown in Table 1. For census tracts with increasing percentages of the population employed, insured, and college educated, rates of influenza hospitalizations decreased (RII 0.5, 95% CI 0.4–0.7; RII 0.6, 95% CI 0.5–0.7; and RII 0.5, 95% CI 0.3–0.6, respectively) (Table 1). Figure 2 shows age-standardized rates for variables by levels of SES. For census tracts having the lowest percentage of persons below the poverty level (i.e., <5% of the population), the age-standardized incidence rate of influenza hospitalization was 11.5/100,000 population (95% CI 10.1–13.0; Figure 2). For those tracts with the highest percentage below poverty (≥20% of the population), the incidence rate was 25.7/100,000 population (95% CI 23.7–27.8; Figure 2). RRs increased with increasing percentage of the population living below poverty. Compared with the <5% below poverty tracts, tracts with 5%–9.9%, 10%–19.9% and ≥20% of persons living below poverty had RRs of 1.2, 1.5, and 2.2, respectively (RII 2.9, 95% CI 2.5–3.5). The RD also increased according to percentage of the population living below poverty (2.4, 5.3, and 14.2, respectively, for tracts with 5%–9.9%, 10%–19.9% and ≥20% living below poverty).

In addition, rates increased from 12.7/100,000 population (95% CI 11.7–13.7) for tracts with <20% female heads of household to 36.0/100,000 population (95% CI 31.5–41.0) for tracts with ≥60% female heads of household (RII 3.2, 95% CI 2.7–3.8). The RD increased from 4.5 for tracts with 20%–39.9% female heads of households to 10.0 for tracts with 40%–59.9% female heads of households to 23.3 for ≥60% female heads of households. Household crowding was also associated with increased risk for influenza hospitalization (RII 1.9, 95% CI 1.5–2.5).

Urban census tracts (i.e., those with population densities ≥700/square mile) had consistently higher influenza hospitalization rates (18.7/100,000 person-years) than did tracts with lower population densities (13.7 and 14.0/100,000 person-years in suburban [201–700 persons per square mile] and rural [≤200 persons/square mile] areas; RII 1.8, CI 1.5–2.2) (Table 1). This trend was consistent across influenza seasons.

Although every variable showed some deviation from the line of equality (Figure 3), percent below poverty and percent female head of household each had a CIndex of –0.16 (Figure 3), indicating strong disparities. The percent employed variable also showed a disparity in hospitalizations with a CIndex of –0.08.

We calculated age-standardized incidence by race for selected characteristics (Table 2). A comparison of white patients residing in neighborhoods with ≥20% of persons living below poverty with those living in areas with <5% below poverty resulted in an RII of 2.5 (95% CI 2.0–3.1); the RII for the same comparison for African Americans was 3.3 (95% CI 2.2–4.8). Approximately two thirds of African Americans hospitalized with influenza during the study period resided in census tracts with the highest percentage of persons living below poverty (i.e., ≥20%). We also calculated incidence for age and race for household crowding and female head of household. The RII for African Americans by percentage of female heads of household was 3.6 (95% CI 2.5–5.1), compared with 2.4 for whites (95% CI 2.0–3.0). Overall age-standardized rates for household crowding were similar for each race group (Table 2).

Discussion

Area-based measures of disparities in SES were strongly associated with incidence of influenza hospitalization in

Middle Tennessee. Increasing incidence of influenza hospitalization was associated with increasing proportion of the population living below poverty or having female-headed households and with increasing population density and household crowding. Decreasing incidence of influenza hospitalizations was associated with increasing percentages

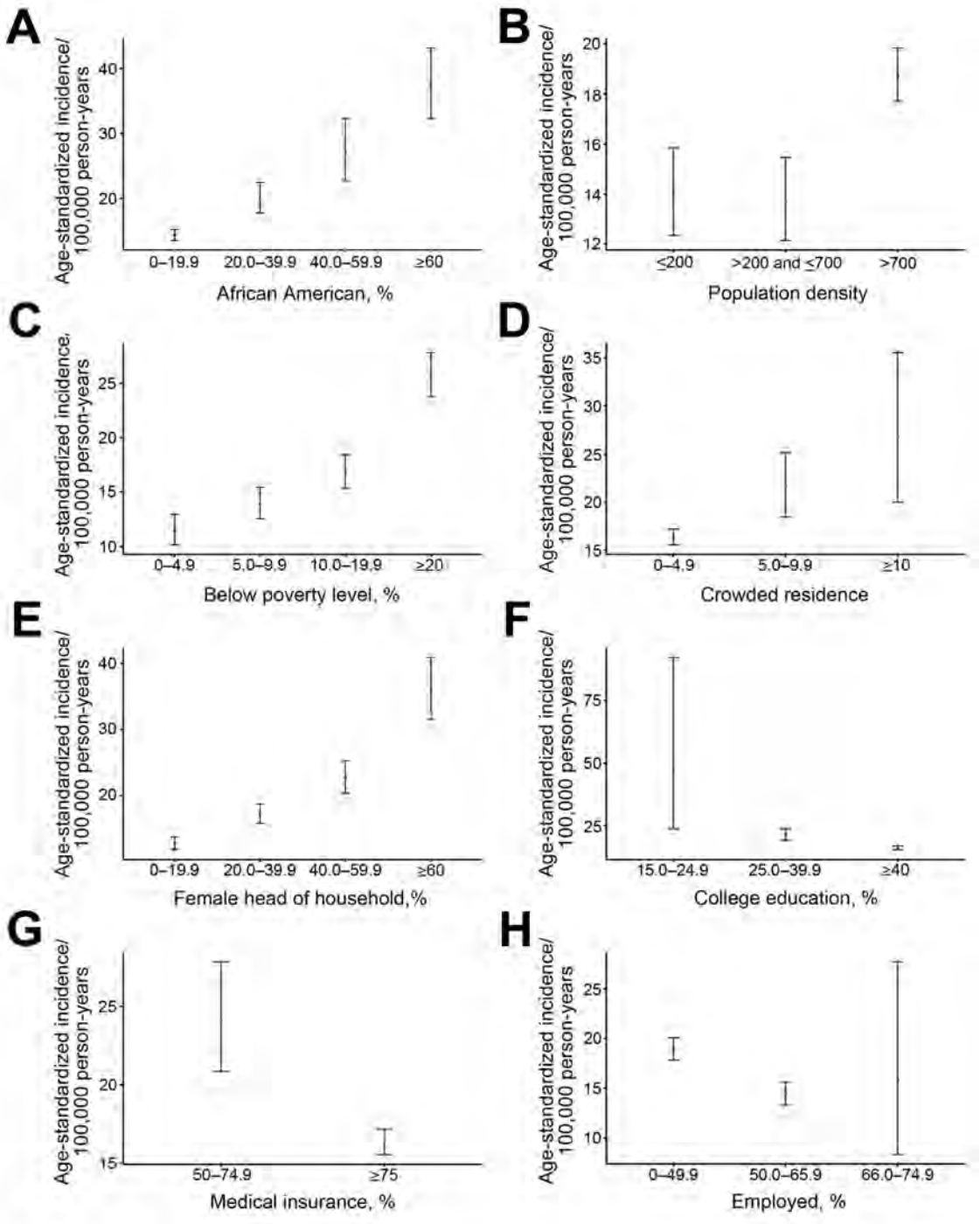

Figure 2. Age-standardized incidence of influenza hospitalizations by census tract socioeconomic variables, Middle Tennessee, USA, October 2007–April 2014. Variables were linked to the American Community Survey. A) Incidence by percentage of African Americans. B) Incidence by population density (≤200 persons/mi^2 [rural]; >200–≤700 persons/mi^2 [suburban]; >700 persons/mi^2 [urban]). C) Incidence by percentage living below poverty level. D) Incidence by level of crowded housing (persons per room). E) Incidence by percentage with female head of household. F) Incidence by percentage with college education. G) Incidence by percentage with medical insurance. H) Incidence by percentage employed. Error bars indicate 95% CIs.

of the population having medical insurance, employment, and college education. RDs also consistently increased with increased percentages of persons living below poverty, of female-headed households, and of household crowding. These associations were consistent throughout each of the 7 influenza seasons studied. Increasing incidence with decreasing SES was also found within each racial group. Among individual-level characteristics, older age, African American race, and female sex were associated with increased incidence of influenza hospitalization. The choice

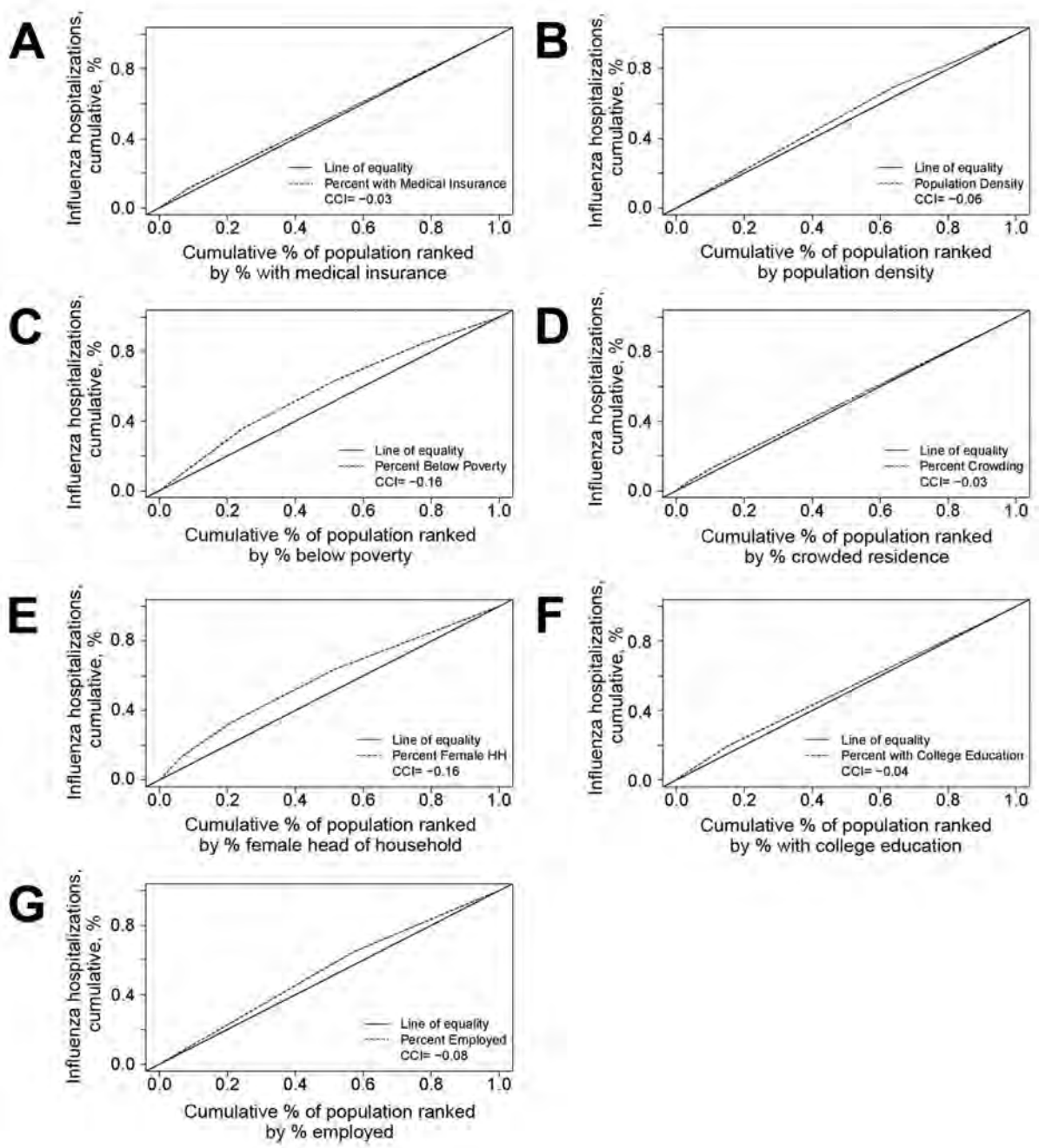

Figure 3. Concentration curves of neighborhood-level disparities in influenza hospitalizations, Middle Tennessee, USA, October 2007–April 2014. Figures show the divergence of cumulative incidence of hospitalizations for factors from the American Community Survey from the line of equality. In the absence of disparities, the dotted and dashed lines would entirely overlap. Cumulative percentage of the population hospitalized for influenza is shown for A) percentage of the population with medical insurance; B) population density; C) percentage of the population below poverty; D) percentage of the population with different levels of residential crowding; E) percentage of the population with female-headed households; F) percentage of the population with a college education; and G) percentage of the population employed. CCI, concentration curve index.

Table 2. Average annual age-standardized and race-stratified incidence of influenza hospitalizations, by neighborhood percentage of households below poverty, household crowding, and percentage of households with female head of household, Middle Tennessee, USA, October 2007–April 2014*

Characteristic	Hospitalizations, no. (%)	Age-standardized annual incidence (95% CI)	Rate ratio	Rate difference	RII†
White, n = 1,242					
% Below poverty					
<5.0	233 (18.8)	11.0 (9.6–12.5)			2.5 (2.0–3.1)
5.0–9.9	320 (25.8)	13.6 (12.2–15.2)	1.2 (1.1–1.4)	2.7 (0.6–4.7)	
10.0–19.9	374 (30.1)	16.3 (14.7–18.1)	1.5 (1.3–1.7)	5.3 (3.1–7.5)	
≥20.0	315 (25.4)	23.0 (20.5–25.7)	2.1 (1.8–2.4)	12.0 (9.1–14.9)	
Household crowding‡					
<5.0	1,113 (89.6)	14.8 (13.9–15.7)			1.9 (1.3–2.8)
5.0–9.9	99 (8.0)	19.1 (15.5–23.2)	1.3 (1.1–1.6)	4.3 (0.4–8.1)	
10.0+	30 (2.4)	26.7 (17.9–38.9)	1.8 (1.3–2.6)	11.9 (2.2–21.6)	
% Female head of household					
<20.0	556 (44.8)	12.4 (11.4–13.5)			2.4 (2.0–3.0)
20.0–39.9	423 (34.1)	16.9 (15.3–18.6)	1.4 (1.2–1.5)	4.5 (2.6–6.4)	
40.0–59.9	190 (15.3)	20.7 (17.8–24.0)	1.7 (1.4–1.9)	8.2 (5.1–11.4)	
60.0+	73 (5.9)	32.3 (25.1–41.3)	2.6 (2.1–3.3)	19.9 (12.2–27.5)	
African American, n = 418					
% Below poverty					
<5.0	20 (4.8)	17.8 (10.7–28.4)			3.3 (2.2–4.8)
5.0–9.9	40 (9.6)	15.9 (11.2–22.6)	0.9 (0.5–1.6)	−1.8 (−11.4 to 7.7)	
10.0–19.9	79 (18.7)	21.7 (17.1–27.3)	1.2 (0.8–1.9)	4.0 (−5.4 to 13.3)	
≥20.0	279 (66.7)	34.6 (30.6–39.0)	1.9 (1.5–2.5)	16.8 (7.8–25.8)	
Household crowding‡					
<5.0	339 (81.1)	26.3 (23.5–29.3)			1.8 (1.1–2.8)
5.0–9.9	64 (14.6)	33.6 (25.2–44.4)	1.3 (1.0–1.7)	7.3 (−2.1 to 16.8)	
10.0+	15 (3.6)	41.3 (22.7–71.1)	1.6 (0.9–2.7)	15.0 (−6.6 to 36.7)	
% Female head of household					
<20.0	49 (11.7)	14.8 (10.9–19.9)			3.6 (2.5–5.1)
20.0–39.9	77 (18.4)	20.8 (16.1–26.8)	1.4 (1.0–1.9)	6.0 (−0.6 to 12.6)	
40.0–59.9	139 (33.3)	31.6 (26.5–37.4)	2.1 (1.7–2.6)	16.7 (10.0–23.5)	
60.0+	153 (36.6)	40.0 (33.8–46.9)	2.7 (2.2–3.3)	25.1 (17.5–32.8)	

*Rates within ethnic subpopulations (i.e., Hispanic) were not calculated because of low numbers for these groups. RII, relative index of inequality.
†RII is calculated as the exponent of the slope of a Poisson regression model by using incidence rate as the outcome variable and the proportion of the population in that socioeconomic group as the predictor variable. The RII can be interpreted similarly to an incidence rate ratio that compares those in the quantitatively highest category with those in the lowest categorization. For example, an RII of 2.5 would indicate a 150% increase in risk when those in the quantitatively highest category are compared with those in the lowest (such as the <49.9% category being compared with the ≥66.0–74.9 category for percentage of patients employed). A low RII with CIs <1 would indicate decreased risk.
‡Household was evaluated for number of persons per room.

of concentration curves as the main measurement of disparities indicated that neighborhood socioeconomic indicators were robust in their influence on disparities in influenza hospitalization.

Our findings that neighborhood SES disparities influence influenza hospitalizations rates extends conclusions found in other studies (*3*,*6*,*7*,*15*,*16*). Population-based influenza hospitalization surveillance data from Connecticut showed that increasing hospitalization rates for both adults and children were associated with decreasing SES measures and increasing household crowding (*6*,*7*). The similar findings in these 2 population-based surveillance systems in different US geographic locations, a highly populated state in the Northeast and a more rural state in the Southeast, support the robustness of these associations. Other studies have also identified neighborhood social and physical characteristics, including housing conditions and environmental exposures, as risk factors for asthma and influenza hospitalization (*6*,*17*–*20*). Charland et al. reported that communities with increasing prevalence of obesity, less physically active populations, and lower fruit and vegetable consumption had higher rates of influenza-related hospitalizations (*21*).

We incorporated 4 distinctive measures of socioeconomic disparities (RR, RD, RII, and CIndex) into the statistical analysis that builds on the work of Krieger (*22*) in measuring the effects of health disparities on influenza hospitalization in Tennessee health outcomes. We also constructed CCs, graphic representations of disparities. Although the RR and RD are traditionally reported in such analyses and are easy to interpret, they are sensitive to the values used in categorization of the socioeconomic variable. In contrast, the RII and CIndex are measures that reflect the experiences of the entire population and are sensitive to the distribution of the population across socioeconomic groups. Any CIndex with a value <0 indicates disparity (*13*).

Surveillance systems have usually not collected individual-level SES data but often use surrogate measures

(e.g., race) to monitor health disparities. These surrogate measures have been inadequate to quantify SES inequalities in health. Area-based measures are the only currently available means to understand health inequities in population-based surveillance systems and may be uniquely relevant for monitoring the role of neighborhood in SES health inequities. Furthermore, the geospatial distribution of infectious diseases and area-based risk factors might be used to design, target, monitor, and assess public health programs, including prevention interventions for influenza. Age and underlying conditions of persons are currently used as the basis for targeted vaccination strategies. However, because area-based measures are strong risk factors for severe influenza, neighborhoods may become major targets for future preventive interventions.

This study has several limitations. First, data from population-based influenza hospitalization represent those who sought care and were tested for influenza by their clinician, and testing practices likely varied across hospitals in the catchment area. However, these data are consistently used each year by the Centers for Disease Control and Prevention to evaluate the severity of influenza and to determine persons at risk in real time during the influenza season. Second, we did not assess differences in influenza vaccination status among patients because data on vaccination coverage by census tract were not available, and the number of reported vaccinations on EIP case report forms was very low. Finally, neighborhood SES may not apply to specific individual-level SES characteristics and may not be the same for different persons. That is, neighborhood characteristics evaluated in this study may not well characterize individual persons living in those neighborhoods. However, these variables offer insight into the role of neighborhood in determining influenza health outcomes. We have defined neighborhoods as census tracts, although nearby neighborhoods may also influence health outcomes and disparities.

In summary, increasing rates of hospitalizations in Middle Tennessee were associated with increasing percentages of the population living below poverty, having female heads of households, living in densely populated areas, and living in crowded household conditions. Decreasing hospitalization rates were seen in areas with increasing percentages of the population with health insurance, college education, and employment. The well-tested procedures for incorporating neighborhood-level data into health studies described by the Harvard Geocoding Project (*11*), along with the application of infrequently used. CIndexes and CCs implemented in this study have shown the importance of measuring neighborhood-level SES disparities in determining health outcomes, such as incidence of influenza hospitalization. These population-based data from Tennessee reinforce the association of area-based measures of SES with incidence of influenza hospitalization and emphasize the important role that neighborhood socioeconomics play in explaining rates described here. The study also suggests that, because neighborhood characteristics are strongly associated with hospitalization rates, they should be considered when designing targeted prevention strategies such as vaccination programs.

Acknowledgment

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Improved Phenotype-Based Definition for Identifying Carbapenemase Producers among Carbapenem-Resistant *Enterobacteriaceae*

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Preventing transmission of carbapenemase-producing, carbapenem-resistant *Enterobacteriaceae* (CP-CRE) is a public health priority. A phenotype-based definition that reliably identifies CP-CRE while minimizing misclassification of non–CP-CRE could help prevention efforts. To assess possible definitions, we evaluated enterobacterial isolates that had been tested and deemed nonsusceptible to ≥1 carbapenem at US Emerging Infections Program sites. We determined the number of non-CP isolates that met (false positives) and CP isolates that did not meet (false negatives) the Centers for Disease Control and Prevention CRE definition in use during our study: 30% (94/312) of CRE had carbapenemase genes, and 21% (14/67) of *Klebsiella pneumoniae* carbapenemase–producing *Klebsiella* isolates had been misclassified as non-CP. A new definition requiring resistance to 1 carbapenem rarely missed CP strains, but 55% of results were false positive; adding the modified Hodge test to the definition decreased false positives to 12%. This definition should be considered for use in carbapenemase-producing CRE surveillance and prevention.

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Multidrug-resistant organisms are a major public health concern worldwide (*1*–*4*). Of particular concern has been the emergence of resistance to carbapenem antimicrobial drugs among *Enterobacteriaceae* (*4*,*5*). In the United States, the reported percentage of common health care–associated infections caused by carbapenem-nonsusceptible *Enterobacteriaceae* increased from 1.2% in 2001 to 4.2% in 2011 (*4*), and the greatest increase (≈10%) occurred among *Klebsiella* species (*4*).

Although carbapenem nonsusceptibility among *Enterobacteriaceae* can result from several mechanisms, much of the recent increase in carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States is likely due to the spread of carbapenemase-producing strains, particularly *Klebsiella* species that produce *Klebsiella pneumoniae* carbapenemase (KPC) (*3*,*4*). In addition to KPC, several other carbapenemases have been identified in the United States: New Delhi metallo-β-lactamase (NDM), oxacillinase (OXA), Verona integron–encoded metallo-β-lactamase (VIM), and imipenemase (IMP) (*5*,*6*). These enzymes are encoded by mobile genetic elements that have the potential to spread between bacterial species. The uptake of these elements among different bacterial species could result in further increases in the prevalence of carbapenem-resistant or panresistant bacteria, or both, and if this occurs, treatment options in the United States would be limited (*7*). Since 2006, the Centers for Disease Control and Prevention (CDC) has identified >100 NDM-producing CRE in the United States, including those that caused 2 hospital-based outbreaks (*8*,*9*). In light of the elements described above, much of the effort to prevent further spread of CRE has targeted carbapenemase-producing CRE. However, these efforts have been hampered because many clinical laboratories do not routinely perform CRE resistance-mechanism testing, so they cannot differentiate carbapenemase-producing CRE from CRE that are carbapenem-nonsusceptible due to other mechanisms. In addition,

resistance-mechanism testing is also not routinely recommended for clinical purposes by the Clinical and Laboratory Standards Institute (CLSI) (*10*).

A phenotype-based CRE definition (i.e., based on antimicrobial drug susceptibility pattern) that is specific for carbapenemase-producing strains has the potential to facilitate CRE prevention by allowing health care facilities to target these strains for the most aggressive interventions without the need to rely on resistance-mechanism testing. The pre-2015 CDC CRE surveillance definition—nonsusceptiblity to imipenem, meropenem, or doripenem, and resistance to all third-generation cephalosporins tested, as determined by using CLSI M100-S23 testing standards (*11*)—was originally designed to preferentially identify carbapenemase-producing CRE (*9*). However, because of the number of antimicrobial drugs included and the complexity of the third-generation cephalosporin restriction (resistance to all tested), this phenotype-based definition proved to be complicated and difficult to implement by health care facilities for both surveillance and infection control efforts. In addition, use of this definition led to the mistaken assumption that CRE that did not meet the definition did not warrant any additional infection control precautions beyond standard precautions (*9*).

The objective of this analysis was to identify a phenotype-based definition that accurately differentiates carbapenemase-producing CRE from non–carbapenemase-producing CRE on the basis of antimicrobial susceptibility patterns. To achieve this, we evaluated isolates collected through CDC's Emerging Infections Program (EIP) CRE surveillance system (http://www.cdc.gov/hai/eip/mugsi.html).

Methods

Inclusion Criteria and Data Collection

Isolates of *Enterobacter* spp., *Escherichia coli, and Klebsiella* spp. were collected from clinical laboratories that serve 6 EIP sites in the United States: Minnesota and Tennessee (both statewide); the 5-county Denver, Colorado, metropolitan area (Arapahoe, Adams, Denver, Douglas, and Jefferson Counties); the 4-county Baltimore, Maryland, metropolitan area (Baltimore City, Baltimore County, Howard County, and Carroll County); the Albuquerque, New Mexico, metropolitan area (Bernalillo County); and the Rochester, New York, metropolitan area (Monroe County). Four sites (Colorado, Maryland, New Mexico, and New York) submitted isolates from a preselected group of laboratories during March 10, 2013–January 30, 2014; two sites (Minnesota and Tennessee) submitted isolates received from statewide reporting starting January 1, 2011, and continuing through January 30, 2014. If >1 isolate of the same genus was obtained from a single patient, only 1 was included. Isolates that met the following 3 criteria were included: 1) evidence of nonsusceptibility (intermediate or resistant) to any carbapenem (imipenem, meropenem, doripenem, or ertapenem), as determined on the basis of susceptibility testing conducted at the local clinical laboratory by using 2013 CLSI breakpoints (*11*); 2) availability of susceptibility testing data from the reporting clinical laboratory for all antimicrobial drugs tested in the assessed phenotype-based definitions (Table 1); and 3) documentation of methods used for susceptibility testing.

Confirmatory Testing at CDC

Eligible *Enterobacter* spp., *E. coli, and Klebsiella* spp. isolates were sent to CDC for reference susceptibility testing (broth microdilution and Kirby-Bauer disk diffusion testing) for ertapenem, doripenem, imipenem, meropenem, 3 third-generation cephalosporins (ceftriaxone, cefotaxime, and ceftazidime), and cefepime (*11*). Three methods were used to evaluate each isolate for the presence of carbapenemases: the modified Hodge test (MHT), a broth microdilution screening test for metallo-β-lactamases that compares

Table 1. Summary of 11 phenotype-based definitions evaluated for reliability in identifying carbapenemase producers among carbapenem-resistant *Enterobacteriaceae*, United States, January 1, 2011–January 30, 2014*

Antimicrobial included	Study inclusion criteria	Definition†										
		1	2	3	4	5	6	7	8	9	10	11
Any carbapenem‡	NS				R		R	R		NS§	R	
Any carbapenem (without ertapenem)		NS	NS	NS		R						NS
≥2 carbapenems‡									NS§			
All third-generation cephalosporins tested			R				R					
Any third-generation cephalosporins tested				R				R				
Cefepime										R	R	R

*NS, nonsusceptible; R, resistant. Blank cells mean not included in the definition.
†Interpretation based on Clinical and Laboratory Standards Institute breakpoints (M100-S23) (*11*). Definitions: 1, nonsusceptible to any carbapenem, excluding ertapenem; 2, nonsusceptible to any carbapenem, excluding ertapenem, and resistant to all third-generation cephalosporins tested (pre-2015 Centers for Disease Control and Prevention carbapenem-resistant Enterobacteriaceae surveillance definition); 3, nonsusceptible to any carbapenem, excluding ertapenem, and resistant to any third-generation cephalosporins tested; 4, resistant to any carbapenem; 5, resistant to any carbapenem, excluding ertapenem; 6, resistant to any carbapenem and resistant to all third-generation cephalosporins tested; 7, resistant to any carbapenem and resistant to any third-generation cephalosporin tested; 8, nonsusceptible to at least 2 carbapenems (ertapenem resistant, if tested); 9, nonsusceptible to any carbapenem (ertapenem resistant, if tested) and resistant to cefepime; 10, resistant to any carbapenem and resistant to cefepime; and 11, nonsusceptible to any carbapenem, excluding ertapenem, and resistant to cefepime.
‡Ertapenem, doripenem, imipenem, and meropenem.
§If ertapenem used in the definition, isolate would need to be resistant (i.e., MIC ≥2 μg/mL).

the MIC of imipenem in the presence and absence of metal chelators (*12*), and PCR for the most common carbapenemases in the United States (i.e., bla_{KPC}, $bla_{NDM,}$ and bla_{OXA-48}). Isolates that were bla_{NDM}-negative by PCR but bla_{NDM}-positive by metallo-β-lactamase screening were further evaluated by PCR for bla_{VIM} and bla_{IMP}.

Analysis

Eleven phenotype-based definitions (Table 1) were initially evaluated: 1) nonsusceptible to any carbapenem, excluding ertapenem; 2) nonsusceptible to imipenem, meropenem, or doripenem and resistant to all third-generation cephalosporins tested (pre-2015 CDC CRE surveillance definition); 3) nonsusceptible to any carbapenem, excluding ertapenem, and resistant to any third-generation cephalosporins tested; 4) resistant to any carbapenem; 5) resistant to any carbapenem, excluding ertapenem; 6) resistant to any carbapenem and resistant to all third-generation cephalosporins tested; 7) resistant to any carbapenem and resistant to any third-generation cephalosporin tested; 8) nonsusceptible to at least 2 carbapenems (ertapenem resistant, if tested); 9) nonsusceptible to any carbapenem (ertapenem resistant, if tested) and resistant to cefepime; 10) resistant to any carbapenem and resistant to cefepime; and 11) nonsusceptible to any carbapenem, excluding ertapenem, and resistant to cefepime. All susceptibility interpretations were determined on the basis of the 2013 CLSI breakpoints (*11*). With the exception of CRE that are OXA-48–like producers, most carbapenemase producers are multidrug resistant and should be resistant to third-generation cephalosporins. Thus, in an attempt to improve detection of carbapenemase-producing CRE, we included third-generation cephalosporins in certain definitions. Similarly, we added cefepime to certain definitions to ascertain if it might help discriminate between AmpC-producing and carbapenemase-producing CRE.

For each of the 11 phenotype-based definitions, we performed 4 calculations based on the clinical laboratory–determined susceptibility results for carbapenem-nonsusceptible isolates. The calculations determined the number and percentage of 1) carbapenemase-producing isolates that screened positive (true positives [TP]); 2) carbapenemase-producing isolates identified that screened negative (selected false negatives [sFNs]); 3) non–carbapenemase-producing isolates that screened positive (false positives [FPs]); and 4) non–carbapenemase-producing isolates identified that screened negative (selected true negative [sTN]). The denominator for each of the calculations was the number of isolates for which the definitions could be applied on the basis of results at the clinical laboratory. Because we limited our isolates to those with nonsusceptibility to a carbapenem and could only calculate sFN and sTN screening results, we could not determine the specificity, sensitivity, or negative predictive value of a definition. Three of the 11 definitions were further stratified by EIP site and organism tested to evaluate differences in their FP and sFN results by geographic region and by genus. The 3 definitions were the one that obtained the lowest number of sFNs, the one that obtained the lowest number of FPs among definitions with potentially acceptable levels of sFNs (defined as <10%), and the pre-2015 CDC CRE surveillance definition. Analysis was limited to EIP sites that submitted >50 isolates. We performed 2-step testing by adding MHT results to the susceptibility results for the isolates meeting the definition with the lowest number of sFNs to determine if the results of the MHT affected the the percentage of isolates classified as FP and sFN.

Results

A total of 312 isolates were included in this evaluation; the number from each EIP site and the number for each included genus are shown in Table 2. A carbapenemase gene was identified in 94 (30%) of the 312 isolates. Seventy-two (65%) *Klebsiella* spp. isolates had a carbapenemase gene, of which 67 (93%) were KPC and 5 (7%) were NDM. Of all *Enterobacter* spp. and *E. coli* isolates, 14 (14%) and 8 (8%), respectively, had a carbapenemase gene, and all were KPC. The percentage of carbapenemase-producing CRE at the various sites was 73% in Maryland (40 [93%] KPC, 3 [7%] NDM); 30% in Minnesota (31 [94%] KPC, 2 [6%] NDM); 20% in Tennessee (13 [100%] KPC); 6% in New York (3 [100%] KPC); 7% in New Mexico (1 [100%] KPC); and 0 in Colorado.

The numbers and percentages of FPs and sFNs obtained with each of the 11 evaluated definitions are shown in Table 3. The percentage of FPs and sFNs ranged from 5.5% to 55.0% and 0.7% to 27.7%, respectively. The 3 phenotype-based definitions meeting the requirements for

Table 2. Isolates used in a study evaluating phenotype-based definitions for reliability in identifying carbapenemase producers among carbapenem-resistant enterobacterial isolates from 6 US Emerging Infections Program sites, January 1, 2011–January 30, 2014

Site	No. (%) isolates			Total no. isolates, N = 312
	Klebsiella spp., n = 111	*Enterobacter* spp., n = 103	*Escherichia coli*, n = 98	
Minnesota	30 (27)	63 (56)	19 (17)	112
Tennessee	17 (25)	11 (16)	41 (59)	69
Maryland	48 (81)	0	11 (19)	59
New York	11 (20)	20 (38)	22 (42)	53
New Mexico	5 (33)	6 (40)	4 (27)	15
Colorado	0	3 (75)	1 (25)	4

Table 3. False-positive and selected false-negative results in a study evaluating phenotype-based definitions for reliability in identifying carbapenemase producers among carbapenem-resistant enterobacterial isolates from 6 US Emerging Infections Program sites, January 1, 2011–January 30, 2014

Result	No. isolates/no. tested (%), by definition no., N = 307*										
	1	2	3	4	5	6	7	8	9	10	11
False-positive	117/307 (38.1)	82/307 (26.7)	91/307 (29.6)	169/307 (55.0)	57/307 (18.6)	146/307 (47.6)	153/307 (49.8)	60/307 (19.5)	37/307 (12.1)	34/307 (11.1)	17/307 (5.5)
Selected false-negative	12/307 (3.9)	15/307 (4.9)	13/307 (4.2)	2/307 (0.7)	17/307 (5.5)	7/307 (2.3)	4/307 (1.3)	27/307 (8.8)	85/307 (27.7)	85/307 (27.7)	85/307 (27.7)

*False-positive isolates are those meeting the definition but not found to produce a carbapenemase. Selected false-negative isolates were selected on the basis of nonsuceptibility to ≥1 carbapenem not meeting the definition but found to produce a carbapenemase. Definitions: 1, nonsusceptible to any carbapenem, excluding ertapenem; 2, nonsusceptible to any carbapenem, excluding ertapenem, and resistant to all third-generation cephalosporins tested (pre-2015 Centers for Disease Control and Prevention carbapenem-resistant Enterobacteriaceae surveillance definition); 3, nonsusceptible to any carbapenem, excluding ertapenem, and resistant to any third-generation cephalosporins tested; 4, resistant to any carbapenem; 5, resistant to any carbapenem, excluding ertapenem; 6, resistant to any carbapenem and resistant to all third-generation cephalosporins tested; 7, resistant to any carbapenem and resistant to any third-generation cephalosporin tested; 8, nonsusceptible to at least 2 carbapenems (ertapenem resistant, if tested); 9, nonsusceptible to any carbapenem (ertapenem resistant, if tested) and resistant to cefepime; 10, resistant to any carbapenem and resistant to cefepime; and 11, nonsusceptible to any carbapenem, excluding ertapenem, and resistant to cefepime.

the prespecified stratified analysis by site and genus were the one with the lowest number of sFNs (definition 4, resistant to any carbapenem); the one with the lowest number of FPs among definitions with potentially acceptable levels of sFNs, defined as <10% (definition 5, resistant to any carbapenem without ertapenem); and the pre-2015 CDC CRE surveillance definition (definition 2).

The numbers and percentages of FPs and sFNs obtained by using these 3 definitions are shown by EIP site in Table 4. The percentage of FPs was highest in Minnesota and Tennessee, and the percentage of sFNs was highest in Tennessee. The number and percentage of FPs and sFNs obtained by using the same 3 definitions are shown by organism tested in Table 5. The highest percentage of sFNs obtained by using definitions 2 and 5 were among *Klebsiella* spp.; overall, sFNs were generally lower for *E. coli* and *Enterobacter* spp. Of note, definition 4 had the narrowest variability in the percentage of sFNs across all sites (range 0%–1.5%) and among the 3 enterobacterial organisms (range 0%–1.1%). Of the 67 KPC-producing *Klebsiella* spp., 14 (21%), 1 (1%), and 14 (21%) did not meet definitions 2, 4, and 5, respectively. Of the 14 KPC-producing *Klebsiella* spp. isolates that did not meet definitions 2 and 5, a total of 12 (86%) were susceptible to all carbapenems tested except ertapenem. All 5 NDM-producing *Klebsiella* spp. met the 3 definitions.

A comparison of the MHT and PCR results by enterobacterial organism and carbapenem used in the MHT is shown in Table 6. The MHT showed no sFNs for all 3 organisms and a small number of FPs for *Klebsiella* spp. (3%) and *E. coli* (3%–4%); however, the MHT misclassified 31%–34% of non–carbapenemase-producing *Enterobacter* spp. as carbapenemase producers. The effect from adding the MHT to definition 4 is shown in Tables 4 and 5. Addition of the MHT to definition 4 decreased the overall percentage of FPs from 55% to 12%, but the percentage of sFNs remained at 0.7%. FPs were reduced substantially for *Klebsiella* spp. (from 27.9% to 2.7%) and *E. coli* (74.5% to 4%) but remained higher for *Enterobacter* spp. (29%).

Discussion

In this evaluation, no phenotype-based definition identified all carbapenemase-producing CRE without also capturing a substantial number of non–carbapenemase-producing CRE. The percentages of FPs and sFNs varied by enterobacterial organism and by EIP site, likely due to the underlying variation in the prevalence of carbapenemase-producing CRE in different areas and among different *Enterobacteriaceae*. In

Table 4. Results, by study site, for select phenotype-based definitions used to identify carbapenemase producers among 307 carbapenem-resistant enterobacterial isolates from 4 US EIP, Emerging Infections Program sites, January 1, 2011–January 30, 2014*

Site	No. isolates/no. tested (%), by definition no.†							
	2‡		4§		5¶		4 plus MHT#	
	FP	sFN	FP	sFN	FP	sFN	FP	sFN
Minnesota	51/111 (45.9)	3/111 (2.7)	55/111 (49.5)	1/111 (0.9)	25/111 (22.5)	5/111 (4.5)	23/111 (20.7)	1/111 (0.9)
Tennessee	17/65 (26.2)	4/65 (6.2)	50/65 (76.9)	1/65 (1.5)	18/65 (27.7)	4/65 (6.2)	3/65 (4.6)	1/65 (1.5)
Maryland	6/59 (10.2)	5/59 (8.5)	16/59 (27.1)	0/59	3/59 (5.1)	6/59 (10.2)	3/59 (5.1)	0/59
New York	4/53 (7.5)	2/53 (3.8)	31/53 (58.5)	0/53	8/53 (15.1)	1/53 (1.9)	3/53 (5.7)	0/53

*FP, false positive; MHT, the modified Hodge test; sFN, selected false negative.
†False-positive isolates are those meeting the definition but not found to produce a carbapenemase. Selected false-negative isolates were selected on the basis of nonsuceptibility to ≥1 carbapenem not meeting the definition but found to produce a carbapenemase.
‡Definition 2 nonsusceptible to any carbapenem, excluding ertapenem, and resistant to all third-generation cephalosporins tested (pre-2015 Centers for Disease Control and Prevention carbapenem-resistant Enterobacteriaceae surveillance definition).
§Definition 4, resistant to any carbapenem. This definition obtained the lowest number of selected false-negatives.
¶Definition 5, resistant to any carbapenem, excluding ertapenem. This definition obtained the lowest number of false-positives among definitions with selected false-negatives of ≤10%.
#Definition 4 (resistant to any carbapenem) plus MHT (i.e., 2-step testing).

Table 5. Results, by organism tested, for select phenotype-based definitions used to identify carbapenemase producers among 307 carbapenem-resistant enterobacterial isolates from 6 US Emerging Infections Program sites, January 1, 2011–January 30, 2014*

	Definition no., result, no. isolates/no. total (%)†							
	2‡		4§		5¶		4 plus MHT#	
Organism	False-positive	Selected false-negative	False-positive	Selected false-negative	False-positive	Selected false-negative	False-positive	Selected false-negative
Klebsiella spp.	15/111 (13.5)	14/111 (12.6)	31/111 (27.9)	1/111 (0.9)	11/111 (9.9)	14/111 (12.6)	3/111 (2.7)	1/111 (0.9)
Enterobacter spp.	42/102 (41.2)	0/102	68/102 (66.7)	0/102	26/102 (25.5)	0/102	30/102 (29.4)	0/102
Escherichia coli	25/94 (26.6)	1/94 (1.1)	70/94 (74.5)	1/94 (1.1)	20/94 (21.3)	3/94 (3.2)	3/94 (3.2)	1/94 (1.1)

*MHT, the modified Hodge test.
†False-positive isolates are those meeting the definition but not found to produce a carbapenemase. Selected false-negative isolates were selected on the basis of nonsuceptibility to ≥1 carbapenem not meeting the definition but found to produce a carbapenemase.
‡Definition 2 nonsusceptible to any carbapenem, excluding ertapenem, and resistant to all third-generation cephalosporins tested (pre-2015 Centers for Disease Control and Prevention carbapenem-resistant Enterobacteriaceae surveillance definition).
§Definition 4, resistant to any carbapenem. This definition obtained the lowest number of selected false-negatives.
¶Definition 5, resistant to any carbapenem, excluding ertapenem. This definition obtained the lowest number of false-positives among definitions with selected false-negatives of ≤10%.
#Definition 4 (resistant to any carbapenem) plus MHT (i.e., 2-step testing).

this sample of isolates, the pre-2015 CDC CRE surveillance definition misclassified nearly 13% of carbapenem-nonsusceptible *Klebsiella* spp. isolates and 21% of KPC-producing *Klebsiella* spp. isolates as non–carbapenemase producing. In light of this finding, a phenotype-based definition that captures all (or nearly all) carbapenemase-producing CRE should be considered for surveillance and prevention. However, our data demonstrate that alternative definitions that accomplish this also increase the number of FPs and thus have the potential to increase the amount of work and the cost associated with CRE surveillance and prevention efforts.

Current efforts to control CRE in the United States have used infection prevention strategies targeted at carbapenemase-producing strains; however, most clinical laboratories do not routinely differentiate carbapenemase-producing from non–carbapenemase-producing strains. Molecular detection of genes encoding carbapenemases is the reference standard for identifying carbapenemase-producing CRE, but this testing requires substantial expertise and expense. More readily available tests, like the MHT, could likely be performed in most clinical microbiology laboratories, but they require additional technician time and reagents, which creates a burden on laboratory resources and therefore limits their routine use. In addition, the MHT might falsely identify NDM-producing strains as non–carbapenemase-producing CRE and might falsely identify non–carbapenemase-producing *Enterobacter* spp. as carbapenemase-producing CRE (*13*). Another carbapenemase detection test, the Carba-NP, has good performance characteristics and may be a viable alternative; however, it is not yet widely used (*13–16*). Because of the limited availability and technical challenges associated with resistance-mechanism testing for CRE, a definition for CRE that increases detection of carbapenemase-producing strains while reasonably limiting the number of non–carbapenemase-producing strains identified would aid surveillance and infection control efforts until resistance-mechanism–based testing becomes more routinely available.

Our results show that the use of definition 4 (resistant to any carbapenem) obtained one of the lowest percentages of sFN results. In addition, between EIP sites and between the 3 enterobacterial organisms, there was little variability in the percentage of isolates with sFN results, suggesting the results may be reflective of what other hospitals in the United States might experience when using this CRE definition to capture carbapenemase-producing CRE isolates. In January 2015, CDC modified its surveillance definition for CRE. The change was made partly because of the results of findings from this evaluation but also as an effort to simplify the CRE surveillance definition so that it can be applied more easily. The new definition (resistant to imipenem, meropenem, doripenem, or ertapenem or documentation that the isolate possesses a carbapenemase) is to be used with current CLSI breakpoints (*10*). To further reduce the number of non–carbapenemase-producing CRE strains falsely identified as carbapenemase-producing CRE, health care facilities could consider adding resistance-mechanism testing for isolates that meet this definition. Such testing may be particularly helpful in areas with a low prevalence of CRE

Table 6. Results for modified Hodge test evaluation of 312 enterobacterial isolates from 6 US Emerging Infections Program sites, January 1, 2011–January 30, 2014

Organism, carbapenem used	False-positive results, %	Selected false-negative results
Klebsiella spp.		
Meropenem	2.7	0
Ertapenem	2.7	0
Enterobacter spp.		
Meropenem	31	0
Ertapenem	34	0
Escherichia coli		
Meropenem	3	0
Ertapenem	4	0

and with organisms that are less likely to produce carbapenemases (e.g., *E. coli* and *Enterobacter* spp.).

This evaluation has several limitations. First, our testing collection consisted of a relatively small number of isolates from a limited number of sites, and because strain typing was not performed on any of the isolates included in this analysis, we cannot exclude the possibility that some of these isolates might have been related to each other. However, this evaluation did include isolates from diverse locations in the United States that represent areas with low and relatively high prevalences of CRE. Second, isolates from only 3 genera were included, limiting the generalizability of any conclusions beyond these organisms. Last, our sample included mostly KPC-producing CRE among the carbapenemase-producing strains. These results may not be applicable to other emerging carbapenemases, specifically NDM and OXA. However, current epidemiology suggests that KPC remains the most common carbapenemase in the United States.

In conclusion, the pre-2015 CDC CRE surveillance definition failed to identify some carbapenemase-producing strains. A definition that includes only resistance to any 1 of the 4 approved carbapenems is simpler and misses fewer carbapenemase-producing strains, but at the cost of increasing FPs. The addition of the MHT to this definition further limits FPs; however, this testing is not routinely used in the United States. In general, all organisms that are nonsusceptible to a carbapenem are potentially multidrug-resistant and, at minimum, warrant the use of interventions such as contact precautions to minimize transmission. Health care facilities could choose to reserve more aggressive interventions, such as screening of contacts and patient cohorting, for patients with isolates that meet this new definition, which appears to more completely detect carbapenemase-producing CRE. Health care facilities wishing to limit the work and expense associated with more aggressive interventions could perform resistance-mechanism testing on isolates meeting this new definition and apply interventions only when the isolates are confirmed to produce carbapenemase.

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Socioeconomic Status and Foodborne Pathogens in Connecticut, USA, 2000–2011[1]

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Foodborne pathogens cause >9 million illnesses annually. Food safety efforts address the entire food chain, but an essential strategy for preventing foodborne disease is educating consumers and food preparers. To better understand the epidemiology of foodborne disease and to direct prevention efforts, we examined incidence of *Salmonella* infection, Shiga toxin–producing *Escherichia coli* infection, and hemolytic uremic syndrome by census tract–level socioeconomic status (SES) in the Connecticut Foodborne Diseases Active Surveillance Network site for 2000–2011. Addresses of case-patients were geocoded to census tracts and linked to census tract–level SES data. Higher census tract–level SES was associated with Shiga toxin–producing *Escherichia coli*, regardless of serotype; hemolytic uremic syndrome; salmonellosis in persons ≥5 years of age; and some *Salmonella* serotypes. A reverse association was found for salmonellosis in children <5 years of age and for 1 *Salmonella* serotype. These findings will inform education and prevention efforts as well as further research.

Foodborne diseases cause considerable illness, hospitalization, and death in the United States. Each year, an estimated 9.4 million illnesses, 56,000 hospitalizations, and 1,351 deaths can be attributed to the consumption of food products contaminated by 31 major pathogens (*1*). *Salmonella* and Shiga toxin–producing *Escherichia coli* (STEC) are leading bacterial causes of foodborne illness in the United States and result in a combined estimated 1.2 million cases of gastrointestinal illness, ≈22,000 hospitalizations, and 400 deaths per year (*1*).

Food safety is a high priority in the United States (*2*). Although food safety efforts address the entire food chain from production to the retail level (*3*), these processes do not guarantee that food products, especially uncooked fresh foods, are free from potentially pathogenic bacteria. Therefore, an essential strategy for preventing foodborne disease involves educating food preparers and consumers about preventive measures that can be taken in food handling, cooking, and selection of foods to eat (*4*).

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Despite regulatory efforts to improve food supply safety, the incidence of illnesses caused by some foodborne pathogens, including *Salmonella*, has changed little in recent years (*5*). Other than what is known about foodborne illness in younger and older age groups, little is known about which demographic groups in the United States are at highest risk for *Salmonella* or STEC infection and which groups should be targeted for educational efforts. Demographic data other than age and sex, such as income and education level, are not usually available through routine surveillance of illnesses from these infections.

An approach rarely used to identify demographic groups at high risk for bacterial foodborne infections is to examine incidence by area-based socioeconomic status (ABSES) measures. Surveillance data usually include street addresses of residences of persons diagnosed with foodborne infections, making use of ABSES possible. Census tract–level poverty, in particular, is a validated ABSES measure recommended by the Public Health Disparities Geocoding Project on the basis of a series of exhaustive studies (*6*). A previous Connecticut study assessing incident *Campylobacter* data that used census tract–level poverty found that adults and children ≥10 years of age who lived in census tracts where <5% of residents lived below the federal poverty level had twice the risk for campylobacteriosis of those living in census tracts where ≥20% lived below the federal poverty level (*7*). By contrast, children <10 years of age who lived in the lowest SES census tracts had a 1.4-fold higher risk for campylobacteriosis than those living in the highest SES census tracts (*7*). A study in Denmark, where individual SES data were available, found that *Campylobacter* and *Salmonella enterica* serotype Enteritidis were associated with high SES but found no association with *S. enterica* ser. Typhimurium or STEC (*8*). A study that used ABSES to examine *Salmonella* incidence in Michigan, USA, found that persons living in census block groups with high education levels had a higher incidence of *Salmonella* infection than persons living in block groups with lower education levels (*9*).

[1]Preliminary results from this study were presented at the 2014 Annual Conference of the Council of State and Territorial Epidemiologists; June 23–25, 2014; Nashville, Tennessee, USA.

Our study sought to describe the incidence of *Salmonella* (in general and for leading serotypes) and of STEC (O157, non-O157, and hemolytic uremic syndrome [HUS]) for 2000–2011 by census tract–level SES and to assess whether findings changed over time. Our goal was to help direct public health educational efforts to decrease illness from these foodborne pathogens.

Methods

Case Identification and Data Collection

This analysis used data from the Foodborne Diseases Active Surveillance Network (FoodNet) in Connecticut for all incident cases of *Salmonella* and STEC infection with onset during 2000–2011. *Salmonella*, *Escherichia coli* O157:H7 gastroenteritis, Shiga toxin–related disease, and HUS are reportable by physicians and laboratories in Connecticut. All isolates of *Salmonella* and *E. coli* O157:H7 and broths from positive Shiga toxin test results are sent to the Connecticut Department of Public Health (DPH) Laboratory for confirmation, isolation (Shiga toxin–positive broths), and serotyping (*10*). Demographic information was abstracted from the case report form, including street address, age, and sex of case-patients.

Geocoding of Case-Patients and Census Tract–Level SES

Street addresses were geocoded in ArcGIS 10.1 (Esri, Redlands, CA, USA) by using Topologically Integrated Geographic Encoding and Referencing shape files from the US Census Bureau and either a US street locator or a North American address locator. If automatic ArcGIS settings were unsuccessful, interactive geocoding was performed. Case-patients whose addresses were geocoded were matched to census tracts by using a spatial join in ArcGIS: those for 2000–2005 were spatially joined to census tracts by using the 2000 Census; those for 2006–2011 were joined to census tract designations from the 2010 Census. Census tract-specific SES data for percentage of the population living below the federal poverty line were taken from the 2000 Census for case-patients for 2000–2005 (*11*) and from the 2006–2010 American Community Survey for case-patients for 2006–2011 (*12*). Census tract–level SES was categorized into 4 groups based on percentage of residents living below the federal poverty line: <5%, 5%–9.9%, 10%–19.9%, and ≥20% (*6*).

Statistical Analysis

Statistical analysis was limited to case-patients whose address could be geocoded and successfully linked to a census tract. During 2000 and 2010, data were missing for 7 (<1%) census tracts, so they could not be assigned to a poverty category, but no case-patients resided in these tracts. All case-patients were aggregated into 3 age categories on the basis of similar age-specific incidence rates: 0–4, 5–9, and ≥10 years of age for *Salmonella* cases and 0–4, 5–17, and ≥18 years of age for STEC cases. Within age groups, case-patients in each SES category were aggregated to determine the numerator for each group. Denominators by age group for each census tract were obtained from the 2000 Census for case-patients for 2000–2005 and from the 2010 Census for case-patients for 2006–2011 (*13*,*14*). Denominators were similarly aggregated to create age-specific denominators by SES category. Crude, age-adjusted, and age-specific incidence rates (IRs) per 100,000 person-years for all *Salmonella*, STEC, and HUS case-patients were calculated for each SES category. Age-adjusted rates were calculated by using direct standardization with weights taken from the US 2000 Standard Populations (*15*). Age-adjusted IRs per 100,000 person-years were also calculated for each of the 9 leading *Salmonella* serotypes and for O157 and non-O157 STEC subtypes. Incidence rate ratios (IRRs) were calculated for age-adjusted rates for SES categories by using the <5% poverty group as the reference. IRRs were calculated separately for all *Salmonella*, STEC, and HUS case-patients and for the leading *Salmonella* serotypes and O157 and non-O157.

Associations between *Salmonella*, STEC, and HUS incidence and census tract–level SES were examined by using χ^2 tests for trend to test the statistical significance of the gradients among the 4 categories. All analyses were conducted by using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) except χ^2 tests for trend, which were calculated by using Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Results

Overall, the SES category with the most persons in Connecticut was the highest SES group, <5% below the poverty line (55.2% of the population during 2000–2005 and 48.9% during 2006–2011). The lowest SES group, ≥20% below the federal poverty level, was the smallest for both periods (10.5% and 12.4% of the population, respectively).

Salmonella Infection

During 2000–2011, a total of 5,484 case-patients with *Salmonella* infection confirmed by culture were reported to the Connecticut DPH and FoodNET. Of these, 5,204 (94.9%) were matched to a census tract. Case-patients that could not be matched did not differ from matched case-patients by age group or sex; however, a higher percentage of case-patients could not be matched during the earlier years of surveillance than in the later years (8.1% in 2000–2002 vs. 3.0% in 2009–2011; p<0.001). Serotype information was available for all but 1 case-patient. The most frequently observed serotypes were Enteriditis (n = 1,350, 25.9%),

Typhimirium and its variants (n = 1,000, 19.2%), Newport (n = 353, 6.8%), and Heidelberg (n = 178, 3.4%). The overall *Salmonella* IR for 2000–2011 was 12.43 cases per 100,000 person-years. Younger children had the highest IRs; children 0–4 years of age had a 3.47-fold higher rate and children 5–9 years of age a 1.46-fold higher rate of *Salmonella* infection than those ≥10 years of age (Table 1). The *Salmonella* IR in the last 6 years of the study period (2006–2011) was 5.6% higher than for the first 6 years (12.75 vs. 12.08; p = 0.05). No statistical differences were found in *Salmonella* incidence by sex.

Higher census tract–level SES was associated with higher crude *Salmonella* incidence for all 12 years of data combined (Table 1), for each of the two 6-year periods (data not shown), and among children 5–9 and ≥10 years of age (Table 1). A reverse association was found for the 0–4 year age group. The highest *Salmonella* IRs occurred in the 2 lowest SES groups (≥20% = 39.38 and 10%–19.9% = 42.76); the lowest IRs occurred in the 2 highest SES groups (5%–9.9% = 33.46 and <5% = 34.63) (Table 1).

The overall association of higher *Salmonella* incidence with higher SES was amplified after age-adjustment; the lowest SES group had a 0.86-fold lower IRR than the highest SES group (13.18 vs. 11.34; p = 0.01; Table 2). Notable differences in age-adjusted rates also occurred for individual *Salmonella* serotypes. Although the same association of higher incidence and higher census tract–level SES was found for serotypes Enteriditis (IRR 0.67 lowest vs. highest SES groups, p <0.001), Newport (IRR 0.53, p = 0.002), and Montevideo (IRR 0.52, p = 0.046), a reverse gradient of higher incidence and lower census tract–level SES was found for serotype Heidelberg (IRR 1.94, p = 0.001; Table 2). When *S. enterica* ser. Heidelberg was examined by age group, only children 0–4 years of age had a significant association with census tract–level SES; this group of children in the lowest SES group had a 4.98-fold higher IRR than this age group in the highest SES group (p<0.001). No other serotype had an association with census tract–level SES, including Typhimurium, the second most common serotype.

STEC

During 2000–2011, a total of 764 case-patients with STEC confirmed by culture were reported to the Connecticut DPH and FoodNET. Of these, 744 (97.4%) were matched to a census tract. Those that could not be matched did not differ from matched cases. The most frequently observed serotypes were STEC O157 (n = 471, 63.3%), O103 (n = 55, 7.4%), O111 (n = 51, 6.0%), O26 (n = 42, 5.6%), and O45 (n = 26, 3.5%). The overall STEC IR for 2000–2011 was 1.78 case-patients/100,000 person-years. Younger children had higher IRs than persons ≥18 years; children 0–4 years of age had a 4.81-fold higher rate of STEC than those ≥18 years of age, and those 5–17 years of age had a 3.96-fold higher rate of STEC than those ≥18 years of age. The STEC IR in the last 6 years of the study period (2006–2011) was 16% lower than in the first 6 years (1.65 vs. 1.91; p = 0.05). Female patients across all age groups had a 1.31-fold higher IR for STEC than male patients (p<0.001).

Higher census tract–level SES was associated with higher crude STEC incidence for all 12 years of data combined (Table 3), within each 6-year period (data not shown), and for each of the 3 age groups (Table 3). The association was stronger for those ≥5 years of age (IRR for highest SES vs. lowest SES group = 6.21 for persons 5–17 years of age and 4.06 for persons ≥18 years of age; p<0.001 for each) and lower for children ≥4 years of age (IRR = 1.73; p = 0.054; Table 3).

Table 1. Incidence of salmonellosis by age group and census tract–level SES, Connecticut, USA, 2000–2011*

Age group	Census tract–level SES, % living below poverty level					p value†
	Total	<5	5–9.9	10–19.9	≥20	
All ages						
Case-patients, no.	5,204	2,797	1,078	772	557	<0.001
Person-years	41,877,972	21,746,820	8,823,930	6,478,176	4,802,394	
Rate‡	12.43	12.86	12.22	11.92	11.60	
0–4 y						
Case-patients, no.	931	429	170	185	147	0.058
Person-years	2,552,700	1,238,688	508,140	432,696	373,176	
Rate‡	36.47	34.63	33.46	42.76	39.38	
5–9 y						
Case-patients, no.	431	262	66	57	46	0.029
Person-years	2,800,290	1,484,166	539,844	420,924	355,356	
Rate‡	15.39	17.65	12.23	13.54	12.94	
≥10 y						
Case-patients, no.	3,842	2,106	842	530	364	<0.001
Person-years	36,524,982	19,023,966	7,775,946	5,624,556	4,073,862	
Rate‡	10.52	11.07	10.83	9.42	8.94	

*A total of 2,221 persons were living in census tracts unable to be classified by SES level. SES, socioeconomic status.
†By χ^2 test for trend.
‡No. cases/100,000 person-years.

Table 2. Age-adjusted incidence rates and age-adjusted rate ratios of salmonellosis and 9 leading *Salmonella enterica* serotypes by census tract–level SES, Connecticut, USA, 2000–2011*

Salmonella serotype	Census tract–level SES, % living below poverty level				p value†
	<5	5–9.9	10–19.9	≥20	
Total,, N = 5,204					0.012
Age-adjusted IR	13.18	12.50	12.02	11.34	
Age-adjusted IRR	1.00	0.95	0.91	0.86	
Enteriditis,, n = 1,350					<0.001
Age-adjusted IR	3.72	3.09	2.40	2.51	
Age-adjusted IRR	1.00	0.83	0.65	0.67	
Heidelberg, n = 178					0.001
Age-adjusted IR	0.35	0.46	0.47	0.68	
Age-adjusted IRR	1.00	1.31	1.34	1.94	
Montevideo, n = 98					0.046
Age-adjusted IR	0.27	0.28	0.16	0.14	
Age-adjusted IRR	1.00	1.04	0.59	0.52	
Newport, n = 353					0.002
Age-adjusted IR	0.94	0.86	0.77	0.50	
Age-adjusted IRR	1.00	0.91	0.82	0.53	
Oranienburg, n = 109					0.472
Age-adjusted IR	0.29	0.23	0.27	0.23	
Age-adjusted IRR	1.00	0.79	0.93	0.79	
Saintpaul, n = 130					0.053
Age-adjusted IR	0.29	0.29	0.29	0.47	
Age-adjusted IRR	1.00	1.00	1.00	1.62	
I 4,[5],12:i:-, n = 134					0.585
Age-adjusted IR	0.33	0.27	0.40	0.36	
Age-adjusted IRR	1.00	0.82	1.21	1.09	
Thompson, n = 96					0.441
Age-adjusted IR	0.26	0.20	0.22	0.21	
Age-adjusted IRR	1.00	0.77	0.85	0.81	
Typhimurium, n = 1,000					0.913
Age-adjusted IR	2.41	2.53	2.57	2.40	
Age-adjusted IRR	1.00	1.05	1.07	1.00	

*IR, incidence rate; IRR, incidence rate ratio, SES, socioeconomic status. Age-adjusted IRs calculated/100,000 persons; Reference category for age-adjusted IRRs is <5% poverty.
†By χ^2 test for trend.

As with *Salmonella*, the overall association of higher STEC incidence with higher census tract–level SES was stronger after age adjustment (Table 4); the IRR for the lowest versus the highest SES group was 0.26 (p<0.001; Table 4). This association occurred for E. *coli* O157 and for non-O157 STEC (IRRs of 0.24 and 0.29, respectively; p<0.001 for each; Table 4). We also examined the age-adjusted incidence and its relationship with census tract–level SES for the much smaller number of HUS cases (n = 49). The same association of higher HUS incidence with higher SES was found. The IRR for the lowest versus the highest SES census tracts was 0.25 (p = 0.007; Table 4).

Discussion

Few studies are available that examine the relationship between foodborne disease incidence and socioeconomic status. Our study showed the following key findings: 1) STEC disease, whether caused by O157 or non-O157 serotypes or whether manifested as HUS, was uniformly associated with high census tract SES; 2) salmonellosis in persons 5–9 and ≥10 years of age was associated with high census tract SES, whereas salmonellosis in children <5 years of age was associated with low census tract SES; and 3) different *Salmonella* serotypes had different associations with census tract SES, with serotypes Enteriditis, Newport, and Montevideo associated with high census-tract SES, serotype Heidelberg associated with low census-tract SES, and serotype Typhimurium having no association. These findings provide additional information about the epidemiology of these foodborne diseases and should inform efforts to reduce their incidence.

Our findings study are similar to those found in a study of campylobacteriosis in Connecticut during the same period (*7*): higher disease incidence among those living in higher SES census tracts. A previous study in Michigan found that *Salmonella* incidence increased with higher education and income levels (*9*). An analysis of recent FoodNet data by race/ethnicity showed that overall STEC rates were highest for whites (a surrogate for higher SES) and lowest for blacks (a surrogate for lower SES) (*16*). The current study results were consistent with results from these studies that examined surrogates for SES.

Several explanations have been suggested to explain why persons in higher SES census tracts might have higher incidence of *Salmonella* and STEC infections and HUS (and *Campylobacter* infection), compared with persons

Table 3. Incidence of STEC by age group and census tract–level SES, Connecticut, USA, 2000–2011*

All STEC, N = 744	Census tract–level SES, % living below poverty level					p value†
	Total	<5	5–9.9	10–19.9	≥20	
All ages						<0.001
Case-patients, no.	744	498	138	77	31	
PY	41,877,972	21,746,820	8,823,930	6,478,176	4,802,394	
Rate‡	1.78	2.29	1.56	1.19	0.65	
0–4 y						
Case-patients, no.	124	69	25	18	12	0.054
PY	2,552,700	1,238,688	508,140	432,696	373,176	
Rate‡	4.86	5.57	4.92	4.16	3.22	
5–17 y						
Case-patients, no.	296	220	49	19	8	<0.001
PY	7,399,518	3,977,634	1,435,740	1,088,280	897,636	
Rate‡	4.00	5.53	3.41	1.75	0.89	
≥18 y						
Case-patients, no.	324	209	64	40	11	<0.001
PY	31,925,754	16,530,498	6,880,050	4,957,200	3,531,582	
Rate‡	1.01	1.26	0.93	0.81	0.31	

*PY, person-years; SES, socioeconomic status; STEC, Shiga toxin–producing *Escherichia coli*. Includes 2,221 persons living in census tracts unable to be classified by socioeconomic level.
†p-value is for χ^2 test for trend.
‡Rate = number of cases/100,000 person-years.

in lower SES census tracts. A commonly proposed reason is that those living in areas with higher census tract–level SES might have increased access to care and might be more likely to submit specimens, regardless of disease severity, whereas those in lower socioeconomic groups might seek care or diagnostic testing only when illness is serious or prolonged (*8*,*9*,*17*). Several lines of evidence argue against this explanation in the United States. For 2000–2003, FoodNET assessed factors associated with seeking medical care and submitting a fecal specimen among persons with acute diarrheal illness and found that ≈20% of persons with acute diarrheal diseases sought medical care, 19% of whom submitted a fecal specimen (*18*). The analysis found that a household income <$25,000 was associated with seeking medical care (*18*). This association of lower income with seeking medical care for diarrheal illness, the uniform trend of increasing incidence from lowest to highest SES group, and the opposite association for some *Salmonella* serotypes indicate that medical-seeking behavior is not a major explanatory factor for our results. Furthermore, HUS, a disease almost always requiring hospitalization and thus less subject to potential health-seeking bias, had the same association with higher SES as did milder forms of STEC infection.

The more likely explanation for these findings is that SES affects the prevalence of known high-risk factors, such as international travel, consumption of high-risk food items (e.g., raw fruits and vegetables and undercooked meat), and eating at restaurants (*16*). That is, high SES itself is not a risk factor but rather a surrogate for certain high-risk behaviors. An analysis of the Connecticut portion of 3 FoodNet population surveys during 2000–2007 found that higher-income residents were more likely than lower-income residents to have traveled internationally, eaten in restaurants, and eaten chicken in the previous 7 days (*17*). An analysis of population survey data from the 2006–2007 Connecticut FoodNet found that residents with higher SES ZIP codes were more likely than those with lower SES ZIP codes to have eaten fresh hamburger at home that was pink, to have consumed salad containing lettuce or greens, and to have traveled internationally in the previous 7 days (J. Wagner, unpub. data). Studies outside the Connecticut FoodNET have had similar results. Several studies have found that contaminated raw fruits and vegetables are a growing source of outbreaks in the United States and have increased in both numbers and proportions of all reported foodborne outbreaks (*19*,*20*). A recent food attribution study attributed 32% of all bacterial foodborne illnesses, of which *Salmonella* and STEC make up a large proportion, to produce commodities, including fruits, nuts, and vegetables of the fungi, leafy, root, sprout, and vine-stalk variety (*21*). High SES is associated with more fruit and vegetable consumption, which may be an explanatory factor for our findings. A study in the United States found that higher neighborhood SES was positively associated with fruit and vegetable intake and that an increase of 1 SD in neighborhood SES was associated with 2 additional servings of fruit and vegetables per week (*22*). Low SES communities often have access to fast food and prepackaged food but lack adequate supermarkets, which causes limited access to fresh fruits and vegetables (*23*,*24*). In addition, ≈40% of adolescents from low SES backgrounds have less than daily consumption of fruits and vegetables (*25*). A study addressing fruit and vegetables as vehicles for transmission of foodborne pathogens found that the association of *Salmonella* with fresh produce appears to be serotype-specific because of adhesion mechanisms in some serotypes (*26*), a finding that may partly explain why the

Table 4. Age-adjusted incidence rates and age-adjusted rate ratios of STEC O157, non-O157, and HUS by census tract–level SES, Connecticut, USA, 2000–2011*

STEC category	Census tract–level SES, % living below poverty level				p value†
	<5	5–9.9	10–19.9	≥20	
All STEC, N = 744					<0.001
Age-adjusted IR	2.36	1.67	1.22	0.62	
Age-adjusted IRR	1.00	0.71	0.52	0.26	
STEC O157, n = 471					<0.001
Age-adjusted IR	1.48	1.20	0.70	0.36	
Age-adjusted IRR	1.00	0.81	0.47	0.24	
STEC non-O157, n = 273					<0.001
Age-adjusted IR	0.89	0.48	0.52	0.26	
Age-adjusted IRR	1.00	0.54	0.58	0.29	
HUS, n = 49					<0.001
Age-adjusted IR	0.16	0.17	0.03	0.04	
Age-adjusted IRR	1.00	1.04	0.19	0.25	

*IR, incidence rate; IRR, incidence rate ration; HUS, hemolytic uremic syndrome; SES, socioeconomic status; STEC, Shiga toxin–producing *Escherichia coli*. Age-adjusted IRs calculated/100,000 persons; Reference *category* for age-adjusted IRRs is <5% poverty.
†By χ^2 test for trend.

association of higher SES with higher incidence was seen only among some serotypes of *Salmonella*.

In contrast to the findings in adults, children <5 years of age who live in low SES census tracts were more likely than those living in high SES census tracts to have *Salmonella* infection. In addition, all persons with *S. enterica* ser. Heidelberg infection were more likely to live in a low SES census tract. These findings are novel: the Michigan study did not look at age, and no reported studies in the United States have systematically examined the relationship between census tract–level SES and *Salmonella* serotype incidence. However, the previously published Connecticut campylobacteriosis study had similar findings: children living in low SES census tracts had the highest incidence (*7*,*27*). Several studies have shown that young children in low SES circumstances are more likely to be exposed to raw meat–contaminated surfaces inside and outside the home (e.g., in shopping carts in grocery stores) (*16*,*17*). Also, different *Salmonella* serotypes are associated with different food items (*21*). *S. enterica* ser. Heidelberg has been associated with the consumption of eggs and poultry (*28*–*30*), and a study assessing *Salmonella* prevalence in 6 commodities at point of processing found high prevalence of *S. enterica* ser. Heidelberg in chicken and turkey (*31*). Possibly, more eggs and poultry are consumed in lower SES groups than in higher SES groups.

Our findings have several implications for risk communication and research. Efforts could be made to increase awareness among persons in high SES groups about their relatively high risk for STEC and *Salmonella* infection and about what actions they can take to reduce risk. Education campaigns about high-risk foods other than meat and about the importance of properly handling produce could be run in publications with a higher SES target audience. Regarding research, several considerations need to be explored further. Whether our findings in Connecticut are representative of STEC and salmonellosis incidence nationwide is unknown. The specific reasons behind SES-related risk for foodborne illness still need to be made clear, including for each of the leading *Salmonella* serotypes. For young children with salmonellosis, potential intervention points to reduce exposure inside and outside the home need to be identified. It remains unclear why children living in areas of higher SES are more at risk for STEC infection and HUS than children living in lower SES areas. These unanswered questions need to be investigated so that effective consumer-level interventions can be developed.

This study has several limitations. First, it was limited to data from Connecticut, and findings might not be generalizable to other states. Second, SES information was unavailable for 7 census tracts; however, they accounted for <1% of all census tracts in Connecticut. Third, although the data came from active surveillance and are therefore complete within the context of laboratory-confirmed disease, not all persons with gastrointestinal illness seek medical care or have diagnostic testing (*1*,*18*), so these data are underestimates of the true incidence of STEC and salmonellosis. Fourth, this study used SES measured at the census tract, not individual level; the results of this analysis should be understood and interpreted within this context. Finally, we did not look at the consistency of the associations of incidence with SES for different adult age groups but assumed they were similar.

Public health infrastructure objective 7.3 of Healthy People 2020 stresses the need to "increase the proportion of population-based Healthy People 2020 objectives for which national data are available by socioeconomic status" (*32*). This study provides additional evidence that area-based SES measures such as census tract–level poverty, especially if other SES measures are unavailable, can be useful for describing the incidence of foodborne illnesses. Our findings show differences in STEC and *Salmonella* serotype-specific incidence by census tract–level SES. The findings suggest direction for risk communication efforts

and for additional studies to explain the differences and to facilitate additional education and outreach activities.

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Incidence of Clinician-Diagnosed Lyme Disease, United States, 2005–2010

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National surveillance provides important information about Lyme disease (LD) but is subject to underreporting and variations in practice. Information is limited about the national epidemiology of LD from other sources. Retrospective analysis of a nationwide health insurance claims database identified patients from 2005–2010 with clinician-diagnosed LD using International Classification of Diseases, Ninth Revision, Clinical Modification, codes and antimicrobial drug prescriptions. Of 103,647,966 person-years, 985 inpatient admissions and 44,445 outpatient LD diagnoses were identified. Epidemiologic patterns were similar to US surveillance data overall. Outpatient incidence was highest among boys 5–9 years of age and persons of both sexes 60–64 years of age. On the basis of extrapolation to the US population and application of correction factors for coding, we estimate that annual incidence is 106.6 cases/100,000 persons and that ≈329,000 (95% credible interval 296,000–376,000) LD cases occur annually. LD is a major US public health problem that causes substantial use of health care resources.

Lyme disease (LD) is a zoonotic infection transmitted by *Ixodes* spp. ticks and caused by the spirochete *Borrelia burgdorferi*. Signs and symptoms of infection range in severity and can include erythema migrans, arthritis, facial palsy, radiculoneuropathy, arrhythmia, and meningitis. Most patients recover fully after antimicrobial treatment (*1*,*2*); however, serious illness and even deaths have been reported, although rarely (*3*–*5*). In the United States, LD is the fifth most commonly reported nationally notifiable disease; ≈36,000 confirmed and probable cases were reported in 2013 (*6*). US cases are concentrated heavily in the Northeast and upper Midwest (*7*).

Surveillance for LD in the United States is based on reports submitted by laboratories and health care providers to state and local health departments. These reports provide valuable insight into the age and sex distribution of patients with LD and the seasonality and geographic distribution of cases, and they enable monitoring of disease trends over time. Unfortunately, underreporting and variation in surveillance practices limit the ability of routine surveillance to capture the true overall frequency of LD within the population (*8*). Studies conducted during the 1990s in high-incidence states suggest that LD cases are underreported by a factor of 3 to 12 (*9*–*12*). These studies were limited to specific states and do not necessarily reflect underreporting nationwide.

Medical claims data provide an additional source of information about the epidemiology and public health importance of LD. Because these data are based on billing records submitted by clinicians for reimbursement, they are less prone to underreporting than are routine surveillance data that require additional documentation. We used information from a large, nationwide medical claims database to 1) describe the epidemiology of LD diagnosed by clinicians, 2) identify similarities and differences with surveillance data, and 3) estimate the number of LD cases per year in the United States.

Methods

Medical Claims Database

During 2013–2014, we retrospectively analyzed the 2005–2010 Truven Health MarketScan Commercial Claims and Encounters Database, which contains health insurance claims information for a median of 27 million persons each year. The database contains records for persons 0–64 years of age with employer-provided health insurance and includes information about employees and their spouses and dependents from all 50 states. Deidentified data on enrollee demographics, outpatient and emergency department visits, inpatient admissions, and prescription drugs are included.

Each patient encounter record is assigned ≥1 diagnostic code from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), by a clinician or billing specialist. Inpatient admissions in the

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database include 1 principal diagnosis and up to 14 secondary diagnoses. Outpatient encounters include up to 4 associated ICD-9-CM codes but do not distinguish between principal and secondary diagnoses. Medication information is available for most enrollees for prescription drugs filled at outpatient pharmacies.

Epidemiology of Clinician-Diagnosed LD in the MarketScan Database

The study population comprised persons enrolled in a participating health plan for the entirety of any year during 2005–2010 and for whom prescription drug information was available. For this analysis, we defined an inpatient event as a hospital admission with the ICD-9-CM code for LD (088.81) as the principal diagnosis or the 088.81 code as a secondary diagnosis plus a principal diagnosis consistent with an established manifestation of LD or plausible co-infection (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/9/15-0417-Techapp1.pdf).

We defined an outpatient event as any outpatient or emergency department visit with the 088.81 code plus a prescription filled for an antimicrobial drug recommended by the Infectious Diseases Society of America for LD treatment (*13*). Three additional antimicrobial drugs also were included because they were closely related to a recommended antimicrobial drug or were a known historical treatment that some practitioners might still prescribe (online Technical Appendix). Only prescriptions of at least 7 days' duration and filled ±30 days from the visit date were considered.

The first outpatient or inpatient event of each year that met the study definition was considered the incident diagnosis for a patient. The date of admission or first outpatient visit that met study inclusion criteria was considered the date of the event. A separate LD diagnosis that met inclusion criteria at least 1 year after the previous diagnosis was included as a new incident event. When both an outpatient event and inpatient admission occurred within 1 year, only the inpatient admission was considered. To maintain consistency with US surveillance data, location was based on the patient's county of residence, not where care was provided.

National Surveillance and US Population Data

State and local health officials report LD cases to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Diseases Surveillance System according to standardized case definitions (*14*). For comparison with MarketScan findings, we analyzed surveillance cases reported during 2005–2010. Cases reported during 2005–2007 reflected a surveillance case definition comprising confirmed cases only. Beginning in 2008, a revised case definition was in place that altered the laboratory criteria and distinguished between confirmed and probable cases; cases reported during 2008–2010 included both categories (*15*). US Census 2010 population data were used for population comparisons and extrapolations (*16*).

Estimation of the Number of Clinician-Diagnosed LD Cases

To estimate the total number of patients with clinician-diagnosed LD in the United States, we calculated age- and county-specific rates derived from the MarketScan database and applied them to the 2010 population of each corresponding county. Counts for all US counties were then summed. Because the MarketScan database is limited to persons <65 years of age, these calculations do not include clinician-diagnosed cases among persons ≥65 years. To adjust for this exclusion, we multiplied by a correction factor of 1.17. This correction factor was inferred from the age distribution of LD patients reported through national surveillance. During 2005–2010, persons <65 years of age accounted for 85.8% of LD cases reported through national surveillance. Therefore, we multiplied the estimated number of cases among persons <65 years by 1.00/0.858, or 1.17, to arrive at an estimate of cases in all age groups.

The estimated number of patients with clinician-diagnosed LD was based on extraction of a single ICD-9-CM code. Research has shown, however, that clinician diagnosis of a medical condition does not necessarily correlate with existence of the ICD-9-CM code in the chart (*17*,*18*). The primary reasons are coding errors and inclusion of codes for accompanying symptoms but not the specific disease (e.g., coding for joint pain but not LD) (*17*,*19*). To correct for omission of the 088.81 code, we relied on 4 evaluations of coding patterns for patients in whom LD was diagnosed. The Minnesota Department of Health found the 088.81 code was present in 145 (56.4%) of 257 charts for which a clinician documented a new case of LD (E. Schiffman, pers. comm.). A Maryland Department of Health and Mental Hygiene study found the 088.81 code in 45 (44.6%) of 101 charts from patients in whom LD was diagnosed and reported by clinicians or clinical centers (*20*). Furthermore, the New York State Department of Health found the 088.81 code in 114 (41.8%) of 273 charts from patients in whom LD was diagnosed (J. White, pers. comm.). Finally, the Tennessee Department of Health found the 088.81 code listed at least once in 9 (37.5%) of 24 charts from patients with Blue Cross Blue Shield insurance in whom LD was diagnosed and who were reported to the Department of Health (*21*). Thus, of 655 collective charts from LD patients, 313 charts had 088.81. Therefore, to account for patients in whom LD was diagnosed but whose charts were not coded with 088.81, we multiplied the estimated number of cases with 088.81 by a correction factor calculated as follows: 313/655 = 1/x, where x = 2.09.

Statistical Methods

We calculated direct standardization and descriptive statistics using SAS software version 9.3 (SAS Institute, Cary, NC, USA). The χ^2 test was used to compare categorical data. Cramer's V values were calculated to compare distributions by using R statistical software version 3.1.1 (http://www.r-project.org/). Methods for credible interval calculation are provided in the online Technical Appendix.

Ethics Review

CDC human subjects review of the protocol determined it was not research involving human subjects. Thus, Institutional Review Board approval was not required.

Results

Study Population

The final study dataset comprised 103,647,966 person-years of observation (median 17,309,054 persons/year). Median age of the study population was 37.0 years; 51.9% of patients were female. For comparison, the median age of the US population in 2010 was 37.2 years, and 50.8% of the population was female.

Epidemiology of Clinician-Diagnosed LD and Comparisons with Surveillance Data

A total of 45,430 clinician-diagnosed LD events were identified during 2005–2010; 985 (2.2%) were inpatient admissions and 44,445 (97.8%) were outpatient events (Figure 1). Average annual incidence within the MarketScan population was 44.8 events per 100,000 persons, with a peak of 56.3 events per 100,000 persons in 2009 (Figure 2). Interannual fluctuation in incidence in MarketScan data was similar to that in surveillance data (χ^2 test, p = 0.81; Cramer's V = 0.037).

Clinician-diagnosed LD events peaked during the summer months, although more so for inpatient admissions (61.9% occurred during June–August) than for outpatient events (50.0% occurred during June–August). In comparison, 65.0% of cases reported through surveillance occurred during June–August (Figure 3). Seasonal distribution of LD events in MarketScan differed significantly from cases reported through surveillance, though this is likely an artifact of the large sample sizes since the magnitude of Cramer's V suggests little difference in the distributions (inpatients: χ^2 test, p<0.001, Cramer's V = 0.019; outpatients: χ^2 test, p<0.001, Cramer's V = 0.154).

Age distribution for both male and female patients did not differ significantly from the distributions reported through surveillance (male: χ^2 test, p = 0.57, Cramer's V = 0.054; female: χ^2 test, p = 0.43, Cramer's V = 0.054) (Figure 4). For inpatients, the highest average annual admission rates were for boys 5–9 years of age (1.8 admissions/100,000 persons) and men 60–64 years of age (1.9 admissions/100,000 persons). For outpatient events, the highest annual incidences were for boys 5–9 years of age (54.5 events/100,000 persons), men 60–64 years of age (55.4 events/100,000 persons), and women 60–64 years of age (54.7 events/100,000 persons). Relative to surveillance data, the incidence of clinician-diagnosed LD was higher than expected for women 15–44 years of age.

The 15 states and district with the highest average incidence represented 80.6% of clinician-diagnosed LD and were as follows, in descending order: Connecticut, Rhode Island, Maryland, New Jersey, Massachusetts, New York, New Hampshire, Pennsylvania, Maine, Delaware, Virginia,

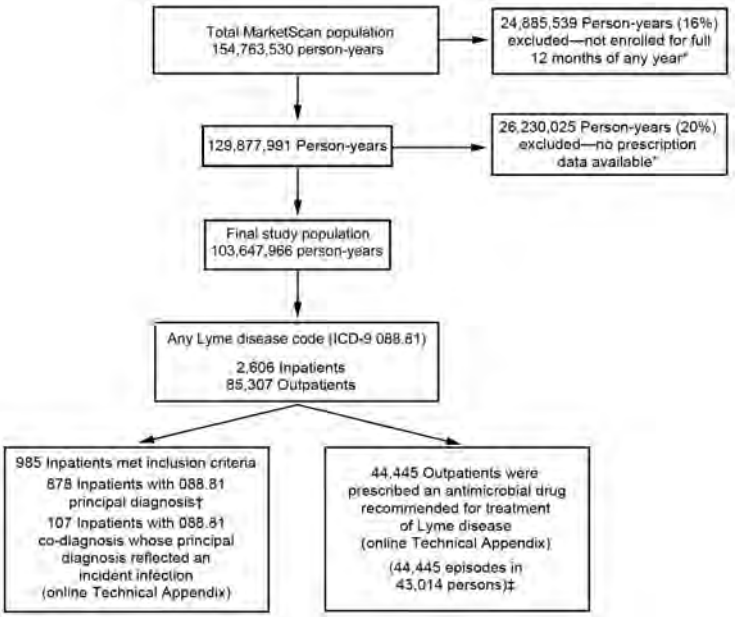

Figure 1. Study population and number of patients with clinician-diagnosed Lyme disease in the MarketScan database, United States, 2005–2010. *Persons not enrolled for the full 12 months of any year and who did not have prescription data were removed from both the numerator and denominator for rate calculations. Therefore, removal of these persons did not substantially affect rate calculations and the final estimated number of cases. †One repeat inpatient was excluded (admitted in a subsequent year but ≤365 days after initial admission). No repeat admissions occurred >365 days after initial admission. ‡A total of 2,945 repeat outpatients (seen in a subsequent year but ≤365 days after previous year's visit) were excluded (http://wwwnc.cdc.gov/EID/article/21/9/15-0417-Techapp1.pdf). ICD-9, International Classification of Diseases, Ninth Revision.

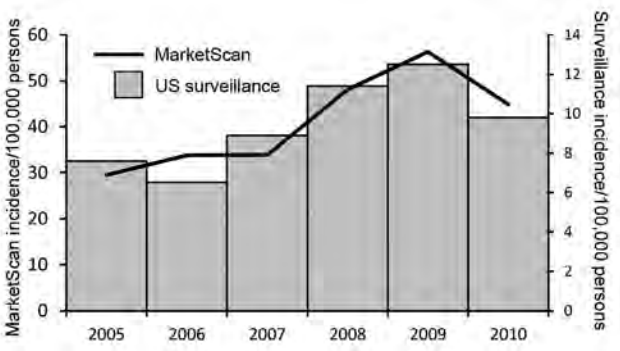

Figure 2. Trends of annual incidence of Lyme disease in MarketScan compared with trends in incidence from US surveillance, 2005–2010. Incidence is per 100,000 persons. Trends in interannual incidence fluctuation did not differ significantly between MarketScan and US surveillance (χ^2 test, p = 0.81). *Cases reported through the National Notifiable Diseases Surveillance System. During 2005–2007, incidence was calculated as the number of confirmed cases/100,000 persons; during 2008–2010, incidence was calculated as the number of confirmed and probable cases/100,000 persons. US 2010 Census population estimates were used as the denominator for incidence calculations.

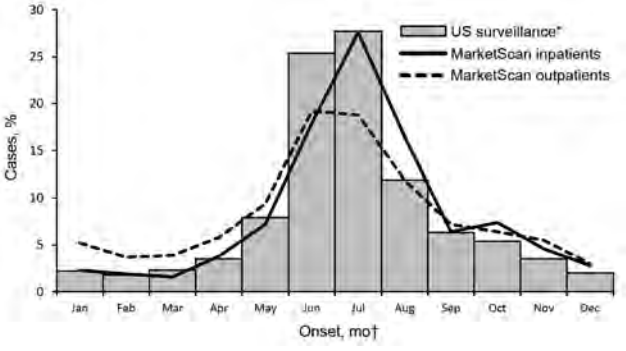

Figure 3. Seasonal distribution of inpatient and outpatient clinician-diagnosed Lyme disease in MarketScan compared with US surveillance cases, 2005–2010. *Because information about hospitalization is not consistently captured by surveillance, US surveillance data include both inpatients and outpatients. †Date of symptom onset for surveillance cases; date of admission or first outpatient visit for MarketScan events.

Vermont, Wisconsin, District of Columbia, and Minnesota (Figure 5). These same 15 states and district were seen in surveillance data, although the rank order differed slightly, and they constituted a significantly greater proportion (96.3%) of reported cases (χ^2 test, p<0.001).

Estimated Number of Clinician-Diagnosed LD Cases

Direct standardization of clinician-diagnosed LD and addition of estimated cases in persons ≥65 years of age produced an estimate of 157,137 cases per year, which was multiplied by 2.09 to correct for omission of the 088.81 code in patient charts. This calculation yielded a national estimate of 329,000 LD cases per year during 2005–2010 (95% credible interval 296,000–376,000). On the basis of this number, the estimated incidence of clinician-diagnosed LD in the United States during this period was 106.6 cases per 100,000 persons per year. In comparison, average US incidence according to surveillance data during this period was 9.4 cases per 100,000 persons per year.

Sensitivity analyses showed that the correction factor for patients in whom LD was diagnosed but who were not given the 088.81 code had the greatest influence on the final estimate (online Technical Appendix). For example, a 10% increase in this correction factor led to a 6% increase in the final estimate, and a 30% decrease led to a 12% decrease in the final estimate.

Discussion

Using medical claims data, we estimated that 329,000 (95% credible interval 296,000–376,000) LD cases occur annually in the United States, which emphasizes the substantial public health effect of this disease. This estimate is consistent with findings from a recent study of diagnostic laboratories that yielded an estimate of 288,000 (range 240,000–444,000) infections among patients for whom a laboratory specimen was submitted in 2008 (*22*). As expected, our estimate is slightly higher because it also includes LD cases diagnosed without laboratory testing (i.e., clinical diagnosis based on presence of erythema migrans after exposure in a Lyme-endemic area).

Presence of a diagnostic code in the chart or a clinician diagnosis of an infectious condition does not necessarily signify a true infection (*19*). Possible reasons include rule-out diagnoses, codes for medical history but not incident infections, and overdiagnosis (incorrect diagnosis of LD when the patient has a different condition). Rule-out diagnoses and medical history codes most likely were reduced—but not completely eliminated—by including only

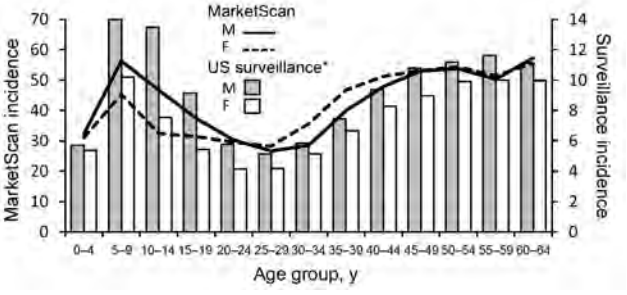

Figure 4. Comparison of trends in the age and sex distribution of persons with Lyme disease in MarketScan with US surveillance, 2005–2010. Incidence is per 100,000 persons. Age distribution of persons with Lyme disease in MarketScan did not differ from those reported through US surveillance (male patients: χ^2 test, p = 0.57; female patients: χ^2 test, p = 0.43). *US 2010 Census population estimates were used as the denominator for surveillance incidence calculations.

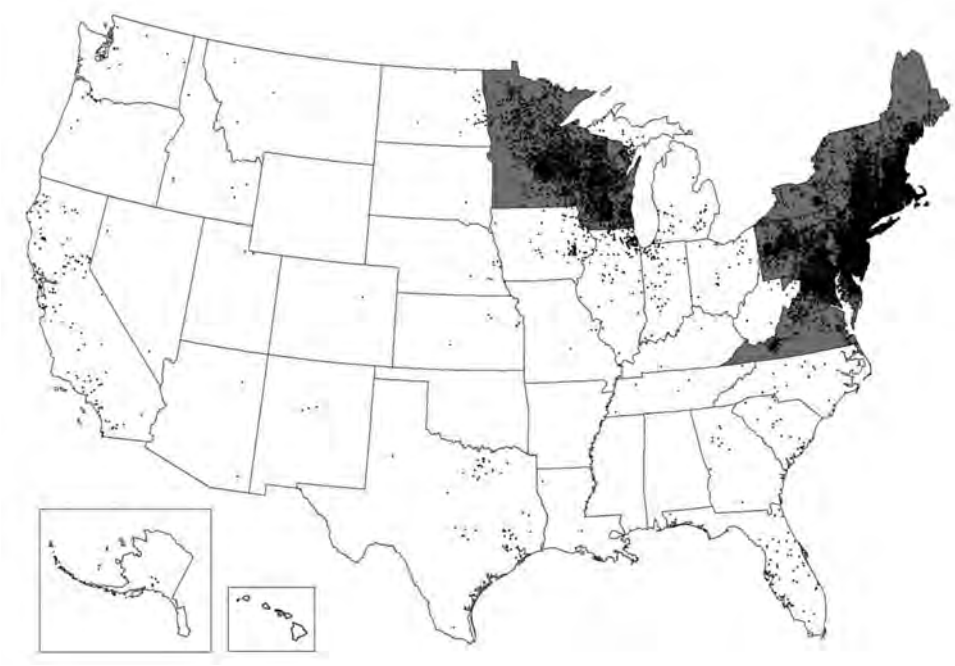

Figure 5. Comparison of states and district with highest incidence per 100,000 persons of Lyme disease in MarketScan (gray fill) and US surveillance (black dots), 2005–2010. Each dot is placed randomly within the county of residence for each confirmed Lyme disease case reported through surveillance during 2010.

outpatients treated with an antimicrobial drug recommended for LD. Overdiagnosis of LD is not uncommon given that, in some circumstances, the differential diagnosis for symptoms of LD can be broad (*23*–*25*). Studies of patient charts with the 088.81 code found that 37.9% in Maryland and 55.2% in Wisconsin were classified after chart review as noncases according to the surveillance case definition (*12*,*20*). Thus, we cannot exclude the possibility that some of the ≈329,000 patients in whom LD was diagnosed were not infected with *B. burgdorferi*.

Epidemiologic patterns of clinician-diagnosed LD were similar to patterns among cases reported through national surveillance; for example, incidence was highest among boys 5–9 years of age and persons 60–64 years of age of both sexes, which is believed to be attributable partially to behavioral factors and increased exposure to ticks in these age groups. However, some discrepancies were also noted. Specifically, incidence of clinician-diagnosed LD was higher than expected among women 15–44 years of age. A study of records with the 088.81 code using Maine's statewide electronic database of inpatient and outpatient encounters also found a higher percentage of female patients compared with surveillance data (*26*). This finding might be attributable to differential overdiagnosis of LD in these groups, variations in insurance coverage and health care–seeking behavior, or other factors. Studies in Europe have found sex discrepancies in risk for tick bites and clinical presentation of LD that should be explored further in US research studies (*27*,*28*).

The estimated number of clinician-diagnosed LD cases in the United States is higher than the number reported through routine surveillance and consistent with previous estimates of LD underreporting (*10*,*11*). Underreporting occurs with other notifiable conditions and should not be confused with lack of treatment (*8*). Indeed, our study confirms that many LD cases not formally reported are nevertheless diagnosed and treated by clinicians. Furthermore, underreporting aside, the general concordance in LD epidemiology seen in MarketScan and surveillance data underscores that LD surveillance serves its central purpose: to identify and track patterns of disease.

Primary advantages of this study are the large sample size, ability to circumvent the obstacles and biases inherent in routine reporting mechanisms, detailed information about clinical and prescription data, and ability to follow patient data over time. Unfortunately, use of the 088.81 code to estimate *B. burgdorferi* infections required several assumptions and correction factors. We calculated these correction factors using data from several analyses, each of which has its own inherent limitations and some of which have not yet been published. Nevertheless, the findings from these analyses were generally consistent with each other and with results expected on the basis of public health experience.

Our findings are subject to additional limitations. The MarketScan population is a convenience sample of the US population <65 years of age; although it is overall fairly representative, some differences exist. For example, certain age groups (20- to 29-year-olds) were 2%–3% underrepresented, and others (50- to 59-year-olds) were 2% overrepresented, compared with the US population. Although our calculations adjust for age and geographic

differences for all persons <65 years of age, other differences from the general population probably remain. In addition, the MarketScan database does not include military personnel, uninsured persons, or Medicaid/Medicare enrollees for whom risk for LD might differ from that of privately insured persons.

Our study highlights the need for continued coding research, particularly as health departments explore the feasibility of using electronic medical records to facilitate LD reporting. Additional information about LD coding practices will enable robust comparisons of ICD codes related to actual cases and facilitate future research using medical databases. In addition, ongoing research using the MarketScan databases and other sources will elucidate detailed epidemiologic and clinical aspects of LD that are not apparent in standard surveillance data.

In conclusion, our findings underscore that LD is a considerable public health problem, both in terms of number of cases and overall health care use. Furthermore, as with other conditions, underreporting in the national surveillance system remains a challenge. Continued research and education are necessary to enhance prevention efforts and improve diagnostic accuracy to reduce the effects of this disease.

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Enhancing Lyme Disease Surveillance by Using Administrative Claims Data, Tennessee, USA

Joshua L. Clayton, Stephen G. Jones, John R. Dunn, William Schaffner, Timothy F. Jones

Lyme disease is underreported in the United States. We used insurance administrative claims data to determine the value of such data in enhancing case ascertainment in Tennessee during January 2011–June 2013. Although we identified ≈20% more cases of Lyme disease (5/year), the method was resource intensive and not sustainable in this low-incidence state.

Lyme disease is the most common tickborne disease in the United States, with >36,000 cases reported to the Centers for Disease Control and Prevention (CDC) during 2013 (*1*). Tennessee, a low-incidence state, reported only 25 Lyme disease cases during 2013 (*2*). In addition, *Borrelia burgdorferi*–infected ticks have been identified in only 1 Tennessee county (G.J. Hickling, unpub. data).

CDC estimates that Lyme disease may be underreported by a factor of 10 (*3*). A study using administrative claims data from a Tennessee health insurance provider similarly estimated that Lyme disease incidence is 7-fold higher than is reported to the Tennessee Department of Health (TDH) (*4*). To determine the usefulness of claims data, which can vary in accuracy (*5*,*6*), we evaluated medical records of persons given a Lyme disease diagnosis in claims data or surveillance in Tennessee.

The Study

We examined Lyme disease cases reported to TDH and compared them with diagnoses identified from Blue Cross Blue Shield of Tennessee (BCBST) claims data during January 2011–June 2013. BCBST is a health insurance provider covering ≈50% of Tennessee's population. TDH cases met the national surveillance case definition for Lyme disease (*2*), consisting of the following criteria: clinical (erythema migrans [EM] rash or late manifestation of disease), laboratory (positive results by immunoassay followed by positive western blot results), and exposure and endemicity (possible exposure to infected ticks ≤30 days before rash onset). A person with physician-diagnosed disease who met laboratory criteria was considered to have a probable case. A person with a confirmed case had an EM rash and either met laboratory criteria, had possible exposure to ticks, or had a late manifestation of disease and positive laboratory results. We defined Lyme disease diagnosis for a BCBST-insured person as assignment of ≥3 primary or secondary codes for Lyme disease (088.81, International Classification of Diseases, Ninth Revision [ICD-9]), recorded in the claims data.

We used deterministic matching to identify persons in BCBST and TDH data. Medical records of one third of BCBST-insured persons whose cases were not reported to TDH were selected for review. Records were requested from the office visit on the date of Lyme disease diagnosis and for 1 office visit before and after diagnosis. BCBST-insured persons with a Lyme disease diagnosis were then classified according to the case definition (*2*). BCBST-insured persons not meeting the case definition were assigned into the following categories: 1) subsequently ruled out through negative laboratory testing, 2) self-reported or physician-recorded history of Lyme disease (before the study period), or 3) insufficient data for case determination. This analysis was exempted from institutional review board review.

During the study period, ≈3 million Tennessee residents were insured by BCBST, and 391 (0.01%) met criteria for diagnosed Lyme disease. During the same period, TDH received 74 reports of Lyme disease (9 confirmed, 65 probable). Of these, 24 (32%) persons were BCBST-insured at time of diagnosis (Figure). No differences by age and sex were noted between the 391 BCBST-insured persons and 74 TDH case-patients, and most were identified in highly populated counties (Davidson, Hamilton, Knox, Shelby).

Five Lyme disease cases were identified in both BCBST and TDH data, 386 appeared in BCBST data only,

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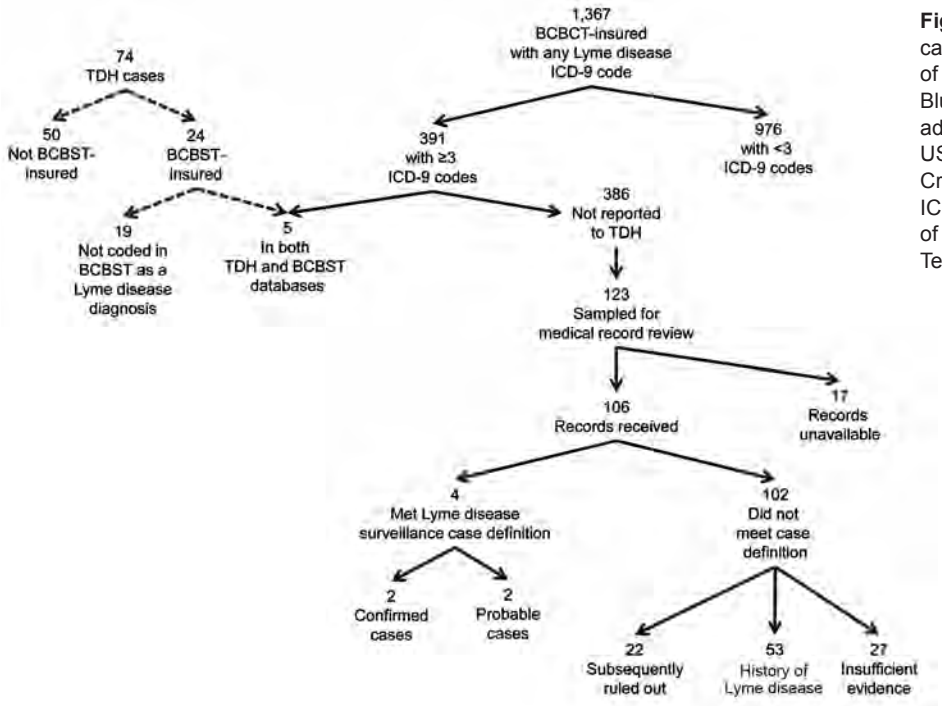

Figure. Identification of Lyme disease cases from the Tennessee Department of Health case-based surveillance and Blue Cross Blue Shield of Tennessee administrative claims data, Tennessee, USA, 2011–2013. BCBST, Blue Cross Blue Shield of Tennessee; ICD-9, International Classification of Diseases, Ninth Revision; TDH, Tennessee Department of Health.

and 19 appeared in TDH data only. All 5 matched persons were classified by TDH as having probable cases. Of the 386 persons only in BCBST, 123 were randomly sampled; 106 medical records were reviewed; only 4 (3.8%) met the case definition (2 confirmed, 2 probable). Extrapolating the proportion of true cases (3.8%) identified from this sample, we believe that ≈14 additional cases would have been identified through review of BCBST claims data during the 2.5-year study period. Adding 14 additional cases to the 24 confirmed and probable cases already reported to TDH among BCBST-insured persons, 38 cases would have been identified. Only 19 of the 38 cases would be identified through review of BCBST data (sensitivity 50%). Of 391 BCBST-insured persons with ≥3 ICD-9 codes for Lyme disease, 19 met the national case definition (positive predictive value 5%).

Of 102 BCBST-insured persons selected for review whose conditions did not meet the case definition, 22 were subsequently ruled out by laboratory testing after the visit in which the diagnosis was coded. For 27, evidence was insufficient to determine case classification, and 53 had a history of Lyme disease (23/53 [43%] had been prescribed antibiotic medications to treat Lyme disease).

Nineteen BCBST-insured persons met the case definition and were reported to TDH as having Lyme disease but were not identified as such in BCBST claims data during the study period. In all instances, no ICD-9 code for Lyme disease was coded in billing records, despite the diagnosis in the medical record and subsequent reporting to TDH. The 4 most frequent ICD-9 codes used for these persons were fever (21%), myalgia/myositis (21%), malaise and fatigue (16%), and gynecologic examination (16%).

Conclusions

By supplementing passive surveillance with BCBST claims data, we identified 20% more Lyme disease cases than were reported to TDH. The additional cases were diagnosed by clinicians and coded as Lyme disease in administrative claims. In this low-incidence state, most BCBST-insured persons with diagnosed Lyme disease did not meet the case definition, and the positive predictive value of BCBST data was low. The resources required to determine true cases from those diagnosed in BCBST claims data were substantial. Without an improved algorithm for identifying true cases, using these administrative data to supplement health department surveillance would be unsustainable.

Medical records of one fourth of the sample lacked sufficient information for case determination, and records of half showed a history of Lyme disease. Strikingly, none of the persons with a history of Lyme disease had any previous ICD-9 code for Lyme disease recorded by BCBST. Also surprisingly, 8 persons who first appeared to be incident case-patients, according to the BCBST algorithm, had been reported to TDH in the past (for 1 case-patient, >10 years earlier). These previously reported cases decreased the positive predictive value of BCBST data.

Among BCBST-insured persons not meeting the case definition, diagnoses were made by a limited number of clinicians. Understanding how these few clinicians

came to diagnose many persons with Lyme disease may aid physician training. Of BCBST-insured persons with a history of Lyme disease, approximately half had current prescriptions for antimicrobial drugs. Although we were unable to assess whether any of these prescriptions represented long-term treatment for a chronic Lyme disease diagnosis, providers and patients should be educated regarding the lack of effectiveness and risks associated with long-term antimicrobial therapy (*7*).

Half of the BCBST-insured persons had a self-reported or physician-recorded history of Lyme disease that could not be verified by our cross-sectional analysis. One quarter of medical records had insufficient information to make a case determination, stemming from a lack of timely and adequate laboratory testing. Whether these data quality deficiencies biased our results is unknown. A history of Lyme disease does not exclude the potential for reinfection (*8*), but the large proportion of persons in this category would be unlikely, given the low incidence of Lyme disease. Southern tick–associated rash illness, caused by *B. lonestari*, produces an EM-like rash and may have confounded our use of administrative claims to identify Lyme disease (*9*).

This study was a special collaboration between TDH and BCBST medical informatics staff and required substantial resources of personnel and time, a level of surveillance not sustainable long-term. Although claims data offer an opportunity for identifying additional Lyme disease cases for public health surveillance, a more efficient means for differentiating cases from noncases is needed before such a system will be practical.

Dr. Clayton is an Epidemic Intelligence Service officer at CDC, assigned to the Tennessee Department of Health. His primary research interests include vector-borne diseases.

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Who Is this Person?

He founded the Epidemic Intelligence Service (EIS) and developed modern public health surveillance.

Is he

A) William Farr
B) Wade Hampton Frost
C) Alexander Langmuir
D) Joseph Mountin
E) David Sencer

Decide first. Then turn the page.

Alexander Duncan Langmuir

Myron G. Schultz, William Schaffner

This is a photograph of Alexander Duncan Langmuir (September 12, 1910–November 22, 1993). Langmuir, a renowned epidemiologist who created the Epidemic Intelligence Service (EIS), developed the practice of modern public health surveillance in the United States and abroad.

Alex Langmuir was born in Santa Monica, California, and grew up in New Jersey. His uncle, Irving Langmuir, a physicist and chemist, won the Nobel Prize in Chemistry in 1932. At Harvard College, Alex Langmuir tried to follow in his uncle's footsteps, but he found that the mathematics of advanced physics was beyond him and thus decided to pursue a career in medicine. He received his AB (cum laude) in 1931 from Harvard and his MD in 1935 from Cornell University Medical College. As a college student, Langmuir was inspired by Massachusetts Commissioner of Health George Hoyt Bigelow to enter the field of public health. His first 2 jobs were with the New York State Health Department; he began as a medical consultant and then became an assistant district health officer in Albany. After graduating with an MPH from the Johns Hopkins School of Hygiene and Public Health in 1940, Langmuir became a deputy commissioner of health in Westchester County, New York. His family was dismayed that he chose a career in public health rather than clinical medicine, but Langmuir expressed in his later years that his time in local public health taught him lessons that were fundamental to his achievements. From 1942 to 1946, he served as an epidemiologist with the Armed Forces Epidemiologic Board's Commission on Acute Respiratory Diseases, stimulating his lifelong interest in influenza. In 1946, Langmuir returned to Johns Hopkins University as an associate professor of epidemiology. However, by 1949 he was restive in academia and was attracted to the challenge of becoming the first chief epidemiologist of the newly established Communicable Disease Center (now the Centers for Disease Control and Prevention [CDC]) in Atlanta, Georgia, a position he held for over 20 years. When Langmuir retired from CDC, he became a visiting professor of epidemiology at Harvard Medical School and, later, a visiting professor of epidemiology at Johns Hopkins School of Hygiene and Public Health. He wrote extensively on all phases of epidemiology and public health surveillance on a global basis and was recognized internationally as an assertive public health authority.

In 1951, following the start of the Korean War, Langmuir established the EIS program as an early warning system against biologic warfare. EIS officers then and now are physicians, veterinarians, nurses, and health scientists who serve 2-year assignments. In an obituary written for the *New York Times*, Lawrence Altman said Langmuir "taught what he called 'shoe leather epidemiology,' stressing that investigators go into the field to collect their own data and view directly the locale of the public health problem they were investigating." Langmuir said: "Each epidemic aid call was an adventure and a training experience, even the false alarms." He stressed that field epidemiology should be taught in the field, not in the classroom. Admission into the EIS program was highly selective. Langmuir believed that when competent persons were thrust into challenging circumstances with supportive supervision, excellent results were certain. He regarded the EIS officers as members of his extended family, backing them firmly when they found themselves in difficulty and joining them for the roasts of CDC leaders during the officers' annual skit night—often at his own expense.

In 1955, Langmuir and his young staff achieved early recognition due to the "Cutter Incident." The new inactivated (Salk) polio vaccine was causing cases of polio. Surgeon General Leonard Scheele asked Langmuir to develop a surveillance system to determine the extent of the problem. Langmuir deployed his staff, and within days they determined that the cases were caused by vaccine from a single manufacturer: Cutter Laboratories. "Langmuir was able to predict with great accuracy the expected size of the epidemic and the number of secondary

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cases that would occur," former CDC director William Foege noted. This response enhanced the reputation of the young agency and established epidemic aid as one of its singular characteristics.

Today, the EIS program has evolved into a surveillance and response unit for all types of health problems. During 1951–2014, more than 3,500 physicians, veterinarians, nurses, and health scientists were trained as EIS officers. Many of the nation's medical and public health leaders, including CDC directors, state health department directors, state epidemiologists, and deans of the country's premier schools of public health, are EIS alumni. Since 1980, CDC has supported the development and implementation of 48 two-year field epidemiology training programs that cover 60 countries and are modeled after the EIS in their teaching and practice of applied field epidemiology. More than 3,000 epidemiologists have graduated from these programs; many of these graduates now hold leadership positions within their countries' ministries of health, the World Health Organization, and other global health organizations.

The idea of effective national disease surveillance captured Alex Langmuir's imagination throughout his career. He believed that surveillance is the foundation for evidence-based public health action. Langmuir preached the importance of the systematic collection of pertinent data, the consolidation and analysis of these data into useful information, and the dissemination of the results to all who need to know so that they can take action. His goal was to use surveillance systems to define populations at risk for disease, determine interventions, and monitor their impact. Langmuir and his staff developed novel national surveillance programs for an array of communicable diseases and for chronic diseases, injuries, and reproductive health. Indeed, he considered the population explosion to be the most serious epidemic of all.

Altman described Langmuir as "a tall man who could command immediate attention when he stood to speak to audiences in his deep voice. He thrived on controversy and took pride in overcoming local political pressures to crusade for preventive medicine and other measures to safeguard public health." Philip Brachman, who succeeded Langmuir as EIS director, described Langmuir as "visionary, clairvoyant, tenacious, well prepared, scientifically honest, and optimistic." Langmuir enjoyed being a civil servant and working to benefit the public. "His concerns were to control and prevent disease by applying the principles of epidemiology to the identification of causes and solutions," Brachman wrote. Foege described Langmuir as someone with a public health message who arrived at the right time and place in history to be able to broadly disseminate his message.

In 1979, when Alex Langmuir was interviewed by D.A. Henderson about being recruited to work at CDC in 1949, Langmuir said, "As I looked it over and saw the vision, there was no question, [former CDC director] Justin Andrews took me to the mountain and showed me the Promised Land." At CDC, Alex Langmuir changed the way epidemiology is used in public health practice, first in the United States and then throughout the world. In the 65 years since Langmuir's arrival at CDC, his disciples—EIS and field epidemiology training program officers—have played pivotal roles in combating the root causes of major public health problems. Millions of persons live longer and healthier lives because of the accomplishments of Langmuir and his progeny in controlling and preventing disease. This is Alex Langmuir's grand legacy.

Suggested Reading

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SYNOPSIS

Mycobacterium abscessus Complex Infections in Humans

Meng-Rui Lee, Wang-Huei Sheng, Chien-Ching Hung, Chong-Jen Yu, Li-Na Lee, Po-Ren Hsueh

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Release date: August 13, 2015; Expiration date: August 13, 2016

Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe clinical and nosocomial aspects of *M. abscessus* infections, based on a literature review
- Compare clinical and treatment aspects of infections with *M. abscessus* subspecies
- Describe treatment of *M. abscessus* infections

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Mycobacterium abscessus complex comprises a group of rapidly growing, multidrug-resistant, nontuberculous mycobacteria that are responsible for a wide spectrum of skin and soft tissue diseases, central nervous system infections, bacteremia, and ocular and other infections. *M. abscessus* complex is differentiated into 3 subspecies: *M. abscessus* subsp. *abscessus, M. abscessus* subsp. *massiliense*, and *M. abscessus* subsp. *bolletii.* The 2 major subspecies, *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense*, have different *erm*(41) gene patterns. This gene provides intrinsic resistance to macrolides, so the different patterns lead to different treatment outcomes. *M. abscessus* complex outbreaks associated with cosmetic procedures and nosocomial transmissions are not uncommon. Clarithromycin, amikacin, and cefoxitin are the current antimicrobial drugs of choice for treatment. However, new treatment regimens are urgently needed, as are rapid and inexpensive identification methods and measures to contain nosocomial transmission and outbreaks.

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Mycobacteria are divided into 2 major groups for the purpose of diagnosis and treatment: *Mycobacterium tuberculosis* complex, which comprises *M. tuberculosis,* and nontuberculous mycobacteria (NTM), which comprise all of the other mycobacteria species that do not cause tuberculosis. NTM can cause pulmonary disease resembling tuberculosis, skin and soft tissue infections (SSTIs), central nervous system infections, bacteremia, and ocular and other infections (*1*,*2*). Over the past decade, the number of NTM disease cases worldwide has markedly increased (*3*,*4*), and the upsurge cannot be explained solely by increased awareness among physicians and advances in laboratory methods (*3*).

M. abscessus complex is a group of rapidly growing, multidrug-resistant NTM species that are ubiquitous in soil and water (*1*). Species comprising *M. avium* complex (MAC) are the most common NTM species responsible for disease; however, infections caused by *M. abscessus* complex are more difficult to treat because of antimicrobial drug resistance (*5*). *M. abscessus* complex is also resistant to disinfectants and, therefore, can cause postsurgical and postprocedural infections (*2*,*5*). Although *M. abscessus* complex most commonly causes SSTIs and pulmonary infections, the complex can also cause disease in almost all human organs (*2*,*5*). To improve our understanding of *M. abscessus* complex infections, we reviewed the epidemiology and clinical features of and treatment and prevention measure for diseases caused by the organisms as well as the taxonomy and antimicrobial susceptibilities of these organisms.

Search Strategy and Selection Criteria

We performed a PubMed search for *M. abscessus* complex articles published during January 1990–December 2014, using the following search terms: *M. abscessus*, *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii*, *M. abscessus* subsp. *massiliense*, *M. massiliense*, *M. bolletii*, and nontuberculous mycobacteria. Only articles published with abstracts in English were selected.

Taxonomy and Epidemiology

Bacterial Classification

M. abscessus was first isolated from a knee abscess in 1952 (*1*). *M. abscessus* and *M. chelonae* were originally considered to belong to the same species ("*M. chelonei*" or "*M. chelonae*"), but in 1992, *M. abscessus* was reclassified as an individual species (*1*). After *M. abscessus* was recognized as an independent species, new subspecies, including *M. massiliense* and *M. bolletii*, were discovered. Debate has ensued over whether *M. massiliense* and *M. bolletii* should be reunited to form one subspecies, *M. abscessus* subsp. *bolletii* (*6*). It is hoped that the debate will be settled as a result of findings from several recent studies that clearly demonstrated, by genome comparison, that *M. abscessus* complex comprises 3 entities: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. abscessus* subsp. *bolletii* (*7*–*11*). Serial changes in the taxonomic classification and nomenclature of *M. abscessus* complex, from 1992 to 2013, are shown in Figure 1.

M. abscessus subsp. *bolletii* is recognized as a rare pathogen with a functional inducible erythromycin ribosome methyltransferase (*erm*) (41) gene. In most *M. abscessus* subsp. *abscessus* mycobacterium, this gene leads to macrolide resistance. *M. abscessus* subsp. *massiliense* has been proposed to have a nonfunctional *erm*(41) gene, leading to macrolide susceptibility and a favorable treatment outcome for infections (*7*–*11*).

Laboratory Identification

Definitive diagnosis of *M. abscessus* complex infection in humans is invariably determined by the isolation of *M. abscessus* complex from clinical specimens. The correct subspecies identification of *M. abscessus* complex has traditionally relied on phenotypic methods (e.g., biochemical testing for the utilization of citrate) to distinguish them from closely related species like *M. chelonae* (*1*). However, this method is not accurate enough to differentiate between the 2 main subspecies of the complex. Instead,

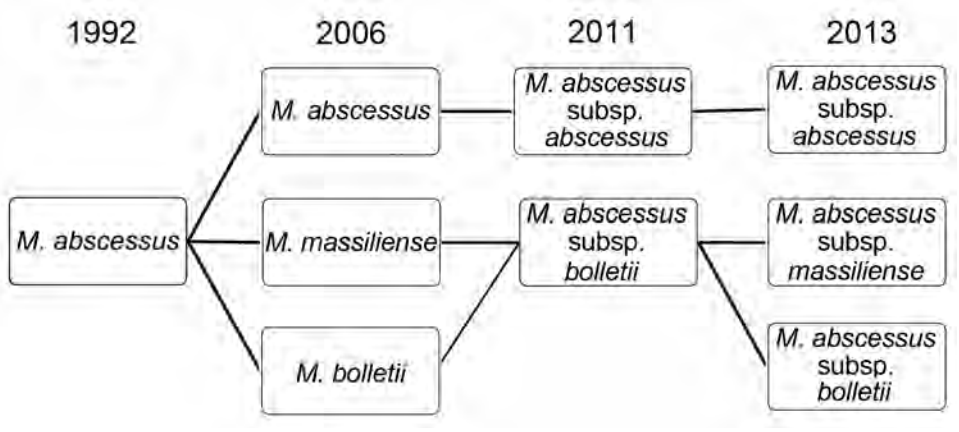

Figure 1. Serial changes in the nomenclature and taxonomic classification of *Mycobacterium abscessus* complex, 1992–2013.

rpoB gene–based sequencing is a more reliable method for correctly identifying *M. abscessus* complex to the subspecies level (*10*). However, because of the limited differences between the subspecies of *M. abscessus* complex, some researchers have questioned the accuracy of identification results from the sequencing of a single gene, especially the *rpoB* gene (*10*). Many schemes have been used in an attempt to accurately differentiate between subspecies, such as multilocus gene sequence typing, sequencing of the *erm* gene, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Figure 2) (*10*,*12*). Nonetheless, because the taxonomic classification is still changing, the debate over the optimal identification method will probably also continue.

Disease Burden

The global isolation and epidemiology of *M. abscessus* complex are diverse. Furthermore, due to limitations in correct and detailed species identification, previous epidemiologic studies often referred to *M. abscessus* complex as *M. chelonae/abscessus* group or rapidly growing mycobacteria (*13*). In the United States, *M. abscessus/chelonae* complex infections are secondary only to MAC infections, compromising 2.6%–13.0% of all mycobacterial pulmonary infections across various study sites. This percentage correlates to an annual prevalence of <1 *M. abscessus*/*chelonae* pulmonary infections per 100,000 population, but the prevalence is increasing (*13*). *M. abscessus* complex is especially prevalent in East Asia. For example, in Taiwan, *M. abscessus* complex comprises 17.2% of all clinical NTM isolates, which correlates to 1.7 cases/100,000 population (*4*). According to current studies, the proportion of *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *abscessus* is about the same among all clinical isolates (*12*). *M. abscessus* subsp. *bolletii* is rarely isolated (*7*).

Clinical Diseases

Respiratory Tract Infections

M. abscessus complex can cause pulmonary disease, especially in vulnerable hosts with underlying structural lung disease, such as cystic fibrosis, bronchiectasis, and prior tuberculosis (*2*). *M. abscessus* complex pulmonary disease usually follows an indolent, but progressive, course, causing persistent symptoms, decline of pulmonary function, and impaired quality of life; however, the disease can also follow a fulminant course with acute respiratory failure (*2*,*14*). Establishing a diagnosis of pulmonary disease due to *M. abscessus* complex is not straightforward because isolation of *M. abscessus* complex from respiratory samples is not, in and of itself, diagnostic of pulmonary disease (*2*). According to guidelines published by the American Thoracic Society/Infectious Diseases Society of America in 2007, the diagnosis of *M. abscessus* complex pulmonary disease requires the fulfillment of clinical and microbiological criteria, such as the presence of clinical symptoms; radiographic evidence of lesions compatible with NTM pulmonary disease; appropriate exclusion of other diseases; and, in most circumstances, positive culture results from at least 2 separate expectorated sputum samples (*2*). Common radiographic findings of *M. abscessus* complex pulmonary infection (i.e., bronchiolitis; bronchiectasis; nodules; consolidation; and, less frequently, cavities) are shown in Figure 3 (*2*).

M. abscessus complex is especially prevalent in respiratory specimens from patients with cystic fibrosis (*7*,*15*). Recent studies have shown that *M. abscessus* complex infection is no longer a contraindication for lung transplantation, although postoperative complications and a prolonged treatment course can be expected (*7*).

Pulmonary disease caused by *M. abscessus* complex is notoriously difficult to treat. Although there is no standard

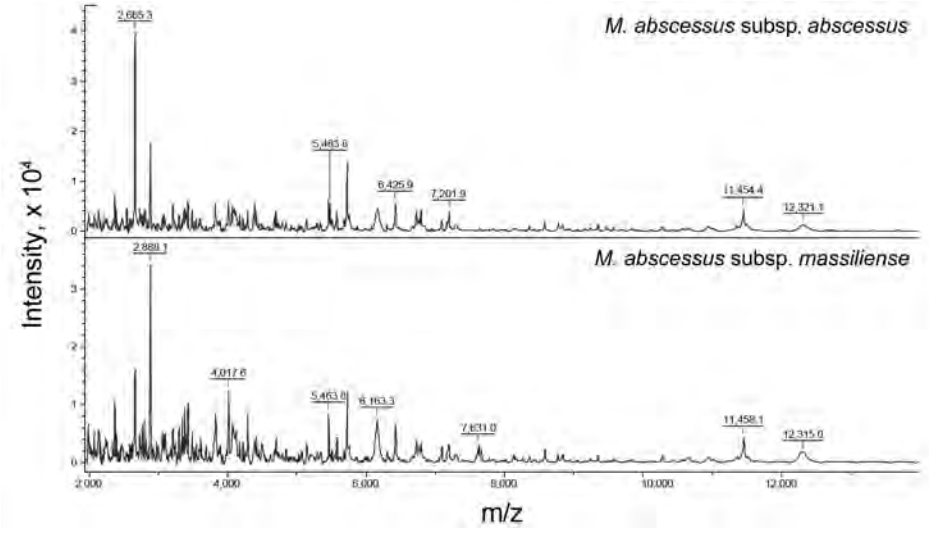

Figure 2. Spectrum of *Mycobacterium abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* created by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry Biotyper system (Microflex LT; Bruker Daltonik GmbH, Bremen, Germany). The absolute intensities of the ions are shown on the *y*-axis, and the masses (m/z) of the ions are shown on the *x*-axis. The m/z values represent the mass-to-charge ratio.

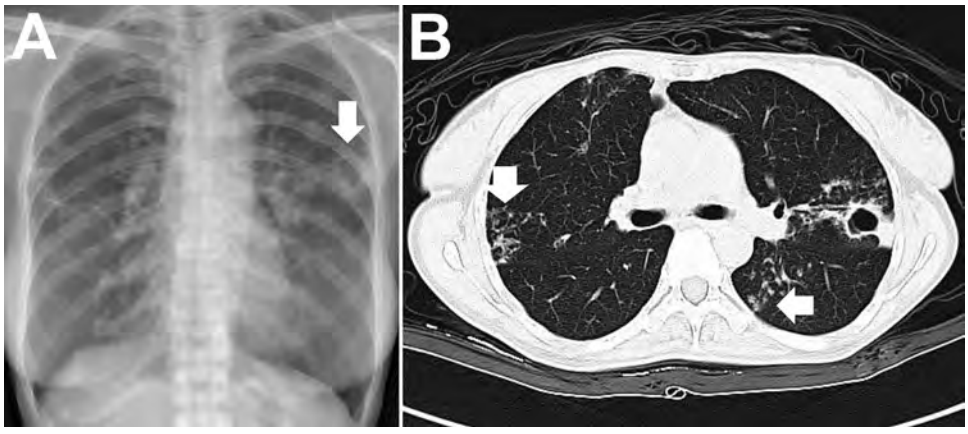

Figure 3. Chest radiograph (A) and computed tomography scan (B) images for a patient with pulmonary disease due to *Mycobacterium abscessus* subsp. *abscessus*. A) The arrow indicates a cavity with surrounding consolidation over the left upper lung. B) Vertical arrow indicates bronchiectasis; horizontal arrow indicates nodules.

treatment, current guidelines suggest the administration of macrolide-based therapy in combination with intravenously administered antimicrobial agents; however, this regimen has been shown to have a substantial cytotoxic effect (*2*). Of 65 patients with pulmonary disease due to *M. abscessus* complex who received an initial 4-week course of intravenous antimicrobial agents followed by macrolide-based combination therapy, 38 (58%) had *M. abscessus*–negative sputum samples >12 months after treatment (*16*). Surgical resection of localized disease in addition to antimicrobial therapy has been shown to elicit a longer microbiologic response than antimicrobial agents alone: sputum samples were *M. abscessus* complex–negative for at least 1 year in 57% versus 28% of these treatment groups, respectively (*17*). According to the 2007 American Thoracic Society/Infectious Diseases Society of America guidelines, the treatment options remain limited with current antimicrobial agents, and *M. abscessus* complex pulmonary disease is still considered a chronic incurable disease (*2*).

The advancement of subspecies differentiation has allowed for more effective management of pulmonary disease caused by *M. abscessus* complex. For example, unlike *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense* does not have inducible resistance to clarithromycin (*7*). Therefore, knowing that a patient's infection is due to *M. abscessus* subsp. *massiliense* rather than 1 of the other 2 subspecies enables the physician to confidently administer clarithromycin (*7*,*18*). In a large study on treatment outcome in patients with pulmonary disease caused by *M. Abscessus* subsp. *massiliense* or *M. abscessus* subsp. *abscessus*, all patients had similar clinical signs, radiographic findings, and treatment regimens (*18*). However, after treatment, the percentage of patients who had negative sputum culture results was much higher in the *M. abscessus* subsp. *massiliense*–infected group (88%) than in the *M. abscessus* subsp. *abscessus*–infected group (25%) (*18*). The lack of efficacy of clarithromycin-containing antimicrobial therapy against *M. abscessus* subsp. *abscessus* isolates in the study could be explained by the subspecies' inducible resistance to clarithromycin. The study clearly demonstrated how *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *abscessus* have different susceptibility profiles to combination therapy containing clarithromycin and different outcomes from such treatment (*18*).

SSTIs

SSTIs are also commonly caused by *M. abscessus* complex; infections range from deep tissue infections to localized skin infections. The 2 major mechanisms for acquiring an *M. abscessus* complex–associated SSTI are by 1) direct contact with contaminated material or water through traumatic injury, surgical wound, or environmental exposure and 2) secondary involvement of skin and soft tissue during disseminated disease (*19*). SSTIs caused by *M. abscessus* complex have been reported in patients who recently underwent cosmetic procedures (e.g., mesotherapy), tattooing, and acupuncture (*19*). *M. abscessus* complex SSTIs can also develop after exposure to environmental sources, such as spas and hot springs (*19*,*20*). More often, however, these SSTIs develop among hospitalized postsurgical patients, in whom surgical wound infections are most commonly due to *M. abscessus* subsp. *massiliense* (*21*,*22*). Disseminated *M. abscessus* complex infections with skin and soft tissue involvement also commonly occur (*23*). Of note, however, the presence of *M. abscessus* complex SSTIs can result in or from disseminated *M. abscessus* complex infections (*23*). *M. abscessus* complex skin infection have diverse presentations, including cutaneous nodules (usually tender), erythematous papules/pustules, and papular eruptions or abscesses (Figure 4) (*19*).

Central Nervous System Infections

Central nervous system (CNS) infections caused by *M. abscessus* complex are rare, but when they do occur, meningitis and cerebral abscesses are the most common manifestations (Figure 5). Although MAC is responsible for most

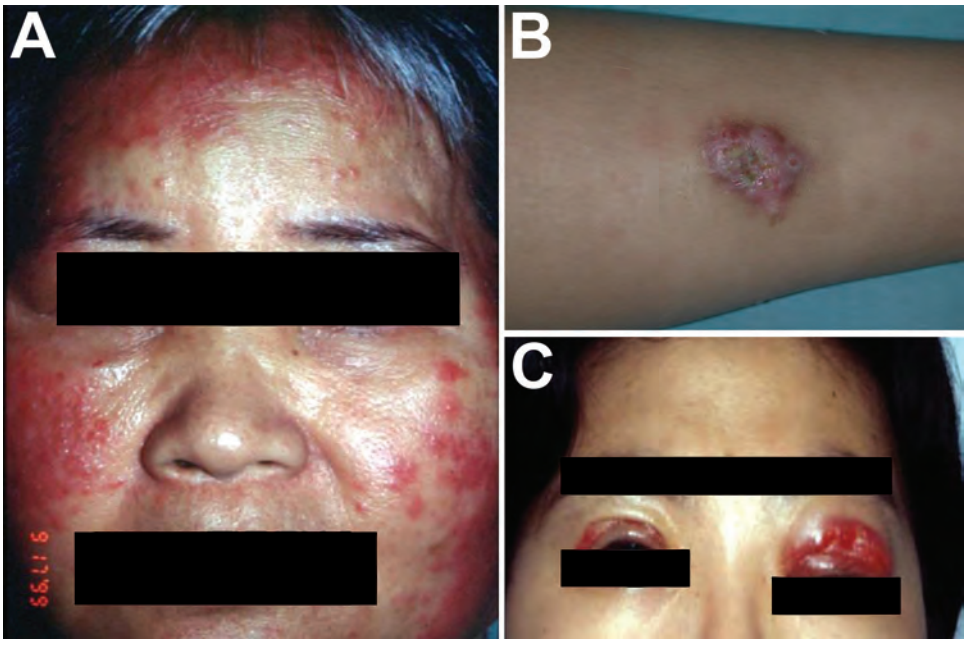

Figure 4. Skin lesions caused by *Mycobacterium abscessus* subsp. *abscessus*. A) Diffuse erythematous papular eruptions on the face and bilateral cervical lymphadenitis in a middle-aged man. B) A circumscribed subcutaneous nodule with pus discharge on the right arm of a 12-year-old boy. C) Wound infection over both upper eyelids of a 36-year-old woman; the infection developed 1 week after cosmetic surgery.

NTM CNS infections, especially in HIV-infected hosts, *M. abscessus* complex has increasingly been reported to cause CNS infections in HIV-negative patients (*21*). In one study, *M. abscessus* was responsible for most NTM CNS infections in HIV-seronegative patients (8/11 patients), especially in patients who had undergone neurosurgical procedures, patients who had intracranial catheters, and patients with otologic diseases. Treatment outcome depended on the patient's underlying disease and health status. Clarithromycin-based combination therapy for at least 1 year plus surgical intervention, if needed, offered the best chance for cure (*21*).

Disseminated Diseases and Bacteremia

Disseminated *M. abscessus* complex infections, such as lymphadenopathy, SSTIs, pulmonary infections, and bacteremia, are on the rise (*23*), and bacteremia caused by *M. abscessus* complex is most often associated with catheter use (*24*,*25*). A recent study showed that surgical wound infection may be the portal of entry, especially for *M. abscessus* subsp. *massiliense* (*26*). Optimal treatment modalities include removal of intravascular catheters, surgical debridement, and administration of intravenous antimicrobial agents chosen on the basis of drug susceptibility test results.

Disseminated *M. abscessus* complex infections tend to occur in immunocompromised hosts, including persons with HIV. However, these infections can also occur in HIV-negative patients. Browne et al. (23) recently showed that neutralizing anti–interferon-γ autoantibodies were present in 81% of HIV-negative patients with disseminated NTM-associated infections, and in adults, these antibodies were associated with adult-onset immunodeficiency similar to that seen in advanced HIV infection. This adult-onset immunodeficiency status can lead to disseminated NTM disease that mimics advanced HIV infection (*23*).

Ocular Infections

The incidence of NTM ocular infections (keratitis, endophthalmitis, scleritis, and other tissues of the ocular area) has increased over the past decade, and the increase has been attributed to the *M. chelonae/abscessus* group (*27*). Interpreting the real trend in ocular infections caused by *M. abscessus* complex is difficult because most studies have not used reliable tests to differentiate between *M. abscessus* complex and *M. chelonae* (*27*).

Initial treatment of *M. abscessus* complex ocular infections involves the discontinuation of topical corticosteroids, if used. The optimal treatment strategy (topical therapy, systemic antimicrobial agents, and surgical intervention) depends on the site of the ocular infection (*28*). Topical therapy, particularly topical amikacin and clarithromycin, can be used to treat some *M. abscessus* complex ocular infections (e.g., conjunctivitis, scleritis, keratitis, endophthalmitis) (*28*), and systemic antimicrobial agents can be used for all ocular infections (*28*). Surgical debridement, including removal of infected tissue, should be considered and is necessary for treatment of infections in some patients (*28*). Treatment outcome varies according to the site of infection, and early recognition of the infection is crucial.

Nosocomial Outbreaks and Transmission

Outbreaks of *M. abscessus* complex infections in hospital and clinic settings have been reported worldwide (*19*). Many of the outbreak events occur in clinics conducting cosmetic surgery, liposuction, mesotherapy, or intravenous

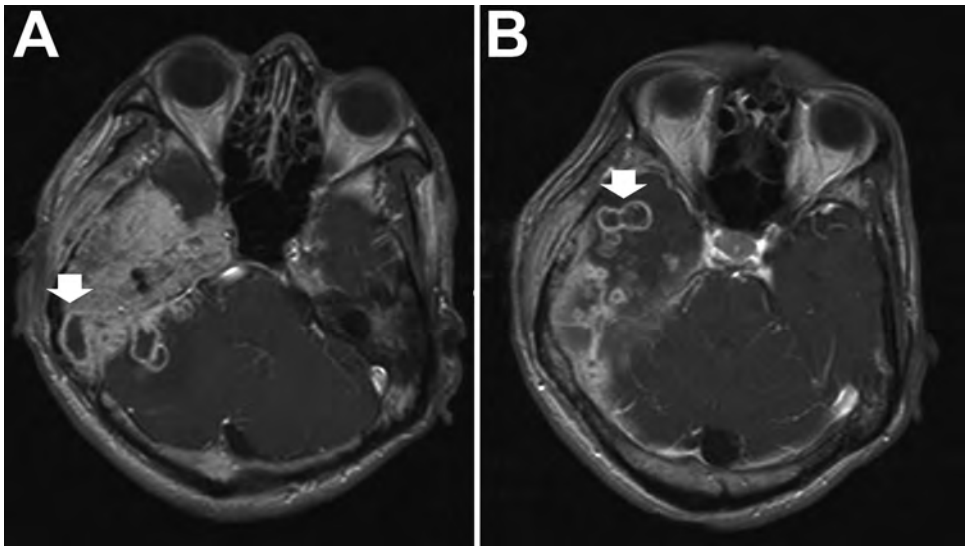

Figure 5. Brain computed tomography scan images for a patient with central nervous system infection caused by *Mycobacterium abscessus* subsp. *bolletii*. Arrows indicate abnormal nodular pachymeningeal thickening and leptomeningeal and intraparenchymal extension with multiple rim-enhancing lesions in the right cerebellum (A) and right temporal lobe (B), indicating cerebral abscesses.

infusion of cell therapy (*29*). Proposed sources of transmission include contaminated disinfectants, saline, and surgical instruments as well as contact transmission between patients (*19*,*30*,*31*).

M. abscessus complex transmission involves vulnerable hosts and causes substantial illness and death; thus, concern is also rising regarding outbreaks in centers specializing in lung transplantation and treatment of cystic fibrosis (*30*). Whole-genome sequencing of outbreak isolates has provided evidence of patient-to-patient transmission of *M. abscessus* complex; this transmission is most likely indirect rather than direct (*30*).

Antimycobacterial Susceptibilities

M. abscessus complex is notoriously resistant to standard antituberculous agents and most antimicrobial agents (*5*). The Clinical and Laboratory Standards Institute recommends testing rapidly growing mycobacteria for susceptibility to macrolides (clarithromycin and amikacin), aminoglycosides, fluoroquinolones, imipenem, doxycycline, tigecycline, cefoxitin, cotrimoxazole, and linezolid (*32*). The recommended drug susceptibility testing method is broth microdilution in cation-adjusted Mueller-Hinton broth supplemented with oleic albumin dextrose catalase (*32*). Among the agents suggested for *M. abscessus* complex susceptibility testing, clarithromycin, amikacin, and cefoxitin have the best in vitro antimycobacterial activity (*7*,*32*,*33*).

Recent major studies presenting susceptibility and resistance rates for *M. abscessus* subsp. *massiliense*, *M. abscessus* subsp. *abscessus*, and *M. abscessus* complex against 7 antimicrobial agents are summarized in Table 1. Most of the studies are from Asia, and the resistance rate for clarithromycin ranges from 0 to 38%. The resistance rates for cefoxitin (overall 15.1%) and amikacin (overall 7.7%) are also low. Doxycycline, quinolones (including moxifloxacin and ciprofloxacin), and imipenem had high resistance rates. Therefore, local susceptibility data are needed to guide treatment.

Because of its rarity, *M. abscessus* subsp. *bolletii* is discussed separately here. These mycobacteria are uniformly resistant to drugs recommended for use against *M. abscessus* complex. In one study, high MICs of tested antimycobacterial agents were observed, and amikacin probably had the highest activity (i.e., the lowest MIC) (*33*).

Recent studies have reported on the importance of the *erm*(41) gene in *M. abscessus* complex; this gene confers macrolide resistance through methylation of 23S ribosomal RNA (*39*). The *erm*(41) gene is present in the *M. abscessus* complex group but absent in *M. chelonae* (*39*). Many strains of *M. abscessus* subsp. *massiliense* have a nonfunctional *erm*(41) gene, and because of this, the rate of clarithromycin susceptibility is higher in *M. abscessus* subsp. *massiliense* than in *M. abscessus* subsp. *abscessus* (*18*). The Clinical and Laboratory Standards Institute recommends testing for inducible macrolide resistance because subspecies of *M. abscessus* complex demonstrate susceptibility to clarithromycin during the first 3–5 days of incubation but demonstrate resistance after an extended duration of incubation (preferably 14 days, according to many experts) (*39*).

Another area of strenuous clinical research involves identifying and developing novel anti–*M. abscessus* complex agents. One such agent, the glycylcycline tigecycline, has been shown to exhibit good in vitro activity against rapidly growing mycobacteria, especially *M. abscessus* complex (*12*,*21*). However, no prospective trial has been conducted to evaluate the efficacy of tigecycline, and a breakpoint for interpreting tigecycline susceptibility has not been established (*32*).

Table 1. Summary of recent data on the resistance of *Mycobacterium abscessus* complex bacteria to different antimicrobial agents*

Study authors (reference), species	No. isolates	Antimicrobial drug, no. resistant isolates/no. tested (%)						
		CLR	DOX	CIP	MXF	FOX	AMK	IPM
Lee et al. (*34*)								
M. abscessus subsp. *abscessus*	202	48/202 (24)	NA	184/202 (91)	167/202 (83)	NA	25/202 (12)	NA
M. abscessus subsp. *massiliense*	199	15/199 (8)	NA	174/199 (87)	149/199 (75)	NA	12/199 (6)	NA
Koh et al. (*18*)								
M. abscessus subsp. *abscessus*	64	3/64 (5)	53/64 (83)	37/64 (58)	30/64 (47)	0/64	3/64 (5)	27/62 (44)
M. abscessus subsp. *massiliense*	79	3/79 (4)	58/79 (73)	48/79 (61)	42/79 (53)	1/79 (1)	6/79 (8)	50/75 (67)
Huang et al. (*35*)								
M. abscessus complex	40	3/40 (8)	37/40 (93)	36/40 (90)	31/40 (78)	27/40 (68)	2/40 (5)	35/40 (88)
Brown-Elliott et al. (*36*)								
M. abscessus complex	37	0% (0/37)	NA	29/37 (78)	29/37 (78)	NA	0/37	7/37 (19)
Broda et al. (*37*)								
M. abscessus complex	58	22/58 (38)	57/58 (98)	55/58 (95)	55/58 (95)	16/58 (28)	10/58 (17)	56/58 (97)
Zhuo et al. (*38*)								
M. abscessus complex	70	10/70 (14)	NA	56/70 (80)	NA	3/70 (4)	0/70	15/70 (21)
Overall								
M. abscessus complex	749	104/749 (13.9)	205/241 (85.1)	619/749 (82.6)	503/679 (74.1)	47/311 (15.1)	58/749 (7.7)	190/342 (55.6)
M. abscessus subsp. *abscessus*	266	51/266 (19.4)	53/64 (83.0)	221/266 (83.1)	197/266 (74.1)	0/64	28/266 (10.5)	27/62 (44.0)
M. abscessus subsp. *massiliense*	278	18/278 (6.5)	58/79 (73.4)	222/278 (79.8)	191/278 (68.7)	1/79 (1.0)	18/278 (6.5)	50/75 (66.7)

*AMK, amikacin; CIP, ciprofloxacin; CLR, clarithromycin; DOX, doxycycline; FOX, cefoxitin; IPM, imipenem; MXF, moxifloxacin; NA, not available.

Treatment

Several problems regarding treatment of *M. abscessus* complex infections in different organs are unsolved. For example, there is a lack of consensus on the optimal antimicrobial agents and combination therapy, optimal treatment duration, and the introduction of novel antimicrobial agents (e.g., tigecycline). Reports describing cases of *M. abscessus* complex infection are limited, except for those describing pulmonary disease and SSTIs. Thus, treatment recommendations must rely on retrospective case series. A summary of treatment recommendations from previous studies is shown in Table 2. The treatment of serious *M. abscessus* complex disease usually involves initial combination antimicrobial therapy with a macrolide (clarithromycin 1,000 mg daily or 500 mg twice daily, or azithromycin 250 mg–500 mg daily) plus intravenous agents for at least 2 weeks to several months followed by oral macrolide–based therapy (*2*). The drugs of choice for initial intravenous administration are amikacin (25 mg/kg 3×/wk) plus cefoxitin (up to 12 g/d given in divided doses) or amikacin (25 mg/kg 3×/wk) plus imipenem (500 mg 2–4×/wk) (*2*). As previously mentioned, the in vitro MICs of tigecycline are low, and the drug should be considered in treatment regimens.

Prevention

M. abscessus complex infection can be acquired in the community or in the hospital setting. In the community setting, water supply systems have been postulated to be the source of human infections (*7*,*40*). Membrane filtration,

Table 2. Summary of recommendations from previous studies for the treatment of *Mycobacterium abscessus* complex infections in humans

Type of disease (reference)	Recommended initial regimen	Recommended treatment duration
Pulmonary disease (*2*)	Macrolide-based therapy in combination with intravenous antimicrobial therapy (preferably cefoxitin and amikacin)	Continue until sputum samples are negative for *M. abscessus* complex for 12 mo
Skin and soft-tissue infection (*2*)	Macrolide in combination with amikacin plus cefoxitin/imipenem plus surgical debridement	Minimum of 4 mo, including a minimum of 2 wk combined with intravenous agents
Central nervous system infection (*21*)	Clarithromycin-based combination therapy (preferably including at least amikacin in the first weeks)	12 mo
Bacteremia (*24*,*25*)	At least 2 active antimicrobial agents (preferably including amikacin) plus removal of catheter and/or surgical debridement of infection foci	4 wk after last positive blood culture result
Ocular infection (*28*)	Topical agents (amikacin, clarithromycin) and/or systemic antimicrobial drugs (oral clarithromycin, intravenous amikacin or cefoxitin) and/or surgical debridement*	6 wk to 6 mo

*The treatment of ocular infections was highly dependent on the infection site. In some sites, ≥1 treatment strategies (i.e., topical or systemic antimicrobial drug treatment or surgery) should be considered.

hyperchlorination, maintenance of constant pressure gradients, and the utilization of particular pipe materials have been suggested as methods for reducing the presence of NTM in water supply systems (*7*,*40*). In the hospital setting, disinfectant failure, contamination of medical devices and water, and indirect transmission between patients are considered to be the source of infections (*19*,*30*). In addition, clinics for cosmetic procedures have become sites of frequent outbreaks of *M. abscessus* complex infections (*19*,*29*). It is unclear whether patients with *M. abscessus* complex disease should be isolated from vulnerable hosts, such as patients with cystic fibrosis.

Conclusions

M. abscessus complex comprises a group of rapidly growing, multidrug-resistant, nontuberculous mycobacteria that are responsible for a wide spectrum of SSTIs and other infections. The complex is differentiated into 3 subspecies: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. abscessus* subsp. *bolletii*, which is rarely isolated. The major difference between *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *abscessus* is that the former does not have an intact *erm*(41) gene and thus does not have inducible macrolide resistance; treatment response may thus be better among patients with infections caused by *M. abscessus* subsp. *massiliense*. *M. abscessus* complex can cause infections involving almost all organs, but the infections generally involve the lungs, skin, and soft tissue. Drugs with the best in vitro activity include clarithromycin, amikacin, cefoxitin, and possibly tigecycline. Treatment regimens vary according to the infection site and usually include macrolide-based combination therapy, including parenteral amikacin plus another parenteral agent (cefoxitin, tigecycline, imipenem, or linezolid), for weeks to months, followed by oral antimicrobial therapy. Evidence of nosocomial transmission and outbreaks of *M. abscessus* complex is increasing; therefore, strenuous infection control measures should be taken to reduce the possibility of hospital-acquired *M. abscessus* complex infections.

Because of the complexity of the molecular techniques needed to differentiate between *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense*, it is difficult for most laboratories to identify the different subspecies. A more rapid and less expensive method for subspecies identification is thus needed for epidemiologic and clinical purposes. In addition, prospective trials comparing different regimens of antimicrobial agents are needed to determine the best treatment options; these studies should include novel agents, such as tigecycline. The effect of implementing isolation protocols for patients with infections due to *M. abscessus* complex (particularly pulmonary disease) should also be evaluated in future studies.

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Putative Lineage of Novel African Usutu Virus, Central Europe

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We characterized the complete genome of a putative novel Usutu virus (USUV) strain (Usutu-BONN) detected in a dead blackbird from Germany. Genomic analysis revealed several unique amino acid substitutions among the polyprotein gene. Phylogenetic analyses demonstrated that Usutu-BONN constitutes a putative novel African USUV lineage, which was probably recently introduced to central Europe.

Originally isolated from a *Culex neavei* mosquito in South Africa in 1959 (*1*,*2*), Usutu virus (USUV) was subsequently detected in different mosquito and bird species throughout Sub-Saharan countries (*3*). USUV has recently been introduced to Europe, where it caused widespread deaths among resident bird populations, established a local transmission cycle, and became a resident pathogen (*4*–*6*). USUV is maintained in an enzootic cycle involving mosquitoes as vectors and birds as the main amplifying hosts; humans are considered incidental or dead-end hosts. We have demonstrated that bats could also be infected with USUV and might act as amplifying hosts (*7*), and there is increasing evidence that USUV is pathogenic for humans, thus becoming a potential public health problem (*8*,*9*). On the basis of genetic differences, in comparison with the USUV strains from Africa, the USUV strains from Europe, except those from Spain, form a distinct clade within USUV phylogeny (*7*). The detection and isolation of USUV from different bird species and mammalophilic mosquitoes during the 2011 epizootic in Germany raised questions regarding the USUV host range. Thus, as a part of the German Arbovirus Surveillance Program (*10*), we continued the monitoring of the mosquitoes, birds, and bats for the presence of USUV.

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The Study

During May–October 2014, ≈23,300 female mosquitoes from different parts of Germany were trapped, morphologically identified, and pooled (up to 250 mosquitoes/pool). During January–November 2014, a total of 8 dead *Pipistrellus* bats and 32 dead birds (mainly blackbirds) from different regions of the country were subjected to complete necropsy, and samples were collected for virus detection. Total RNA and DNA from homogenized mosquito pools and tissue samples (brain, liver, lung, and heart) from bats and birds were extracted by using an RTP DNA/RNA Virus Mini Kit (STRATEC Biomedical, Birkenfeld, Germany) according the manufacturer's instructions. Extracted samples were analyzed for the presence of flavivirus RNA by using a modified pan-flavivirus reverse transcription PCR (*5*). Positive results were found for 5 mosquito pools (*C. pipiens* biotype *pipiens*), 5 blackbirds (*Turdus merula*), and 1 bat (*Pipistrellus pipistrellus*). Direct sequencing of the pan-flavivirus PCR amplicons showed USUV nucleic acid sequences in each sample. The positive samples were further subjected to PCRs for the amplification of a partial segment of USUV envelope and nonstructural (NS) 5 gene. Sequencing results showed that all samples, except 1 blackbird-derived USUV sequence, were identical (data not shown) and originated from southwest Germany, corresponding to the previously described USUV-endemic area (Figure 1) (*5*,*10*,*11*). The USUV-positive blackbird sample, which exhibited numerous nucleotide and amino acid changes compared with other sequences, had been found outside of the USUV-endemic area, at the beginning of August in Sankt Augustin (50°46′12″N, 7°11′12″E), a city located near Bonn.

Full-length genome sequence of this putative novel USUV strain, designated Usutu-BONN (GenBank accession no. KM659876), was successfully obtained by using a previously described protocol (*7*). The genome contained 11,065 nt with a 96-nt 5′ untranslated region and a 664-nt 3′ untranslated region. The single open reading frame encoded a polyprotein of 3,434 aa. Depending on the USUV strain, the nucleotide sequence similarity ranged from 81% to 98%, whereas amino acid sequence conservation ranged from 94.7% to 99.2% (Table 1). Comparison of the Usutu-BONN complete polyprotein sequence with the other USUV strains showed several identical synonymous and nonsynonymous mutations characteristic for African USUV strains and some unique substitutions (Table 2). Usutu-BONN contained 15 aa substitutions, 7 of which

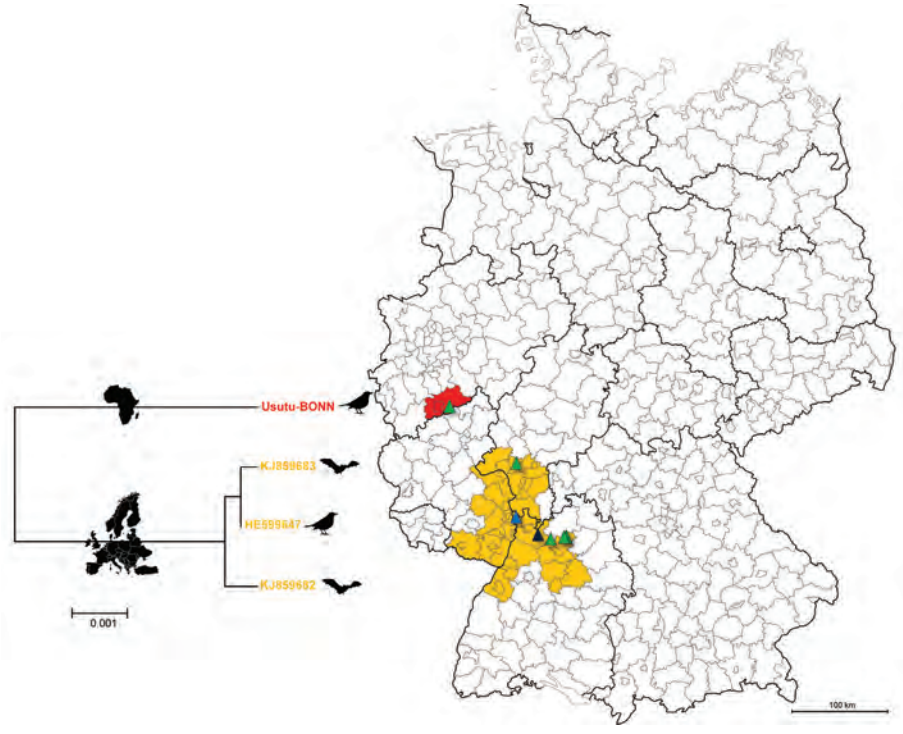

Figure 1. Region of Germany where Usutu virus (USUV) is endemic (orange) and location where the putative novel USUV strain Usutu-BONN was detected (red). Phylogenetic tree illustrates the genetic relationship between the strains circulating in the USUV-endemic region of Germany (belonging to the European USUV clade) and Usutu-BONN (belonging to the African USUV clade) (*7*), based on complete amino acid sequences of the polyprotein-encoding gene. Triangles indicate locations of the USUV-positive samples according to hosts; blue, mosquitoes; green, blackbirds; black, bat. Scale bar on tree indicates amino acid substitutions per site.

were unique mutations (Table 2). Most were located in the envelope (E) and NS2a proteins (Table 2). We also found 1 putative change in the C/anchC cleavage site of the polyprotein (Table 2); this mutation was observed also in the highly divergent African USUV strain (ArB1803; GenBank accession no. KC754958). We detected 2 more unique amino acid substitutions in the domain II of the E protein. Strikingly, no potential N-glycosylation sites or substitutions were found in well-known features of the protein E fusion peptide or antibody binding sites. Unique mutations (V142 and V189) in the NS2a protein were also observed (Table 2). Alignment of the deduced amino acid sequences of the complete polyprotein (including all previously described strains for which complete polyprotein-encoding sequences are available) by using the MAFFT plugin in Geneious 7.1.5 (Biomatters, Ltd, Auckland, New Zealand) and subsequent phylogenetic reconstruction by using a maximum-likelihood tree (JTT+Γ model) with 1,000 bootstrap replicates in PhyML (*12*) and parallel Bayesian Markov Chain Monte Carlo method implemented in MrBayes 3.0 software (*13*) (data not shown) demonstrated that Usutu-BONN forms a separate lineage (basal

Table 1. Comparison of Usutu-BONN virus with Usutu virus strains from other countries

Strain/GenBank accession no.	Country of origin	Host	Year of detection/isolation	Usutu-BONN* % Identity of nt sequence	Usutu-BONN* % Identity of aa sequence
ArD192495/KC754957	Senegal	Mosquito	2007	97.3	99.2
HB81P08/KC754955	Central African Republic	Human	1981	98.0	99.2
MB119/06/KF573410	Spain	Mosquito	2006	95.7	98.5
ArD19848/KC754954	Senegal	Mosquito	1974	96.5	99.0
SAAR-1776/AY453412	South Africa	Mosquito	1959	96.5	98.9
ArD101291/KC754956	Senegal	Mosquito	1993	97.5	99.2
BH65/11–02–03/HE599647	Germany	Avian	2011	97.2	99.2
BAT2USUTU-BNI/KJ859683	Germany	Bat	2013	97.2	99.1
BAT1USUTU-BNI/KJ859682	Germany	Bat	2013	97.2	99.1
Bologna 2009/HM569263	Italy	Human	2009	97.3	99.1
Italia 2009/JF266698	Italy	Avian	2009	97.3	99.1
Vienna 2001/AY453411	Austria	Avian	2001	97.5	99.1
Budapest/EF206350	Hungary	Avian	2005	97.4	99.1
Meise H/JQ219843	Austria	Avian	2002	97.4	99.1
ArB1803/KC754958	Central African Republic	Mosquito	1969	81.0	94.7

*Usutu-BONN strain was isolated from a blackbird in Germany in 2014.

Table 2. Comparison of amino acid substitutions of Usutu-BONN strain with those of all available complete Usutu virus polyprotein sequences*

Protein	Amino acid substitution Usutu-BONN	Unique substitutions	Total substitutions	Changed putative cleavage sites
C	No	No	0/0	No
anchC	$S_{105†}$→G; A_{120}→V	No	0/2	TKKKR/S†NNGP
PrM	N_{120}→Y	N_{120}	1/1	No
M	N_{28}→Y	N_{28}	1/1	No
E	L_{231}→S; T_{238}→ I/L	$L_{231;}$ T_{238}	2/2	No
NS1	V_{146}→ A/G	No	0/1	No
NS2A	A_{91}→ V/T; L_{123}→F; V_{142}→A; V_{189}→ A/S	$V_{142;}$ V_{189}	2/4	No
NS2B	No	No	0/0	No
NS3	F_{46}→ L; V_{338}→A/T	No	0/2	No
NS4A	No	No	0/0	No
2K	No	No	0/0	No
NS4B	F_{189}→ L	F_{189}	1/1	No
NS5	S_{274}→T/A	No	0/1	No

*USUTU-Bonn strain was isolated from a blackbird in Germany in 2014.
†Substitution in cleavage sites. GenBank accession numbers of Usutu virus polyproteins used for sequence alignments are shown in Table 1.

position of the African clade) within the USUV phylogeny (Figure 2). Furthermore, the phylogenetic tree showed moderate genetic relatedness of the Usutu-BONN strain with USUV strains circulating in central Europe.

Conclusions

We detected and genetically characterized a putative novel USUV strain (Usutu-BONN) by determining its complete genome sequence and comparing it with USUV strains for which complete polyprotein-encoding sequences are available. We demonstrated that the Usutu-BONN strain from Germany constitutes a putative novel USUV lineage. The unique synonymous mutations detected in the E and NS2a genes of Usutu-BONN strains may suggest an adaptive evolution. In this strain, 1 putative cleavage site of the viral polyprotein responsible for processing of structural proteins was changed. Given that Usutu-BONN has not led to massive deaths among birds and has not yet been found in other hosts or mosquito vectors, it seems evident that this strain was recently introduced into Germany and evolved in another geographic region, probably Africa (Figure 1, 2). The possibility of an African origin of this virus strain is

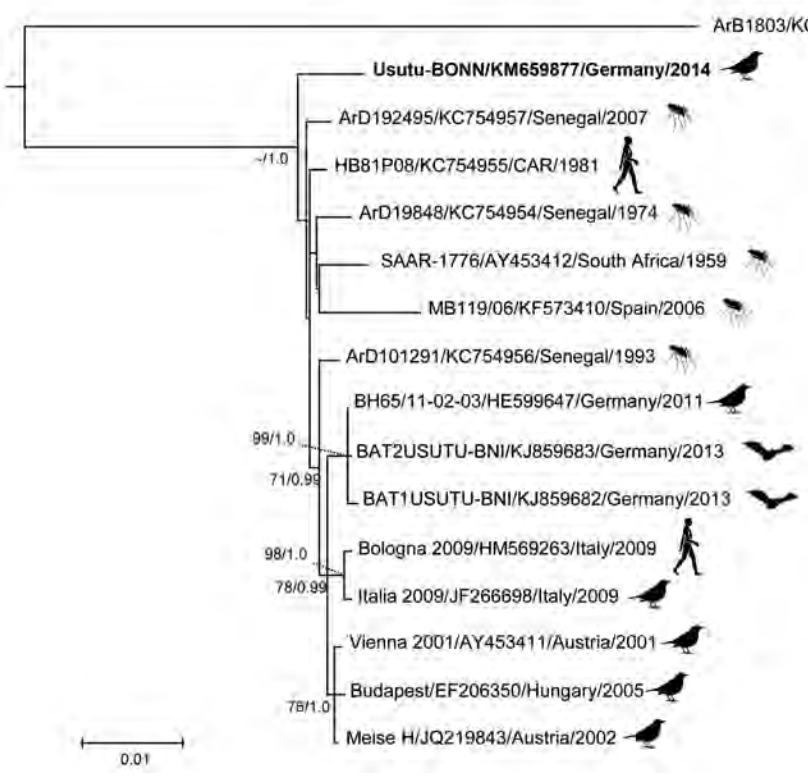

Figure 2. Phylogenetic relationship of the Usutu virus Usutu-BONN strain (from Germany, 2014) and other Usutu viruses, based on complete amino acid sequences of the polyprotein-encoding gene. The phylogenetic tree was constructed by using the maximum-likelihood method PhyML 3.0 (*12*) with 1,000 pseudoreplicates and, in parallel, Bayesian Markov chain Monte Carlo tree-sampling methods by using MrBayes 3.1.2 (*13*). The Akaike information criterion was chosen as the model selection framework, and the Johnes-Taylor-Thorton model of sequence evolution with gamma-distributed rate variation among sites (JJT + Γ) was chosen as the best model. Maximum-likelihood bootstrap replicate scores (>70%) and posterior probabilities of the Bayesian analysis (>90%) are shown next to the nodes. Taxon information includes strain designation, GenBank accession number, country of origin, and year of detection/isolation. Boldface indicates the Usutu-BONN strain. Scale bar indicates amino acid substitutions per site.

strengthened by the fact that phylogenetic analysis of complete polyprotein sequence established a separate basal lineage for the Usutu-BONN strain in a sister relationship with the African USUV strains, suggesting that Usutu-BONN has evolved in parallel with strains from Africa sharing a recent common ancestor. This putative novel USUV strain was introduced into Europe probably as other strains, via viremic migratory birds returning from winter migration from Africa to Europe or through ship- or aircraft-borne transportation of USUV-infected mosquitoes from Africa. However, identification of the possible sources (e.g., infected mosquitoes, resident or short-ranging migratory birds) of this new USUV strain will require sequence information from neighboring countries where USUV has been detected. The detection of USUV in a *Pipistrellus* bat 1 year after the first detection of USUV in bats from the same area in 2013 further strengthens our previous hypothesis that bats may contribute to the epizootic by serving as amplifying/reservoir hosts (*7*). The unique mutations (V142 and V189) in the NS2a protein of the Usutu-BONN strain are located very close to the identical mutation observed in the previously described bat-derived USUV strains. Although the biological consequences of these mutations are not known, similar mutations in West Nile virus were responsible for inhibition of interferon signaling (*14*).

Further monitoring studies are necessary to evaluate the pathogenic potential of this newly introduced USUV strain in central Europe for susceptible and receptive avian/mammalian hosts and for humans. This information could be used to predict future epidemics and to implement adequate preventive and control measures.

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Randomness of Dengue Outbreaks on the Equator

Yirong Chen, Alex R. Cook, Alisa X.L. Lim

A simple mathematical model without seasonality indicated that the apparently chaotic dengue epidemics in Singapore have characteristics similar to epidemics resulting from chance. Randomness as a sufficient condition for patterns of dengue epidemics in equatorial regions calls into question existing explanations for dengue outbreaks there.

Dengue, a vectorborne infectious disease, has complex epidemiologic dynamics (*1*). The recent expansion of the range of dengue makes this disease a considerable public health concern worldwide (*2*). In the city-state of Singapore, the number of dengue cases has increased dramatically since the 1990s, and all 4 serotypes of the dengue virus are endemic (*3*). Cyclical outbreaks of dengue of increasing magnitude have been observed with a cycle of 5–6 years (*4*), but this pattern appeared to cease in 2005, and no obvious cycle has occurred since then. Although other tropical and subtropical countries in Southeast Asia have distinct seasonality (*5*) so that dengue epidemics occur at distinct and predictable times of the year (*6*), Singapore's proximity to the equator gives it an aseasonal climate, and the timing of dengue epidemics is irregular (*7*,*8*).

Many factors have been postulated to contribute to dengue's spread in Singapore, such as a consistently warm and humid climate that favors year-round vector proliferation, high urbanization, and a tendency for vectors to live in human residences (*9*). The extent to which these factors affect dengue epidemics in aseasonal Singapore, if they do at all, is unclear. Competing explanations for the timing of large dengue outbreaks in Singapore can be found in the literature. One study attributes dengue epidemics to conducive temperatures and precipitation variations (*10*); another attributes them to variable maximum and minimum temperatures (*11*). Rainfall and temperature have been shown to be related to dengue outbreaks in Brazil, another equatorial country (*12*).

The tendency to see patterns where none exists has been well recognized. When 2 events happen contemporarily and a plausible story connects the events, the tendency to assume that 1 causes the other is strong (*13*). Cancer cases cluster around mobile phone masts (base stations), not because the radiation from a mast is carcinogenic at typical exposures but because numerous masts exist and occasionally cancer cases cluster together, similarly to spilled grains of rice (*14*). A study in the heuristics and biases program discusses a famous example from sports (*15*), which are notorious for stories being concocted around essentially chance outcomes. Basketball fans, coaches, and pundits often believe that players have "hot hand" streaks when they have a run of good form, making many shots in succession and playing above their usual level during a match. The study systematically deconstructed this belief by a series of statistical tests that showed that the patterns of actual hits and misses was consistent with mere chance—analogous to sequences of coin tosses rather than an illusory hot hand (*15*).

In probabilistic models, chance is represented by error terms, or noise, encompassing all the many complicating factors that are not worth including in the systematic signal. Past models for dengue in Singapore have accounted for chance alongside systematic effects of the weather and other factors (*10*,*11*). However, is chance alone sufficient to explain the frequent, large, and ostensibly chaotic outbreaks we observe? We sought to assess whether the rise and fall of dengue outbreaks from week to week in Singapore come in runs or are indistinguishable from random noise and thereby whether it is necessary to consider other possible drivers of these epidemics.

The Study

We reviewed data on the weekly incidence of clinically diagnosed dengue in Singapore during 2003–2012. We compared the number of dengue cases per week to a simple simulation model (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/9/14-1030-Techapp.pdf) with no environmental drivers other than the dependence of weekly number of cases from up to 4 weeks before. Summaries of observed incidence and of the simulated aseasonal model were compared for assessing proximity of the behavior of observed cases to the behavior of simulated cases.

The simulation model used was a standard autoregressive time series model in which the number of cases during any week affects the mean number of cases for the 4 weeks that follow. We allowed the simulated number to have a random variation around that mean; data were log-transformed to ensure that incidence was positive. The fitted autoregressive model was used to simulate synthetic dengue outbreaks over multiple decades, and incidence

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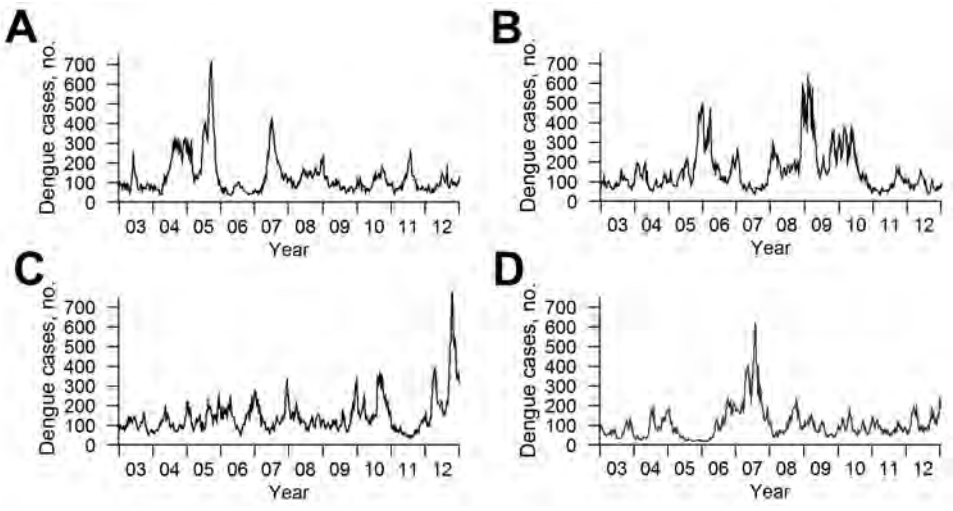

Figure 1. Weekly trends for observed and simulated dengue incidence, 2003–2012, Singapore. A) Weekly trends for the actual scenario of observed dengue incidence. B–D) Three randomly generated simulated scenarios from the aseasonal model described in the text and the online Technical Appendix (http://wwwnc.cdc.gov/EID/article/21/9/14-1030-Techapp.pdf). Although the peaks are not synchronized, similar patterns can be discerned; large and small outbreaks of similar scale and frequency occur in all 4 scenarios.

of simulated outbreaks was compared with observed incidence. We devised a series of statistical measures that were inspired by the "hot hand" in basketball study (*15*) and that might falsify the model that accounted for chance alone. This model included correlation between dengue incidence by week and the preceding week (the autocorrelation function), the probability distribution for the weekly incidence aggregated over 10 years, the distribution of the annual number of cases, the maximum number of cases observed over the previous decade, and the probability of a rise in incidence each week following a series of rises (i.e., the possible beginning of an epidemic) or a series of declines (i.e., the possible ending of an epidemic). We also created simulated trajectories (Figure 1).

Conclusions

For all metrics considered, the actual scenario (i.e., the observed dengue incidence) was fully consistent with the aseasonal model; both the autocorrelation function (Figure 2, panel A) and the cumulative probability of dengue

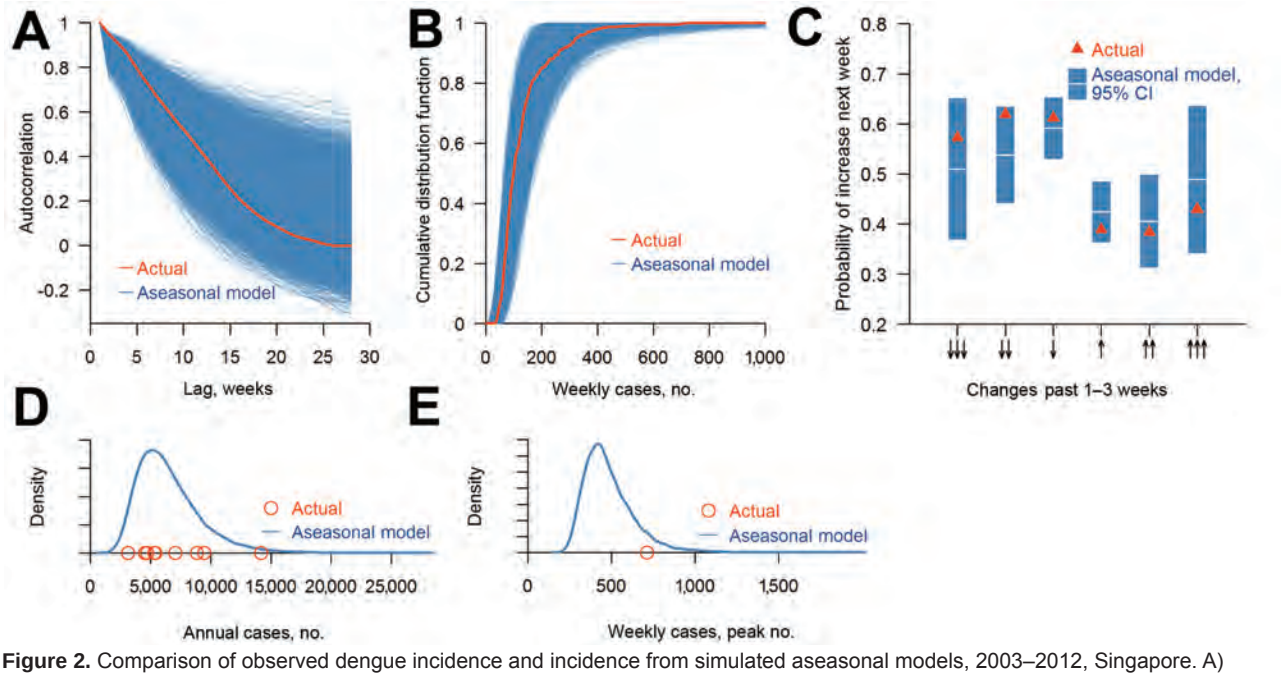

Figure 2. Comparison of observed dengue incidence and incidence from simulated aseasonal models, 2003–2012, Singapore. A) Distribution of actual and simulated autocorrelation functions at different time lags (e.g., this week versus next week; last week versus next week, etc.) B) Distribution of cumulative distribution function of the simulated weekly number of dengue cases and cumulative density function of the actual numbers of cases. C) Conditional probabilities of an increase in number of dengue cases and 95% CIs for simulated scenario and actual data, given 1–3 consecutive decreases or increases. D) Density plot of simulated and actual annual number of dengue cases. E) Density plot of simulated 10-year maximum number of cases and actual 10-year number of cases.

incidence (Figure 2, panel B) from the historical incidence data lie within the distribution resulting from the aseasonal model. The probabilities of an increase in incidence each week that follows a series of rises or falls and corresponding 95% CIs calculated on the basis of simulations from the aseasonal model all include the proportions observed historically (Figure 2, panel C). Furthermore, the distribution of the annual incidence (Figure 2, panel D) and the maximum observed incidence over the decade (Figure 2, panel E) are consistent with the aseasonal model. Similarly, the number of successive increases or decreases over the decade was consistent with chance ($p = 0.18$).

These metrics are not conventional measures of dengue surveillance data; they capture more complex, emergent properties of the epidemic process. However, our findings show that, for dengue incidence in equatorial Singapore, where average monthly temperatures vary only from 26°C–28°C, randomness alone is sufficient to explain the apparent epidemics of dengue. Although seasonal factors may have a role, as the literature suggests (*10*,*11*), seasonality or other temporal drivers such as fluctuation in the intensity of the country's vector control program are not necessary to explain the qualitative and quantitative patterns of dengue in this equatorial city-state. As our results suggest, the possibility that dengue outbreaks occur in aseasonal locations because of chance should be considered.

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Data used in this paper are available at http://www.moh.gov.sg.

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Acute Respiratory Infections in Travelers Returning from MERS-CoV–Affected Areas

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We examined which respiratory pathogens were identified during screening for Middle East respiratory syndrome coronavirus in 177 symptomatic travelers returning to Ontario, Canada, from regions affected by the virus. Influenza A and B viruses (23.1%) and rhinovirus (19.8%) were the most common pathogens identified among these travelers.

Middle East respiratory syndrome coronavirus (MERS-CoV) was originally described in 2012 in a patient with severe pneumonia in Saudi Arabia (*1*). The virus has been detected in several countries of the Middle East, causing acute respiratory disease and having a case-fatality rate of ≈35% (*2*). Although the exact epidemiology and mode of transmission remains ill-defined, MERS-CoV appears to be transmitted through respiratory droplets and most likely has zoonotic reservoirs in dromedary camels and possible origin in bats (*1*). Recent evidence suggests human infection results from repeated introduction of the virus from camels to humans, and less severe human-to-human transmission probably requires close contact with infected persons (*2*,*3*).

As of June 16, 2015, the World Health Organization (WHO) reported 1,293 laboratory-confirmed cases of MERS-CoV, of which 458 (35.4%) were fatal, and ongoing transmission in Saudi Arabia (*2*). Reported cases are centralized in and around the Arabian Peninsula (Saudi Arabia, United Arab Emirates [UAE], Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, and Yemen); Saudi Arabia and UAE account for ≈95.8% of cases (*2*). Internationally, imported cases have been reported outside this zone (United Kingdom, France, Germany, Tunisia, Italy, Malaysia, Philippines, Greece, Egypt, United States, the Netherlands, Algeria, Austria, and Turkey) (*2*). Within Saudi Arabia and UAE, cases are predominantly localized to Jeddah, Riyadh, and Abu Dhabi, each of which operates a high-traffic airport that serves 17–26 million international travelers each year (*4*,*5*). To detect imported MERS-CoV cases, public health authorities in Ontario, Canada, advises testing of persons who have acute respiratory infection (ARI; i.e., symptoms and signs consistent with acute upper or lower respiratory tract infections) of any severity and recent travel to MERS-CoV–affected areas or of persons with ARI and recent close contact with ill travelers from affected areas (*6*).

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Peak travel periods to Saudi Arabia (e.g., Ramadan, Umrah, or the Hajj) are of particular concern, although after the 2012 and 2013 Hajj, no MERS-CoV cases were identified in persons returning to France (*7*). High incidences of other respiratory diseases in pilgrims varied by year. In this study, we aimed to explore the array of respiratory pathogens in travelers with ARI returning to Ontario from MERS-CoV–affected areas or in their close symptomatic contacts.

The Study

During November 2012–June 2014, a total of 177 international travelers returning to Ontario were considered persons under investigation (PUIs) for MERS-CoV, according to the guidelines of the Ontario Ministry of Health and Long-Term Care (*6*). PUIs were recommended to be isolated and screened for MERS-CoV and other respiratory pathogens (*6*).

Nasopharyngeal swab samples and, for persons on ventilators, bronchoalveolar lavage specimens were collected from patients and submitted to Public Health Ontario Laboratories (PHOL), the provincial reference laboratory for MERS-CoV testing (*6*). Fecal specimens were collected when patients had diarrhea, and urine was collected during early phases of the outbreak when appropriate specimens were ill-defined (*6*).

MERS-CoV real-time reverse transcription PCR (rRT-PCR) targeted regions upstream of the E gene and within open reading frame 1b, as recommended by WHO (*8*). Influenza rRT-PCRs targeted the influenza A matrix gene and influenza B nonstructural 1 gene using Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) protocols. If the rRT-PCR was positive for influenza A virus, we conducted subtyping for seasonal influenza A(H3N2) virus hemagglutinin gene (CDC assay) and influenza A(H1N1) pdm09 virus neuraminidase gene (in-house assay) (*9*). Respiratory specimens were further tested by using Seeplex RV15 ACE multiplex respiratory viral assay (Seegene Inc., Seoul, South Korea). Targets included human rhinovirus, enterovirus, influenza A and B viruses, parainfluenza viruses 1–4, respiratory syncytial virus A and B, adenovirus, bocavirus, human metapneumovirus, human coronavirus OC43, and human coronavirus 229E/NL63. *Mycoplasma pneumoniae* and *Chlamydophila pneumophila* testing was conducted by using ProPneumo-1 multiplex assay (Gen-Probe Inc., San Diego, CA, USA). PCR was conducted for *Legionella* species by using a protocol developed by CDC (*10*); BinaxNOW Legionella Urinary Antigen Test (Binax

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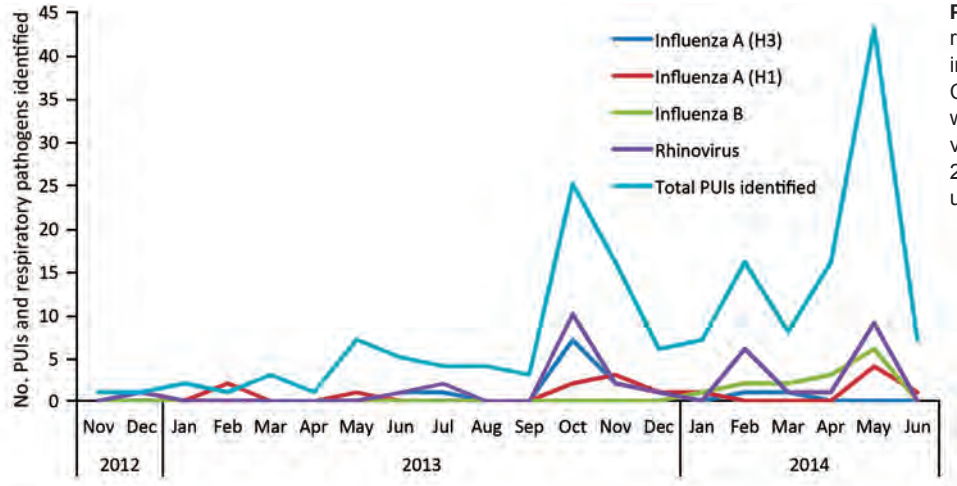

Figure. PUIs and counts of major respiratory pathogens identified in travelers returning to Ontario, Canada, from countries affected with Middle East respiratory virus coronavirus, December 2012–June 2014. PUI, persons under investigation.

Inc., Portland, ME, USA) was also conducted to test for *L. pneumophila* serogroup 1.

Of 177 PUIs (mean age 48.1 years, range <1–88 years; 56% male), 54.8% returned from Saudi Arabia or UAE. Identification of PUIs peaked after the October 2013 Hajj and after the first 2 MERS-CoV cases were imported into the United States in May 2014 (Figure). All PUIs had ARI; of the 85 PUIs for whom data were available, 47 (55%) and 74 (87%) had respiratory specimens collected within 5 and 14 days (median 4 days) from symptom onset, respectively. Specimens collected were as follows: 185 upper respiratory, 10 lower respiratory, 98 urine, 97 blood, 11 fecal, and 1 pleural fluid. Symptom onset varied from 17 days before return to 10 days after return (median ≤1 day after return) for the 20 PUIs for whom this information was supplied. One patient was excluded from the time-to-collection analysis because the specimen was collected under extenuating circumstances: testing was conducted because of worsening respiratory symptoms beginning 57 days before the patient returned from overseas.

At least 1 respiratory pathogen (bacterial or viral) was detected in 89 (50.3%) PUIs; however, for most (87 [98%] of 89) patients, only viral pathogens were identified (Table). Influenza was the most common virus identified: 27 (15.3%) persons tested positive for influenza A, 14 (7.9%) for A(H3N2) and 13 (7.3%) for A(H1N1)pdm09;

Table. Respiratory pathogens detected among 177 persons tested for MERS Co-V at Public Health Ontario Laboratories, Ontario, Canada, November 2012–June 2014*

Pathogen†	Case count		
	No. (%)‡	Highest no. imported in 1 mo	Time of highest no.
Influenza viruses			
Influenza A (H3) virus	14 (7.9)	7	2013 Oct
Influenza A(H1N1)pdm09 virus	13 (7.3)	4	2014 May
Influenza B virus	14 (7.9)	6	2014 May
Other respiratory viruses			
Rhinovirus	35 (19.8)	10	2013 Oct
Parainfluenza viruses 1–4	5 (2.8)	1	NA
Human metapneumovirus	4 (2.6)	2	2014 May
Respiratory syncytial virus (A and B)	4 (2.6)	1	NA
Enterovirus	1 (0.6)	NA	NA
Adenovirus	1 (0.6)	NA	NA
Bocavirus	0	NA	NA
Human CoVs			
Human CoV OC43	6 (3.4)	3	2014 Feb
Human CoV 229E/NL63	2 (1.1)	1	NA
MERS-CoV	0	NA	NA
Bacteria			
Chlamydophila pneumoniae	1 (0.6)	NA	NA
Legionella spp.	1 (0.6)	NA	NA
Mycoplasma pneumoniae	0	NA	NA

*CoV, coronavirus; MERS, Middle East respiratory virus; NA, not applicable.
†Among the 177 returned travelers, no respiratory pathogen was found for 88 (49.7%). Among the remaining 89 (50.3%) returned travelers, at least 1 respiratory pathogen was found; 12 (6.8%) of these persons had viral co-infections. Among the 12 co-infections were 8 rhinovirus co-infections (4 persons with influenza A and 1 each with influenza B, enterovirus, CoV OC43, parainfluenza); 1 influenza A–CoV OC43 co-infection; 1 influenza B–respiratory syncytial virus; 1 CoV 229E/NL63–adenovirus; and 1 CoV 229E/NL63–human metapneumovirus co-infection.
‡Comprises all reported infections, including viruses that were involved in co-infections.

14 (7.9%) tested positive for influenza B. Rhinovirus was also common, detected in 35 (19.8%) persons, with a peak in the fall, in keeping with its seasonality in Canada (Figure; Table). Similarly, influenza A(H3N2) peaked in the fall, whereas influenza B and A(H1N1)pdm09 peaked in late spring.

No specimen submitted to the PHOL tested positive for MERS-CoV. Given the relatively low volume of travelers arriving to Canada and Ontario from MERS-CoV–affected areas (0.6% of total global travel from MERS-CoV–affected areas entered Canada during June–November, 2012, and <50,000 nonresident travelers entered Ontario from affected countries in 2012 [*11*,*12*]) and lower rates of human-to-human transmission, risk of importation to Ontario and subsequent local spread is likely low (*1*,*13*).

Conclusions

Although the risk for MERS-CoV importation is low, respiratory virus infections acquired abroad or locally after returning to Canada might be relatively high and consistent, occurring in 87 (49.2%) of 177 PUIs during the study period. Most influenza B cases were detected shortly after the 2014 Ontario peak (PHOL, unpub. data). Furthermore, 75% of PUIs with influenza B reported symptom onset within 4 days after their return, possibly indicating local acquisition. Similarly, PUIs with enterovirus or rhinovirus detected probably acquired disease in Canada, given the short incubation period (mean 1.9 days) of rhinovirus (*14*).

Because limited information about clinical severity or outcomes was reported to PHOL, we were unable to report on the clinical spectrum of PUI presentation. Furthermore, pathogens were not identified for all samples, possibly because of delays between symptom onset and specimen collection, sampling technique, or other factors.

The number of PUIs with influenza (41 [23.2%]), whether acquired locally or abroad, is of particular concern. Unnecessary identification of PUIs might have been avoided with more comprehensive vaccination coverage. Influenza vaccination should be a priority for all persons and should be recommended by health care practitioners who advise travelers. In addition, surveillance should continue for other respiratory pathogens so that their effects on health systems, when they co-circulate with emerging pathogens with similar clinical presentation, can be better understood.

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Third Wave of Influenza A(H7N9) Virus from Poultry, Guangdong Province, China, 2014–2015

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Fourteen influenza A(H7N9) viruses were isolated from poultry or the environment in live poultry markets in Guangdong Province, China during 2014–2015. Phylogenetic analysis showed that all viruses were descended from viruses of the second wave of influenza A(H7N9) virus infections during 2013. These viruses can be divided into 2 branches.

A new influenza A(H7/N9) virus was detected in China on February 19, 2013, and has caused worldwide concern (*1*). Since 2013, the outbreak of this virus in humans has occurred in 3 waves. The third wave began when 2 additional laboratory-confirmed cases of human infection with this virus were detected in Xinjiang Province, China, on September 2, 2014. This wave has continued with increasing numbers of human cases during 2015, including infections in Fujian, Hong Kong, Guizhou, Jiangsu, and Guangdong Provinces. The largest number of human cases has been reported in southern China; >50 infected patients were detected in Guangdong Province January and February (*2*).

The virus has been identified as a novel triple reassortant of avian influenza A(H7N3), A(H7N9), and A(H9N2) viruses and has low pathogenicity in poultry (*3*–*5*). Influenza A(H7N9) virus is now endemic to China, and its continuing reassortment in poultry makes it probable that humans will continue to be infected sporadically.

Because influenza A(H7N9) virus–contaminated live poultry markets (LPMs) are regarded as major sources of human infections with this virus (*6*–*8*), we implemented LPM sampling programs in Guangdong Province and analyzed the evolution of the virus during the third wave. In this study, we also collected samples from chicken farms and integrated epidemiologic and sequence data to infer the genetic diversity and evolution of influenza A(H7N9) viruses found in poultry in Guangdong Province, China.

The Study

Poultry surveillance for influenza A(H7N9) virus was conducted at LPMs and chicken farms in Guangdong Province (4 LPMs in Guangzhou, 4 LPMs in Dongguan, 1 LPM in Shanwei, 1 LPM in Chaozhou, 2 farms in Huizhou, and 1 farm in Foshan) during September 1, 2014-February 28, 2015. Throat and cloacal swab specimens were collected every 2 weeks. Specific pathogen-free embryonated chicken eggs were used for virus isolation. Hemagglutination-positive isolates, based upon the agglutination of erythrocytes, were collected and were further subtyped by using hemagglutination inhibition assays and reverse transcription PCR.

Fourteen influenza A(H7N9) virus–positive isolates (Figure 1; online Technical Appendix Table 1, http://wwwnc.cdc.gov/EID/article/21/9/15-0635-Techapp1.pdf) were sequenced. Full-genome sequences generated in this study were submitted to the Global Initiative on Sharing All Influenza Data (GISAID; http://platform.gisaid.org/epi3/frontend#41ab15) under accession nos. EPI_ISL_176816–176820, 176824, 176828, 176830, and 176832–176837.

To understand the molecular epidemiology of these viruses, we compared our data with gene sequences of influenza A(H7N9) viruses in public databases at the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/) and GISAID on March 1, 2015. These data included all available complete gene sequences from influenza A(H7N9) viruses and sequences with high degrees of homology from other subtype viruse gene sequences (hemagglutinin [HA], n = 323; neuraminidase [NA], n = 301; polymerase basic [PB] 2, n = 380; PB1, n = 286; polymerase acidic [PA], n = 286; nonstructural [NS], n = 326; nucleoprotein [NP], n = 311; and matrix [M], n = 316).

Maximum-likelihood trees were estimated for all 8 gene segments by using MEGA version 5.01 (http://www.megasoftware.net). To assess the robustness of individual nodes on phylogenetic trees, a bootstrap resampling process (1,000 replications), the neighbor-joining method, and the maximum composite likelihood model were used.

Phylogenetic analyses of HA genes confirmed that all third-wave influenza A(H7N9) viruses in Guangdong Province were descended from viruses of the second wave (Figure 2). It is clear that 2 H7N9 lineages co-circulate in Guangdong because third-wave viruses clustered into 2 major clades designated W3-a and W3-b, both of which emerged from the wave 2 clade. The W3-a clade contains viruses detected in Dongguan, Guangzhou, and Huizhou, and clusters of viruses

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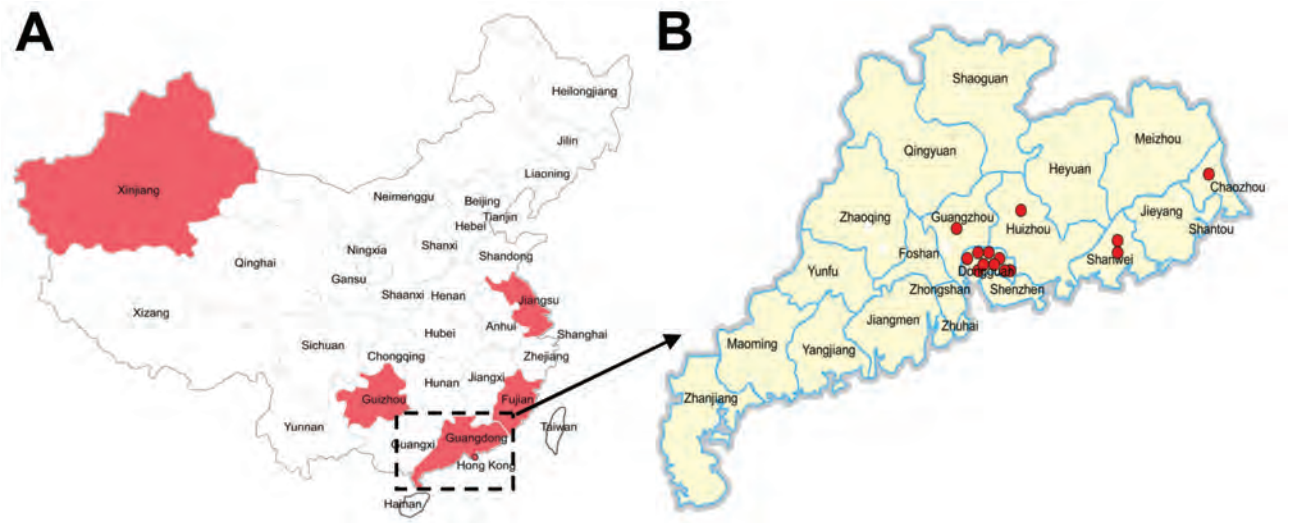

Figure 1. Distribution of influenza A(H7N9) viruses, Guangdong Province, China. A) Shading indicates locations where viruses were isolated from patients during the third wave of the virus mapped according to data from the World Health Organization as of March 1, 2015. B) Circles indicate locations where influenza A(H7N9) viruses were isolated from poultry in Guangdong Province, China, during 2014–2015 (this study).

from Guangdong, Hong Kong, and Guangxi, which suggests that W3-a viruses from poultry were simultaneously prevalent in humans residing in these localities. In contrast, A/chicken/Guangdong/GZ068/2015 (H7N9) virus showed major genetic divergence from these viruses.

The W3-b clade contains viruses detected in Shanwei and Chaozhou, including A/chicken/Guangdong/CZ145/2015 (H7N9), A/chicken/Guangdong/SW153/2015(H7N9), and A/chicken/Guangdong/SW154/2015(H7N9), that clustered with strains detected in Xinjiang, Fujian, Guizhou, and Jiangsu from humans or the environment during the third wave. These data suggest regional spread of the viruses, probably by regional transport of poultry or by migratory bird populations. Phylogenetic analysis of N9 NA genes showed a topology similar to that of H7 HA genes.

Phylogenetic trees were constructed for each internal gene segment against all currently available H7N9 subtype and other subtype virus sequences (highest homology strains from BLAST [http://blast.ncbi.nlm.nih.gov/Blast.cgi]) from the National Center for Biotechnology Information and GISAID. Phylogenetic analysis of the whole-genome sequences showed that all 6 internal genes of DG478/2014, DG592/2014, DG593/2014, DG479/2014, DG527/2014, HZ098/2015, DG120/2015, and DG127/2015, and the PB1, PB2, PA, and NP genes of DG103/2015, DG104/2015 clustered with strains A/Guangdong/02496/2014(H7N9) and A/Hong Kong/8130773/2015(H7N9) from humans. The NS gene of DG103/2015 clustered with A/Guangdong/15SF018/2015(H7N9). The M gene clustered with A/Hong Kong/8122430/2014(H7N9).

The internal genes of CZ145/2015, SW153/2015, and SW154/2015 showed different genetic characteristics. PB1, PB2, NP, and NS genes of SW153/2015 and SW154/2015 clustered with A/Taiwan/2/2014(H7N9), and M and PA genes were closely related to those of strains isolated in eastern China during the second wave. Internal genes, except for the PA gene of CZ145/2015, clustered with strains isolated from humans in Xinjiang. The PA gene also has a close genetic relationship with the PA gene of an H9N2 subtype strain (A/chicken/Suzhou/097–2/2013).

We conjecture that DG103/2015, CZ145/2015, SW153/2015 SW154/2015, and GZ068/2015 viruses might have undergone additional reassortment, but we cannot infer from our dataset the time, place, or with which other strains these isolates reassorted. Phylogenetic analysis of internal genes also suggested that evolution of wave 3 influenza A(H7N9) viruses resulted in a major increase in genetic diversity and sequential reassortment events with local H9N2 subtype or other subtype viruses (online Technical Appendix Figures 1–6).

We conducted mutation analyses of critical and apparent amino acid residues of influenza A(H7N9) virus isolates. All H7N9 subtype viruses isolated have an amino acid PB2-627E, PB2-701D, HA-226L(H3 numbering), NA-289R (N9 numbering), M2-31N, and HA-cleavage sites–PEIPKGRG (online Technical Appendix Table 2). These amino acid residues showed no changes when compared with those of other virus isolates from poultry. All viruses have M2-31N, which might be involved in resistance to adamantane (*9*). Four H7N9 subtype viruses have HA-186V (H3 numbering) and other viruses have HA-186A (H3 numbering). HA-186V may increase binding affinity for the α (2–6)-linked sialic acid receptor (*10*,*11*).

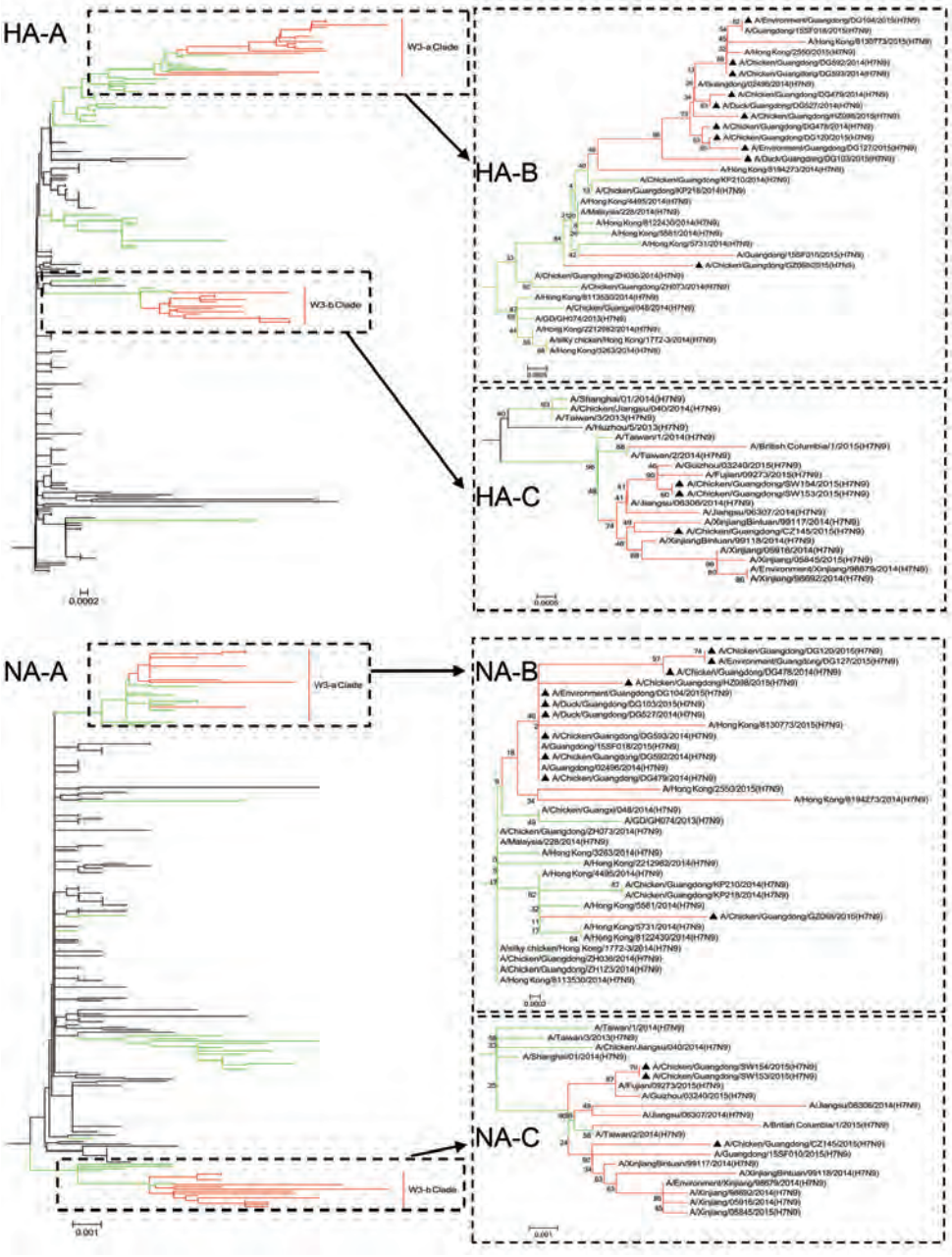

Figure 2. Phylogenetic relationships of influenza A(H7N9) virus hemagglutinin (HA) and neuraminidase (NA) genes isolated from poultry, Guangdong Province, China, 2014–2015. Phylogenetic trees were constructed by using the neighbor-joining method in MEGA software (http://www.megasoftware.net/). B and C are enlargements of A. Branches of the first, second, and third influenza A(H7N9) virus waves are shown in black, green, and red, respectively. Black triangles indicate newly sequenced viruses isolated from poultry in Guangdong during the third wave. Scale bars indicate nucleotide substitutions per site.

PB2-627K can enhance viral replication and virulence in a mice model (*12*), but all H7N9 subtype viruses in our study have PB2-627E. Thus, these strains might be less able to replicate and cause disease in mammals. Although most of the phenotypes associated with the amino acid substitutions have been demonstrated for subtypes other than H7N9, we cannot be sure that these phenotypes are also present in H7N9 subtype viruses.

Conclusions

Fourteen influenza A(H7N9) viruses were isolated from poultry or environment in LPMs in Guangdong Province, China, during 2014–2015. Phylogenetic analyses of HA and NA genes confirmed that all third-wave influenza A(H7N9) viruses in Guangdong Province were descended from viruses of the second wave. Two H7N9 lineages from poultry co-circulated in Guangdong Province during the third wave, and both are closely related to H7N9 strains isolated from humans in local or adjacent regions. These data suggest that the dominant H7N9 strains have a dynamic evolutionary process for adapting to the local environment. Their internal genes show more regional characteristics, which might be related to transportation of live birds across provinces or to migratory birds.

The results of our study are limited by the number of samples obtained and locations of sampling. However, our findings serve as a warning to public health officials to be aware of the risk of poultry farms being infected with influenza A(H7N9) virus.

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Disseminated Enteroviral Infection Associated with Obinutuzumab

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Two cases of disseminated enteroviral infection occurred in patients who received the CD20 monoclonal antibody obinutuzumab. Clinical features included hepatitis, edema, and a dermatomyositis-like syndrome. These manifestations may be unfamiliar to clinicians and are possibly responsive to intravenous immunoglobulin. Clinicians should remain vigilant for enteroviral infections in patients receiving obinutuzumab.

Viral, fungal, and bacterial infections (*1*,*2*) and a recent case of enteroviral meningoencephalitis (*3*) associated with obinutuzumab use have been described. Early recognition is critical because the infection can be effectively treated with intravenous immunoglobulin (IVIg).We report 2 cases of disseminated enteroviral infections in patients in Australia treated for lymphoma with the CD20 monoclonal antibody (mAb) obinutuzumab. Clinical features, including hepatitis, edema, and a dermatomyositis-like syndrome, were similar to those mentioned in the original descriptions of disseminated enteroviral infections in children with X-linked agammaglobulinemia (XLA) (*4*,*5*).

Case Reports

Case 1

During summer 2014, a 63-year-old woman with symptomatic high tumor burden follicular lymphoma achieved a complete clinical and radiologic response to induction treatment with 6 cycles of bendamustine and obinutuzumab, then began maintenance therapy with obinutuzumab for 8 weeks. Eleven months after she began taking obinutuzumab, the patient sought treatment for 4 weeks of fatigue, myalgias, muscle tenderness, and leg edema without fever. Peripheral blood lymphocyte count was 0.52×10^9 cells/L (reference range 1–4 $\times 10^9$ cells/L), and lactate dehydrogenase was 354 IU/L (reference range 100–200 IU/L); serum creatine kinase and inflammatory markers were within reference ranges. Immunoglobulin levels were also within reference ranges: IgG 10.2 g/L, IgM 0.3 g/L, and IgA 1.3 g/L. The patient had moderately impaired liver function and was hypoalbuminemic without evidence of renal protein loss. Magnetic resonance imaging of the thighs showed diffuse inflammatory changes involving subcutaneous tissues, fascia, and musculature (Figure). Results of tests to determine possible causes of muscle pathologic changes were negative; tests included those for autoantibodies, HIV antibodies, thyroid function, and PCR for respiratory viruses (including influenza) and herpesvirus. Bone marrow biopsy results indicated no evidence of lymphoma. Muscle histopathologic findings from a biopsy of the quadriceps showed features of an inflammatory myopathy (interstitial edema, perivascular lymphocytic cuffing, and degenerating fibers) consistent with the features of early dermatomyositis. Reverse transcription PCR of the muscle tissue indicated enterovirus RNA. Reverse transcription PCR also detected enterovirus RNA in plasma, nasopharyngeal, and fecal specimens. Viral protein 1 gene obtained from RNA extracted from muscle was sequenced, and we identified the virus as echovirus 6. When we ceased treatment with obinutuzumab and gave the patient 0.8 g/kg IVIg, her symptoms rapidly improved. Results from a repeat plasma enterovirus PCR 11 days after initiation of IVIg were negative.

Case 2

During summer 2014, a 35-year-old woman with symptomatic follicular lymphoma achieved a complete clinical and radiological response to induction treatment with 6 cycles of bendamustine and obinutuzumab; she subsequently took obinutuzumab for an additional 8 weeks. Twelve months after she began taking obinutuzumab, she sought treatment for fever, headaches, and myalgias. Peripheral blood lymphocyte count was 0.40×10^9 cells/L (*1*,*2*,*4*,*5*). Cerebrospinal fluid was acellular, but we detected enterovirus in cerebrospinal fluid and feces by using PCR. Sequencing of the PCR product was unsuccessful, and we could not identify the enterovirus strain. Immunoglobulin levels were at the lower end of the reference ranges: IgG 7.9 g/L (reference range 7.5–15.6 g/L), IgM 0.6 g/L (reference range 0.5–3.0 g/L), and IgA 1.5 g/L (reference range 0.8–4.5 g/L). Results of liver function tests were initially normal, but liver function deteriorated after 2 weeks. Peak level of bilirubin was 86 μmol/L (reference range 0–20 μmol/L), of alanine aminotransferase was 1,419 IU/L (reference range 7–56 UI/L), of alkaline phosphatase was 117

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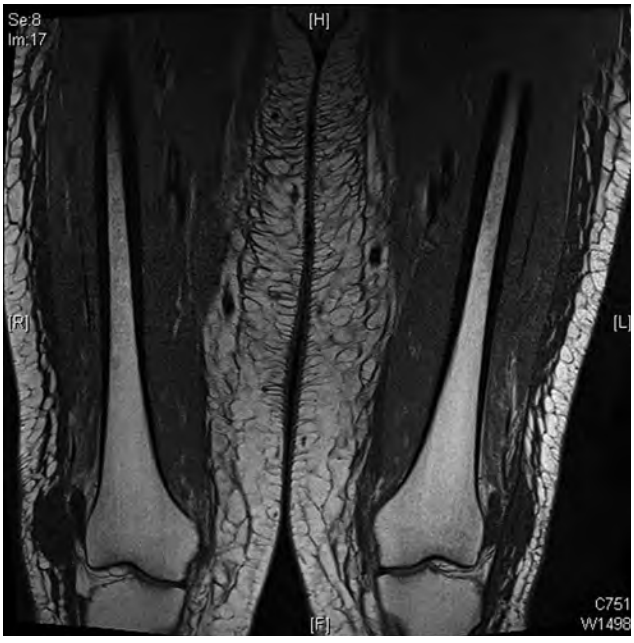

Figure. Magnetic resonance image of 63-year-old woman in Australia with disseminated enteroviral infection that manifested after she received obinutuzumab for lymphoma. Image shows patient's thighs and diffuse inflammatory changes involving subcutaneous tissues, fascia, and musculature.

U/L (reference range 30–120 U/L), and of albumin was 28 g/L (reference range 35–45 g/L); international normalized ratio peaked at 2.0 (reference range 0.8–1.2). Results of liver biopsy showed active hepatitis. Results of tests to determine possible causes of hepatitis and encephalitis were negative; the tests included those for autoantibodies, HIV antibodies, thyroid function, and PCR for respiratory viruses (including influenza) and herpesvirus. Bacterial and fungal cultures were negative. Obinutuzumab was ceased, and the patient was treated with 0.8 g/kg IVIg. All clinical and laboratory features rapidly improved.

Conclusions

Anti-CD20 mABs such as rituximab are now standard of care for treatment of B-cell lymphoma in combination with chemotherapy. The US Food and Drug Administration approved obinutuzumab in September 2013 for use in chronic lymphocytic leukemia, but indications for use probably will expand. Obinutuzumab is glycoengineered to cause more profound and rapid B-cell depletion than rituximab, elicited by subtle differences in the orientation of binding to the CD20 molecule between the 2 drugs (*6*). As a result of these binding differences, compared with rituximab, obinutuzumab has superior induction of apoptosis, natural killer cell activation, and antibody-dependent cytotoxicity but less complement-dependent toxicity (*6*).This mechanism may also explain the differences in susceptibility to, and patterns of, enteroviral infections associated with obinutuzumab, resulting in a phenotype similar to XLA (*5*).

Antibodies are the main form of defense against enteroviruses (*7*), and severe, chronic, and disseminated enteroviral infections are generally limited to neonates or patients with profound B-cell deficiencies (XLA or hematopoietic stem cell transplantation). During the 1970s and 1980s, reports described the clinical manifestation of disseminated enterovirus infection in children with XLA (*4*,*5*) and demonstrated that IVIg is an effective therapy for disseminated enterovirus infection (*7*,*8*). Since then, reports of disseminated enteroviral infections have been uncommon. Enteroviral infection has not featured prominently among patients with partial B-cell or immunoglobulin deficiencies, such as patients with chronic variable immunodeficiency (*7*). Immunoglobulin levels of the 2 patients in our study were within reference ranges, but analysis of lymphocyte subsets was not performed. Both patients received the combination of obinutuzumab and bendamustine; it is possible that an association exists between the 2 drugs that results in increased host susceptibility to disseminated enteroviral infection.

The clinical features described in most cases of disseminated enteroviral infections relate to chronic meningoencephalitis (*2*,*5*). However, several reports describe a dermatomyositis-like syndrome with edema and hepatitis that responded to IVIg (*5*); this syndrome is strikingly similar to the cases reported here. Enteroviral infections (coxsackieviruses and echoviruses) also have been implicated in the pathogenesis of myositis (*9*). Enterovirus PCR was positive from the muscle biopsy of the patient in our report, suggesting that the virus had a direct role in pathogenesis of the myositis.

Reports of enteroviral infections associated with rituximab use since its introduction have been rare, in contrast to obibutuzumab, for which a case of enteroviral meningencephalitis has been reported (*2*,*3*). Of the 11 cases of enteroviral infection associated with rituximab use, 8 were meningoencephalitis and 2 were myocarditis (*2*,*10*–*12*). To our knowledge, enteroviral infection has not previously been associated with rituximab use in patients who also had hepatitis, dermatomyositis, and edema, as in the cases we report and those associated with XLA (*5*).

Future studies could define susceptibility to enteroviruses through the effect of obinutuzumab on B-cell and immunoglobulin function and host defense against enteroviral infections. It would be clinically useful to identify biomarkers or clinical predictors of disseminated infection. Future research might also focus on the development of a screening strategy for enteroviral infections followed by prophylactic or preemptive therapy with IVIg.

The clinical manifestation of disseminated enteroviral infections, particularly those similar to dermatomyositis, may be unfamiliar to clinicians caring for adults because

most experience of the illness is in children and there have been few reports in recent years. Given the therapeutic response to IVIg in the cases we report, enteroviral infection and the use of IVIg therapy should be considered in patients treated with obinutuzumab who develop atypical clinical features of organ inflammation.

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Laboratory Testing for Middle East Respiratory Syndrome Coronavirus, California, USA, 2013–2014

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Since Middle East respiratory syndrome coronavirus (MERS-CoV) first emerged, the California Department of Public Health has coordinated efforts to identify possible cases in travelers to California, USA, from affected areas. During 2013–2014, the department investigated 54 travelers for MERS-CoV; none tested positive, but 32 (62%) of 52 travelers with suspected MERS-CoV had other respiratory viruses.

Middle East respiratory syndrome coronavirus (MERS-CoV) has been a global concern since its discovery in Saudi Arabia in 2012. As of April 29, 2015, >1,100 confirmed MERS cases and >420 associated deaths had occurred globally; all cases were linked to the Middle East (*1*). Importation of MERS-CoV by travelers from the Arabian Peninsula to regions outside the Middle East has been documented (*2*). In May 2014, the first 2 cases of MERS in the United States were identified in unrelated travelers from Saudi Arabia (*3*).

Each year, an estimated 16 million international travelers visit California (*4*), of whom 225,000 are visitors from the Middle East (*5*); thus, a risk exists for importation of MERS-CoV into California. Furthermore, global events such as the annual Hajj and Umrah pilgrimages draw 11,000 Americans to Saudi Arabia each year (*6*).

Because of the possible risk for disease transmission, the Centers for Disease Control and Prevention (CDC) and the World Health Organization have issued MERS-CoV travel advisories for pilgrims traveling to Saudi Arabia (*7*,*8*). In the fall of 2012, the California Department of Public Health (CDPH) addressed the risk of MERS-CoV importation and convened a working group composed of clinicians, laboratory staff, infection control experts, emergency operations staff, and information officers. This working group regularly reviewed the CDC and World Health Organization updates, scientific publications, and laboratory logistics, and took steps at the state level to prepare for MERS. CDPH developed and disseminated guidance on surveillance, specimen collection for laboratory testing, infection control, and contact tracing (*9*). A CDPH clinician was available around the clock 7 days a week to assist with individual suspected cases of MERS.

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The Study

CDPH created a laboratory testing plan to detect or rule out MERS-CoV infection in patients who, after review by CDPH clinicians, met specific clinical and travel criteria, per CDC case definitions (*10*), to be considered a patient under investigation (PUI). Once a MERS PUI was identified, the patient's specimens were transported from the hospital or local public health laboratory to CDPH in Richmond, California, for MERS-CoV testing. Specimens tested for each PUI consisted of ≥1 of the following: upper respiratory tract sample (nasopharyngeal and oropharyngeal swab specimens), lower respiratory tract sample (sputum and lower respiratory tract aspirates or washes), serum, or stool. Time from specimen collection to receipt at CDPH was up to 48 hours for most PUIs (37/52 [71%]). Because subsequent steps in infection control and patient management heavily depended on the test results, MERS-CoV testing at CDPH was expedited; the typical turnaround time was 4 hours from receipt of specimens to reporting of results.

During February–June 2013, specimens from MERS PUIs were tested at CDPH for MERS-CoV by using an in-house real-time reverse transcription PCR (rRT-PCR) assay that amplified the following 3 targets in the MERS-CoV genome: UpE, N2, and N3 (*11*). CDPH implemented CDC's Novel Coronavirus 2012 Real-Time RT-PCR Assay protocol subsequent to its Emergency Use Authorization by the US Food and Drug Administration in June 2013 (*12*).

For persons with a suspected past MERS-CoV infection, CDPH sent serum specimens to CDC for MERS-CoV serologic testing. Once MERS-CoV infection was ruled out, CDPH tested the remaining respiratory specimens from MERS PUIs for other respiratory pathogens. Specimens were tested by real-time PCR and rRT-PCR for the following agents (*13*): influenza A and B viruses, human metapneumovirus, respiratory syncytial virus, adenovirus, parainfluenza virus (types 1, 2, 3, and 4), enterovirus, rhinovirus, and *Mycoplasma* spp. If an adequate amount of specimen remained, specimens were also tested for the presence of human coronaviruses 229E, OC43, NL63, and HKU1 by rRT-PCR (*13*).

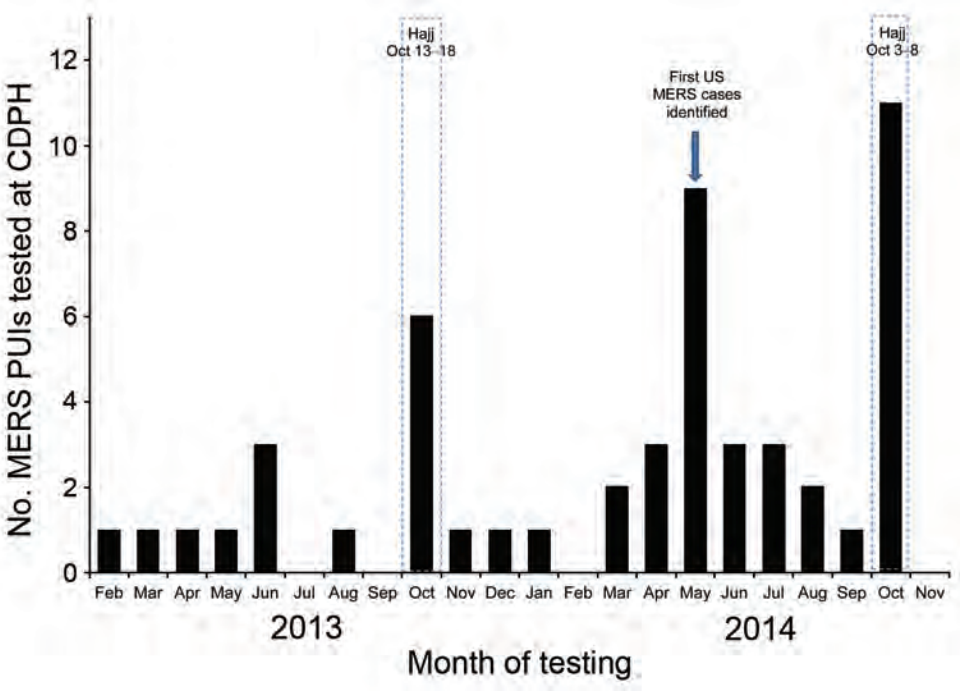

Figure. Middle East respiratory syndrome (MERS) coronavirus patients under investigation (PUIs) tested at the California Department of Public Health (CDPH), 2013–2014. Months during which the Hajj takes place are delineated by dashed lines.

During February 2013–November 2014, CDPH investigated 54 MERS PUIs in California, of whom 52 (total of 188 specimens) had testing conducted by CDPH and 2 had testing conducted by CDC (Figure). The median age for MERS PUIs was 53 years (range 10 months–89 years), and 57% were male and 43% female. A total of 51 (94%) MERS PUIs reported travel from the Middle East, and 2 (4%) were secondary contacts of travelers to the Middle East. A MERS PUI short form or equivalent was submitted to CDC and reported the following clinical outcomes for 42 MERS PUIs: 30 (71%) hospitalized, 11 (26%) admitted to an intensive care unit, 6 (14%) intubated, 21 (50%) received a diagnosis of pneumonia, and 5 (12%) received a diagnosis of acute respiratory distress syndrome.

One or more respiratory viruses were detected in 32 (62%) of the 52 MERS PUIs tested by CDPH; 5 of the 32 patients had a co-infection with rhinovirus plus another respiratory virus. Influenza, the most commonly identified respiratory agent, was detected in 18 (35%) of the 52 MERS PUIs tested by CDPH (Table). *Mycoplasma* spp. was not detected in any specimen tested.

The frequency of MERS PUIs tested by CDPH varied with no apparent seasonality, except for the weeks following the Hajj in 2013 and 2014 (Figure). CDPH also noted an increase in reported MERS PUIs in May 2014 (n = 9) after announcement of the first detected MERS cases in the United States (*3*). This increase likely resulted from media reports that heightened the level of concern among the public and health care workers, which increased the number of suspect MERS cases that CDPH and local partners had to evaluate for subsequent MERS-CoV testing.

Conclusions

As of May 7, 2015, MERS-CoV had not been detected in California. However, MERS-CoV poses a potential threat to global public health because MERS cases continue to be reported in Saudi Arabia, and the reservoir for the virus remains unclear, although camels have been implicated in disease transmission (*14*). CDPH has established a coordinated

Table. Other respiratory viruses detected in MERS patients under investigation tested by California Department of Public Health, 2013–2014*

Virus detected	No. patients, N = 52	% Positive
Influenza only	14	27
Influenza A (H3)	10	19
Influenza A(H1N1)pdm09	3	6
Influenza B	1	2
Noninfluenza only	13	25
Respiratory syncytial virus	1	2
Parainfluenza 3	2	4
Rhinovirus	3	6
Enterovirus	2	4
Human coronavirus 229E	2	4
Adenovirus	3	6
Co-infection	5	10
Influenza A (H3) and rhinovirus	1	2
Influenza A(H1N1)pdm09 and rhinovirus	1	2
Influenza B and rhinovirus	2	4
Parainfluenza 3 and rhinovirus	1	2
No. patients with detected virus	32	62

*MERS, Middle East respiratory syndrome.

statewide system working with local partners to identify potential MERS cases in California travelers returning from MERS-affected regions and their contacts. CDPH has investigated and conducted laboratory testing on >50 MERS PUIs and identified a respiratory virus in 62% of those patients, 35% of which were positive for influenza virus. The high rate of influenza detection underscores the need for all travelers to be immunized for influenza. CDPH continues to evaluate each MERS PUI and expedite MERS-CoV laboratory testing so that prompt implementation of containment procedures and contact investigations may proceed if needed.

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Follow-up of Contacts of Middle East Respiratory Syndrome Coronavirus–Infected Returning Travelers, the Netherlands, 2014

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Notification of 2 imported cases of infection with Middle East respiratory syndrome coronavirus in the Netherlands triggered comprehensive monitoring of contacts. Observed low rates of virus transmission and the psychological effect of contact monitoring indicate that thoughtful assessment of close contacts is prudent and must be guided by clinical and epidemiologic risk factors.

During April 2012–May 2015, the World Health Organization received 1,110 notifications of confirmed cases of infection with Middle East respiratory syndrome coronavirus (MERS-CoV), including at least 422 deaths (*1*,*2*), mostly from countries in the Arabian Peninsula. Travel-related cases have been reported in Europe, Asia, and the United States, with limited, local, person-to-person secondary transmission (*3*).

Although dromedary camels are considered to be the probable source for zoonotic infections in humans, the mode of transmission from animals to humans is not understood (*4*). In 2014, Saudi Arabia experienced an outbreak due to increased zoonotic transmission and amplification by health care–related human-to-human transmission (*3*); the risk for secondary transmission from patients to household contacts was estimated at ≈5% (*5*). To prevent secondary cases and local transmission, the World Health Organization recommends monitoring all contacts of confirmed patients (*6*).

On May 13 and 14, 2014, MERS-CoV infection was confirmed in 2 residents of the Netherlands who had taken pilgrimages to Medina and Mecca, Saudi Arabia (*7*). We undertook comprehensive monitoring of contacts of these patients and evaluated the risk for secondary transmission and the effects of the monitoring on the contacts.

The Study

Formal ethical approval from a medical ethical committee was not required for this research because it was carried out as part of the public health monitoring and evaluation of contacts and did not entail subjecting participants to medical treatment. From the onset of symptoms in the 2 MERS-CoV patients (May 1) until their discharge from the hospital (June 5), they came into contact with 131 persons. Of these, 78 had unprotected exposure (defined as >15 min of face-to-face contact without wearing personal protective equipment) and 53 had protected exposure (defined as providing care while wearing adequate personal protection at all times). Of the unprotected contacts, 29 were members of the patients' travel group, 17 were aircraft contacts, and 32 were contacts in the Netherlands before hospital admission (28 relatives plus 4 persons at a general medical practice and the hospital emergency department, including 1 health care worker). The travel group had traveled with the 2 confirmed case-patients through Saudi Arabia during April 26–May 10 and had direct contact with them. Four travelers reported direct contact with dromedary camels, 11 consumed unpasteurized camel milk, and 4 visited a local hospital. One traveler accompanied 1 case-patient to 4 different hospitals and shared a hotel room with both case-patients (*7*). The aircraft contacts had been seated within 3 rows of the case-patients on the return flight.

All contacts were asked to take their temperature twice a day and report any episode of fever (temperature ≥38°C), cough, diarrhea, or dyspnea for 14 days following their last possible exposure to the case-patients. Unprotected contacts were asked to remain in the country during the monitoring period. Throat swabs were obtained from contacts on days 7 and 14 postexposure, and serum samples were drawn on days 7 and 21 postexposure (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/8/

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Table 1. Laboratory results and compliance of follow-up among 131 unprotected and protected contacts of 2 patients with imported MERS-CoV infections, the Netherlands, 2014*

Type of contact	No. persons	Male sex, %	Median age, y (range)	No. (%) contacts				
				First throat swab sample	Paired throat swab sample	First serum sample	Paired serum sample	Symptomatic
Unprotected contacts	78	40	45 (1–78)	77 (99)	77 (99)	77 (99)	67 (86)	7 (9)
Travel group	29	45	52 (9–70)	29 (100)	29 (100)	29 (100)	28 (97)	2 (7)
Aircraft contacts	17	47	39 (7–78)	17 (100)	17 (100)	17 (100)	14 (82)	2 (12)
Other contacts†	32	32	44 (1–64)	31 (97)	31 (97)	31 (97)	25 (78)	3 (9)
Protected contacts	53	34	36 (18–63)	44 (83)	29 (55)	53 (100)	32 (60)	1 (2)
Total contacts	131	37	41 (1–78)	121 (92)	106 (81)	130 (99)	99 (76)	8 (6)

*MERS-CoV, Middle East respiratory syndrome coronavirus.
†Other contacts were those who had contact with the case-patients after their return to the Netherlands: 28 relatives, plus 4 persons at a general medical practice and the hospital emergency department, including 1 health care worker.

15-0560-Techapp1.pdf). Throat swab samples from 1 relative contact were unavailable; a second serum sample was missing from 7 relatives, 3 aircraft contacts, and 1 travel contact (a woman who had had no contact with animals, had not visited a hospital, and had no concurrent conditions). Eight contacts who reported symptoms (7 unprotected and 1 protected) were sampled immediately after onset of symptoms. MERS-CoV reverse transcription PCR (RT-PCR) was performed on paired throat swabs from 106 (81%) and serologic analysis on paired serum samples from 99 (76%) of the 131 contacts (Table 1). PCR did not detect MERS-CoV RNA from any throat swab or serum samples, and MERS-CoV–specific IgG responses were absent in serum samples tested (*8*) (Table 1). All specimens obtained from the symptomatic contacts tested negative by RT-PCR and analysis of paired serum samples for MERS-CoV.

All contacts also received an online questionnaire containing questions about demographics, type of contact, quality of information received, perceived severity and vulnerability, feelings of anxiety, interference of the measures with daily life, and knowledge of the measures and travel advice (online Technical Appendix). To evaluate the effect of monitoring, we used the Revised Impact of Event Scale (IES-R), a validated questionnaire designed to assess current subjective distress for a specific traumatic life event (*9*). The IES-R contains 22 items divided into 3 subscales: avoidance (e.g., avoidance of feelings), intrusion (e.g., nightmares) and hyperarousal (e.g., anger). The mean score on 3 subscale domains indicates the level of distress experienced (*9*). Mean scores of unprotected contacts were compared with those of protected contacts by a Wilcoxon rank-sum test or *t*-test. Significance was determined at the 5% level (p value $\leq$0.05). A total subjective stress IES-R score with a maximum score of 88 (Likert scale of 0–4 [0, never; 1, seldom; 2, sometimes; 3, often; 4, very often]) can be calculated. We considered a score $\geq$20 to be an indicator of posttraumatic stress disorder to enable comparison with previous studies (*10*,*11*).

Of 131 contacts, 72 (55%, 48 unprotected and 24 protected) filled out the questionnaire. The median age was 39 years (range 9–77 years); 53% were female, and 51% had at least a college education. Protected contacts were younger (median of 31 vs. 48 years) and had a higher education (88% vs. 31%) than unprotected contacts. The mean IES-R score of all contacts was 7.9 (95% CI 5.5–10.3); the score was $\geq$20 for 16 (22%) contacts. Unprotected contacts had a significantly higher mean IES-R score (10.4 95% CI 7.2–13.6 versus 2.9, 95% CI 0.6–5.3); this result was also seen on the different subscale domains (Table 2).

Conclusions

We monitored 131 contacts of 2 case-patients with imported MERS-CoV infections in the Netherlands. Laboratory testing did not indicate transmission of the virus, including among contacts with high-risk exposures or those who developed respiratory symptoms. We also found no infections among travelers from the same group. Our findings agree with reports from Greece and Italy, in which no and limited secondary transmission, respectively, was found among close contacts of MERS-CoV patients (*12*,*13*).

Survey results show a substantial psychological effect of monitoring on contacts, especially unprotected contacts. As with other emerging infections, such as Marburg hemorrhagic fever and severe acute respiratory syndrome, quarantine or monitoring of contacts leads to psychological

Table 2. Results of survey assessing psychological effects of monitoring among 72 contacts of 2 patients with imported MERS-CoV infections, stratified by unprotected versus protected contacts, the Netherlands, 2014*

Category	Mean IES-R score (95% CI)		
	All contacts	Unprotected contacts	Protected contacts
Total IES-R score	7.9 (5.5–10.3)	10.4 (7.2–13.6)	2.9 (0.6–5.3)
Avoidance	2.2 (1.3–3.1)	3.1 (1.8–4.3)	0.5 (–0.04–1.1)
Intrusion	3.4 (2.5–4.4)	4.3 (3.1–5.5)	1.8 (0.5–3.0)
Hyperarousal	2.0 (1.3–2.7)	2.7 (1.7–3.6)	0.6 (–0.04–1.3)

*IES-R, Revised Impact of Event Scale.

distress, measured by high IES-R scores (*10*,*11*,*14*). When stratifying by type of contact, the total mean IES-R score and the subscale scores were highest for unprotected contacts—those with the highest risk for exposure. We found increased symptoms of posttraumatic stress disorder in a considerable number of contacts, similar to findings by Hawryluck et al. (*11*) and Reynolds et al. (*10*).

The survey response rate of 55% limits interpretation of results; motives for noncompliance remain unknown. Also, recall bias might influence recollection of experiences. Besides exposure, monitoring has contributed to the psychological effect. Whether the number of questions induced stress is not known, but participants did not mention this as a concern.

Our findings illustrate the feasibility of comprehensive follow-up of contacts of MERS-CoV patients and clarify the risk for asymptomatic secondary transmission. The psychological effect of contact monitoring and the observed low rates of MERS-CoV transmission in several studies, including this investigation, indicate that thoughtful but limited assessment of close contacts is prudent. Identification of close contacts of those who are infected should be carefully considered, and decisions about monitoring and testing of contacts should be made primarily on the basis of clinical and epidemiologic risk factors.

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Reemergence and Autochthonous Transmission of Dengue Virus, Eastern China, 2014

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In 2014, 20 dengue cases were reported in the cities of Wenzhou (5 cases) and Wuhan (15 cases), China, where dengue has rarely been reported. Dengue virus 1 was detected in 4 patients. Although most of these cases were likely imported, epidemiologic analysis provided evidence for autochthonous transmission.

Four dengue viruses (DENV-1–4) circulate globally (*1*), each associated with either clinically mild dengue fever or, less frequently, with severe disease syndromes including hemorrhagic fever. Dengue is highly prevalent in tropical and subtropical regions, reflecting the distribution of the vector, *Aedes aegypti* mosquitoes. Nearly one third of the global human population is at risk for infection (*2*).

Dengue outbreaks were recorded in China during World War II (*3*). The disease then was not reported for ≈30 years, and reemerged during the late 1970s in Guangdong Province, located in the far south end of the country (*4*). Since then, dengue has been reported each year in China, mainly in Guangdong Province and its neighboring provinces (*4*,*5*). The geographic restriction of dengue to these southern provinces likely reflects temperature constraints in the range of *A. aegypti* mosquitoes. However, increasing travel has resulted in imported dengue cases in other provinces, including northern temperate regions (*6*,*7*), and some instances of autochthonous transmission (*8*).

During 2014, a dengue epidemic occurred in southern China (Figure 1); >40,000 cases were reported (*5*,*9*). This outbreak led to an increase in dengue surveillance in tropical and subtropical regions of China. We describe 20 dengue cases in the eastern coastal city of Wenzhou in Zhejiang Province and in Wuhan, the capital city of Hubei Province in the eastern central region of China (Figure 1), where the virus has rarely been described.

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The Study

During July–November 2014, a total of 20 suspected cases of illness were clinically diagnosed as dengue in Wenzhou (5 cases) and Wuhan (15 cases). The cohort comprised 14 male and 6 female patients 7–61 (median 31) years of age. Of the patients from Wuhan, 11 had recently traveled to Guangdong Province; 3 had recently returned from Indonesia and 1 from Thailand after >1 year away from China. Similarly, 3 of the patients from Wenzhou had traveled recently in Fujian, Thailand, and Surinam. However, there was no evidence of recent travel to endemic regions for the remaining 2 patients, including a 7-year-old boy. Close contacts of these patients denied recent travel to endemic regions, suggesting autochthonous dengue virus transmission in Wenzhou.

Blood samples from each of the 20 patients were collected on day 1 of hospitalization (2–4 days after onset of fever), and were tested for DENV IgM by a non–serotype-specific dengue dual IgM- and IgG-capture ELISA Kit (PanBio, Windsor, NSW, Australia). ELISA results showed 16 serum samples were positive for dengue-specific IgM and 3 for dengue-specific IgG. Although the remaining 4 serum samples were negative for dengue-specific IgM, we amplified DENV sequences from them, as described in the next section. Results of routine microbiologic examinations for bacteria by culture and antigen detection were negative in all cases, as were serologic and genetic tests for hantaviruses, phleboviruses, and *Rickettsiales* bacteria, performed as described (*10*).

The 20 dengue case-patients showed a variety of clinical symptoms (Table): high fever (100%), headache (100%), dizziness (45%), myalgia (50%), nausea and vomiting (40%), rash (40%), and petechiae (25%). In addition, chills, arthralgia, anorexia, enlarged lymph nodes, cough, and diarrhea were observed in some patients, and most displayed leucopenia (60%) and thrombocytopenia (65%). However, none showed plasma leakage, severe bleeding, or severe organ involvement. All patients recovered within a week of admission.

Total RNA was extracted from all blood samples as described by Chen et al. (*10*). Viral RNA in blood samples from individual patients was detected by reverse transcription

[1]These authors contributed equally to this article.

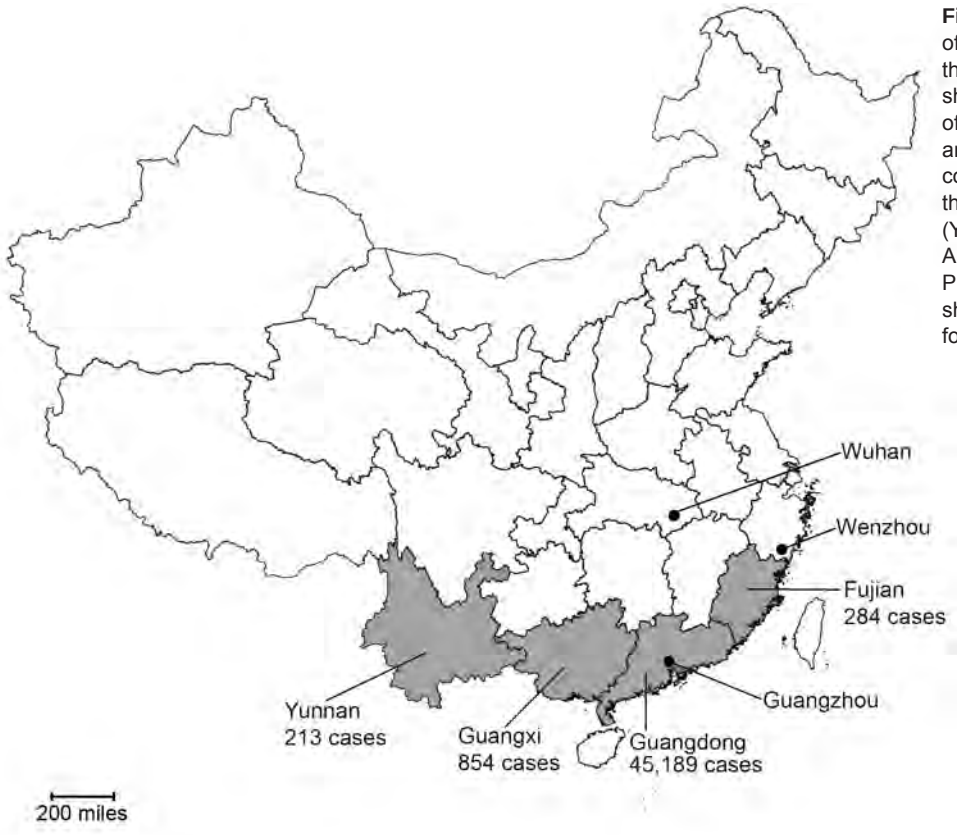

Figure 1. Geographic distribution of dengue cases reported during the 2014 epidemic in China, showing the location of the cities of Wenzhou, Zhejiang Province, and Wuhan, Hubei Province, in comparison to the focal area of the epidemic in southern China (Yunnan Province, Guangxi Zhuang Autonomous Region, Guangdong Province, and Fujian Province; gray shading). Case counts are shown for provinces in the focal area.

PCR based on the conserved regions of the E gene (*11*). Consequently, dengue viral RNA was recovered in serum samples from 4 travel-associated patients with dengue (1 from Wenzhou and 3 from Wuhan) within 6 days after onset of disease, but not in the remaining serum samples. By using 24 pairs of primers, complete genome sequences were amplified successfully from the serum samples of 4 patients, all of which were characterized as DENV-1 (online Technical Appendix Figure, http://wwwnc.cdc.gov/EID/article/21/9/15-0622-Techapp1.pdf). The complete genome of all 4 viruses was 10,703 nt, and the isolates showed very high (99.9%) sequence identity to each other.

Using the maximum-likelihood method implemented in PhyML v3.0 (*12*), we estimated phylogenetic trees based on the complete E gene or whole genome sequences of the 4 viruses identified in China and reference sequences from GenBank (Figure 2; online Technical Appendix Figure). As expected, the viruses we identified are most closely related to those isolated in Guangdong Province in 2014, indicating they are part of the same outbreak, although with independent incursions into Wenzhou and Wuhan. The remainder of the phylogenetic trees show a mix of viruses from China and the Indian subcontinent (India, Bangladesh, Sri Lanka), indicative of the movement of viruses among these localities, as well as a small number from Singapore. However, because DENV sequences were only recovered from 4 patients, our molecular epidemiologic analysis was limited in scope, making extensive viral sampling necessary to reveal detailed transmission routes.

Conclusions

Dengue has been relatively commonly reported in China, mainly in the southern provinces (*4*,*13*). Although the sustained transmission of DENV is possible in these localities, many cases appear to have resulted from importation from countries in Southeast Asia (*8*,*13*,*14*). In contrast, DENV has been sporadically reported in other regions of China, and

Table. Clinical characteristics of patients who had dengue fever, eastern China, 2014

Clinical feature	Positive PCR or antibody test result, n = 20	Location	
		Wenzhou, n = 5	Wuhan, n = 15
Fever	20	5	15
Headache	20	5	15
Dizziness	9	1	8
Chills	2	0	2
Myalgia	10	2	8
Arthralgia	2	1	1
Nausea and/or vomiting	8	2	6
Anorexia	4	0	4
Enlarged lymph nodes	3	0	3
Cough	4	0	4
Diarrhea	2	0	2
Rash	8	3	5
Petechiae	5	2	3

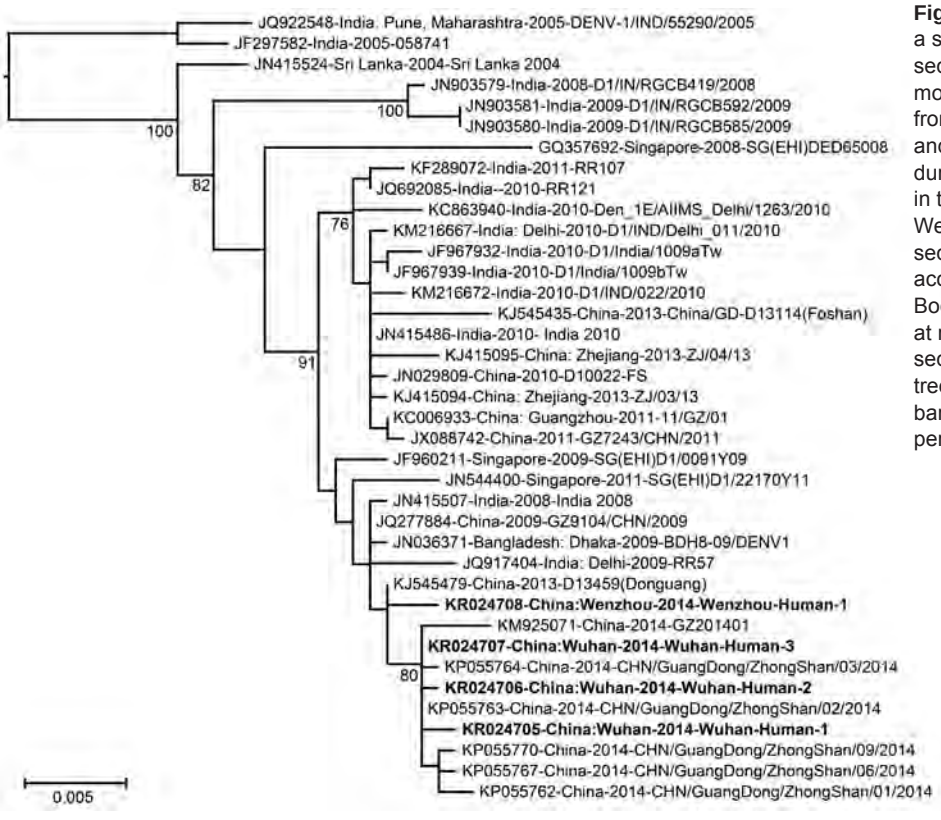

Figure 2. Phylogenetic analysis of a subset of dengue virus 1 E gene sequences within genotype III that are most closely related to those sampled from Wenzhou, Zhejiang Province, and Wuhan, Hubei Province, China, during 2014. The viruses identified in this study were designated as the Wenzhou-human and Wuhan-human sequences, respectively (GenBank accession nos. KR024705–KR024708). Bootstrap values (>70%) are shown at relevant nodes. Bold text indicates sequences obtained in this study. The tree is midpoint rooted for clarity. Scale bar indicates nucleotide substitutions per site.

those cases have been strongly associated with importation (*6*–*8*). Epidemiologic, serologic, and virologic investigations all confirmed the presence of dengue in Wenzhou and Wuhan, even though dengue has not been reported from either region for several decades. Although 90% of patients had a recent history of travel to dengue-endemic areas within and external to China, 2 patients from Wenzhou had no recent travel history to regions in which dengue was endemic, suggesting the occurrence of autochthonous transmission.

Although all 4 DENVs have been identified in China in recent years, DENV-1 appears to be the most common (*4*,*5*,*13*) and was observed in this study (Figure 2). These viruses were most closely related to those from Guangdong province, where the greatest number of cases were identified during the 2014 epidemic (Figure 1).

The viruses in this study were most closely related to those from the Indian subcontinent. Although India likely has the highest dengue incidence globally (*15*) and is therefore expected to harbor high levels of genetic diversity, the viruses endemic to India were identified ≥3 years before those found in China. Hence, although it is possible that the DENV-1 viruses in China originated in India and made multiple incursions in recent years, limited sampling in other localities, notably parts of Southeast Asia, mean that the exact origins of the viruses found in China remain uncertain. Finally, sequences recovered during this study from Wenzhou and Wuhan and from Guangdong Province in 2014 are very closely related to a virus isolated in Guangdong Province in 2013 that is likely to be related to the 2014 cluster. Although little is known about this latter virus, it will be critical to determine whether the 2014 epidemic directly arose from local ancestors present in 2013, rather than being imported.

This and previous studies (*6*,*8*) highlight the increasing risk that DENV-infected travelers may pose to public health in China. In humid subtropical regions such as Wenzhou and Wuhan, in which *A. albopictus* mosquitoes circulate with often poor control measures, imported dengue viruses may infect vector populations during permissive climatic conditions. Comprehensive strategies should be used to prevent the circulation of DENV among local *Aedes* mosquitoes.

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Bifidobacterium breve Sepsis in Child with High-Risk Acute Lymphoblastic Leukemia

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To the Editor: Patients with cancer often consume probiotics as part of their diet, although therapeutic use of probiotics is not recommended because of their potential invasiveness. In a recent review, 5 cases of probiotic treatment–related bacteremia were identified in oncology patients, although no cases of invasive *Bifidobacterium* spp. infection were included (*1*). We describe a case of *B. breve* sepsis in a child with Philadelphia chromosome–positive acute B-cell lymphoblastic leukemia.

The patient was a previously healthy 2-year-old boy who had no history of immunodeficiency and whose leukocyte counts had been within reference ranges during checkup visits before his diagnosis. After leukemia was diagnosed, chemotherapy was started (prednisone, vincristine, doxorubicin, and L-asparaginase). During the second week of treatment, the boy experienced abdominal discomfort and constipation. Two weeks later, his condition worsened; he refused food, his abdomen was distended, and he had colicky pain. Thickened intestinal wall and fecal masses were seen ultrasonographically. Twelve hours later he became hypotensive. Laboratory test results showed severe neutropenia and increased inflammatory markers (Figure). Two aerobic and anaerobic blood culture samples were collected from a central venous line (implantable venous access system) in a 30-minute span, and treatment with piperacillin/tazobactam, vancomycin, and gentamicin was empirically initiated according to local recommendations for pediatric febrile neutropenia with shock. Both anaerobic blood cultures were positive. Gram-positive, irregular rods with bifid and branching forms without spores grew anaerobically on blood agar with hemin and vitamin K after 48 hours of incubation and were identified as *B. breve* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Billerica, MA, USA). The bacteria were susceptible to penicillin (MIC 0.250 μg/mL), ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam (MIC 0.125 μg/mL), imipenem, and clindamycin but not metronidazole. Gentamicin and vancomycin were discontinued, and piperacillin/tazobactam was replaced by penicillin (Figure). The patient stayed afebrile, and his neutropenia resolved. A blood culture taken on the eighth day of antimicrobial drug treatment was negative, and the central venous line was not replaced at that time. Bowel movement normalized and was maintained. We reviewed the ingredients of the food that the child received and documented the presence of *Lactobacillus* spp. and *B. longum* but not *B. breve*.

Some probiotics are part of the normal intestinal microbiota and rarely cause invasive infections (*2*). Although *Bifidobacterium* spp. is infrequently associated with infections (<5% of anaerobic isolates), it occasionally causes serious illness. On the rare occasions when it is isolated from patients with bloodstream infections, it is usually isolated along with other causative agents. The number of reported deaths associated with anaerobic nonsporulating gram-positive rods is low (*3*). In this patient, abdominal symptoms coincided with 2 blood cultures that yielded *B. breve*. We assume bacteria translocated through the distended colonic wall during chemotherapy-induced neutropenia and believe that the blood culture isolate was not a contaminant because it was isolated from 2 samples taken in a 30-min span. It is the practice at our institution not to take peripheral blood cultures simultaneously because doing so does not increase diagnostic accuracy.

We found 1 description in the literature of *B. breve* septicemia in a neonate with omphalocele who had received probiotic therapy (*4*). In a review of *Bifidobacterium* spp. isolates during 2000–2007 in 2 US hospitals, *B. breve* was isolated from blood culture from 3 adult patients (*5*). Two of these infections were associated with ileal resection or peritonitis and 1 with decubitus ulcers. No data on antimicrobial drug treatment were available. *Bifidobacterium* spp. sepsis was reported in an infant of extremely low birthweight 10 days after probiotic supplementation who recovered after antimicrobial drug therapy, although stenosis of the colon

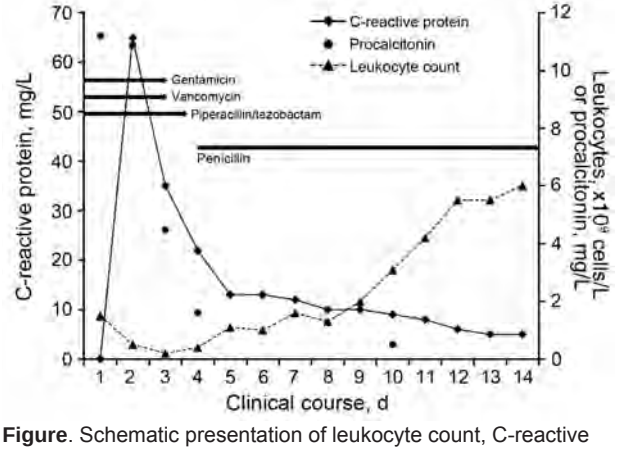

Figure. Schematic presentation of leukocyte count, C-reactive protein, and procalcitonin serum levels in clinical course of *Bifidobacterium breve* sepsis. Arrows indicate the name and duration of each antimicrobial drug treatment.

developed 6 weeks later (*6*). Blood culture grew *B. longum* and *B. infantis*, which were probiotic strains. Apart from 1 case of sepsis caused by *B. longum* associated with acupuncture in a 19-year-old healthy patient (*7*), we did not find other reports of invasive *Bifidobacterium* spp. infections.

Because neutropenic episodes, even with bowel involvement, are common during treatment for cancer (*8*), no reason to promote therapeutic use of probiotics has been proven. Probiotics can cause substantial bacterial overgrowth when stimulating factors are present. In our opinion, avoiding fecal impaction is crucial for preventing colonic bacterial overgrowth and minimizes the chance that bacteria will translocate and cause invasive infection. Nutritional recommendations for a neutropenic diet for children are still debated. The problem is not probiotic therapy but rather fermented food products to which small amounts of probiotics are added. After we reviewed the literature, we did not find enough data to safely recommend the use of these products in children receiving chemotherapy (*9*). Nevertheless, probiotic therapy is recommended for many immunocompromised patients, such as preterm infants and persons with chronic inflammatory bowel disease (*10*). We believe that this case of *B. breve* sepsis in an oncology patient underscores the invasive potential of probiotics.

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Filovirus RNA in Fruit Bats, China

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To the Editor: Filovirus-associated diseases, particularly those caused by Ebola and Marburg viruses, represent major threats to human health worldwide because they have extremely high death rates and antiviral therapies or vaccines against them are not available (*1*). Members of the family *Filoviridae* are classified into 3 genera: *Marburgvirus*, *Ebolavirus*, and the recently approved *Cuevavirus* (*2*,*3*). Marburg virus (MARV) and Ebola virus (EBOV) were initially isolated in Africa, but other filoviruses have been identified on other continents. The initial *Cuevavirus*, Lloviu virus (LLOV), was identified in Europe (Spain) (*3*), and Ebola-Reston virus has been found in pigs in Asia (the Philippines) (*4*).

Bats are natural reservoirs for filoviruses (*5*). Viral isolation and serologic studies indicate that filovirus infections have occurred in various bat species in central Africa countries (*6*), the Philippines (*7*), China (*8*), and Bangladesh (*9*). However, identification of these viruses in bats has been difficult; although isolates of MARV have been obtained (*6*) and the genome of LLOV has been fully sequenced (*3*), very short sequences of EBOV have been obtained from bats, and only in Africa (*5*). Reports of molecular detection or isolation of filoviruses in bats in Asia are lacking. We conducted a study to investigate the presence of filoviruses in bats in China.

In June 2013, twenty-nine apparently healthy *Rousettus leschenaultia* fruit bats were captured in Yunnan Province, China. All bats were humanely killed, and their intestines, lungs, livers, and brains were collected and subjected to viral metagenomic analysis by a previously described method (*10*). As a result, we obtained and reassembled de novo

[1]These authors contributed equally to this article.

10 million reads into 590,010 contigs. Of these contigs, 3 (129–354 nt) were genetically close to filovirus, corresponding to the nucleoprotein gene of LLOV (74% nt identity), the viral protein 35 gene of Sudan Ebola virus (69% nt identity), and the L gene of Tai Forest Ebola virus (72% nt identity) (online Technical Appendix Table 1, http://wwwnc.cdc.gov/EID/article/21/9/15-0260-Techapp1.pdf).

For further screening, we used the longest contig as a template for design of specific seminested primers. Nested degenerate primer pairs were also designed and focused on the most conserved region of the L gene of all currently known filoviruses (online Technical Appendix Table 2). After screening, 2 reverse transcription PCRs of tissues from 1 bat (Bt-DH04) showed positive amplification in specimens from its lung but not from intestine, liver, or brain tissue. Moreover, 5 blind passages in Vero-E6 cells failed to isolate the virus from the lung homogenate. In an attempt to obtain its genomic sequence, 24 primer pairs covering the full genome were further designed by alignment of these contig sequences with the full genomes of representative filoviruses within the 3 genera. All amplifications used ddH_2O as a negative control; positive controls were not available because filoviruses were not available in China. Two fragments of 2,750-nt (F1) and 2,682-nt (F2) were successfully amplified from lung tissue of Bt-DH04; attempts to amplify the remaining regions failed. Alignment with sequences of 26 representative filoviruses of 7 species from 3 genera revealed that F1 covered the 3′ end of the nucleoprotein gene and almost the entire viral protein 35 gene, and that F2 covered the middle region of the L gene, corresponding to nt 1,313–4,085 and nt 12,613–15,302 of the full genome of EBOV (GenBank accession no. HQ613402). The 2 fragment sequences were submitted to Genbank (accession no. KP233864), and the strain has been tentatively named Bt-DH04.

Phylogenetic analysis showed that the Bt-DH04 strain is placed, together with LLOV, at basal position and intermediate between EBOV and MARV (Figure). It is divergent from all known filoviruses, with F1 sharing the highest nucleotide identities (46%–49%) to members of the genus *Ebolavirus*, followed by 44% to LLOV and <40% to MARV (Figure, panel A). The L gene is the most conserved region of filoviruses, and F2 of Bt-DH04 strain shared relatively closer 66%–68% nt identities with members of the genus *Ebolavirus*, followed by 64% with LLOV and ≈60% with MARV (Figure, panel B). This sequence diversity is likely the main factor for unsuccessful amplification of the full genome of Bt-DH04.

Increasing PCR evidence has identified the existence of filoviruses in bats in Africa and Europe (*3*,*5*); however, although serologic studies have shown that filovirus antibodies are prevalent in bats in a few countries in Asia (e.g., the Philippines, Bangladesh and China [*7*–*9*]), filovirus or filovirus RNA have not been reported in bats in Asia. Our results show that the Bt-DH04 strain is likely a novel batborne filovirus in Asia and provide evidence that bats in Asia harbor more divergent filoviruses than previously thought.

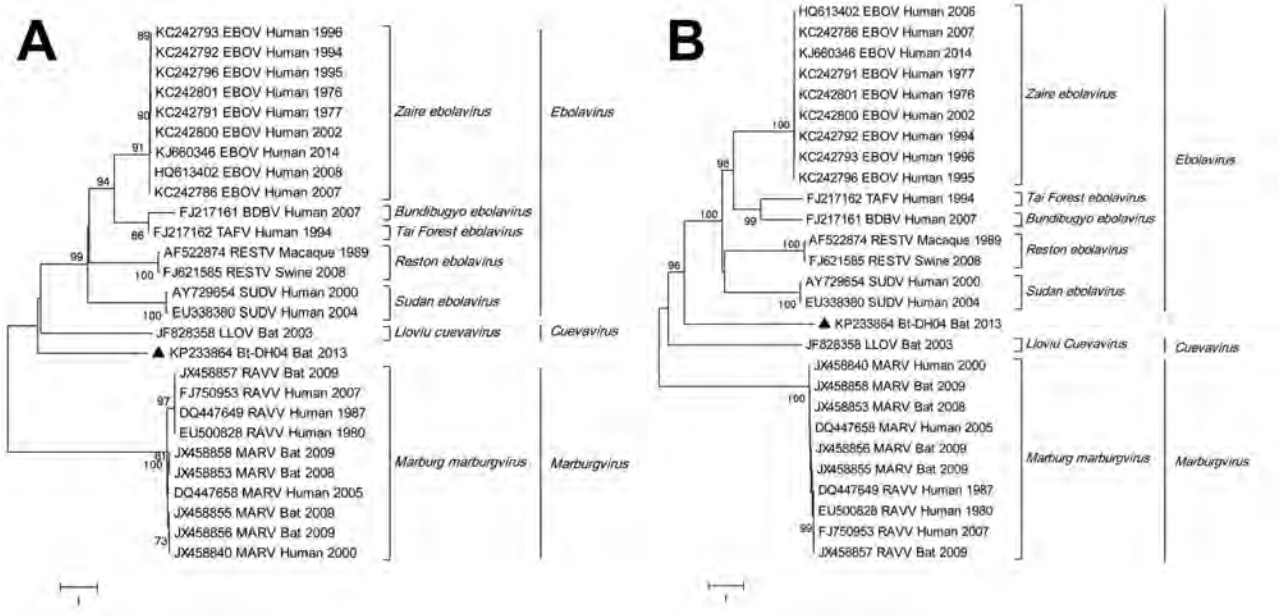

Figure. Phylogenetic analysis of 2 fragments of filovirus Bt-DH04 and other filoviruses. Full genomes of representatives from the family *Filoviridae* were trimmed and aligned with F1 (partial nucleoprotein/viral protein 35 gene, panel A) and F2 (middle L gene, panel B) of filovirus strain Bt-DH04 by using ClustalW version 2.0 (http://www.clustal.org), then phylogenetically analyzed by using MEGA6 (http://www.megasoftware.net) by the maximum-likelihood method, resulting in a bootstrap testing value of 1,000. Sequences are listed by their GenBank accession numbers, followed by the virus name, host, and collection time. Triangles identify the novel filovirus strain Bt-DH04 (China). Scale bars indicate nucleotide substitutions per site.

Fruit bats in the genus *Rousettus* are widely distributed throughout Southeast Asia, South China, and the entire Indian subcontinent and have had positive serologic results for Ebola viruses in these regions (*7*–*9*), indicating that these bats play a role in the circulation of filoviruses in Asia. The possibility of new emerging filovirus-associated diseases in the continent emphasizes the need for further investigation of these animals.

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Increase in Lymphadenitis Cases after Shift in BCG Vaccine Strain

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To the Editor: Bacillus Calmette-Guérin (BCG) vaccine is one of the most commonly used vaccines for tuberculosis (TB) worldwide (*1*). The original BCG strain was developed in 1921. Numerous strains have since been developed, and 5 strains, including Danish SSI 1331 (Statens Serum Institute, Copenhagen, Denmark), account for >90% of BCG vaccine used. Each strain has unique characteristics and a different reactogenicity profile (*2*). The most common severe adverse events related to BCG vaccination are nonsuppurative and suppurative lymphadenitis.

In the country of Georgia, BCG vaccine is administered routinely to infants (estimated coverage 96%); the National Center for Disease Control and Public Health receives its vaccine supply from the United Nations Children's Fund and is responsible for countrywide distribution. Before 2012, Russian BCG-I (Bulbio, Sofia, Bulgaria) and Danish SSI 1331 strains were used (≈50% each). Shortly after a change to exclusive use of the Danish 1331 strain during 2012–2013, an increasing number of BCG-related lymphadenitis cases were reported to the National Center for Tuberculosis and Lung Diseases (NCTLD). We aimed to quantify the increase in cases of BCG lymphadenitis and to evaluate clinical management of the cases. The Institutional Review Boards of Emory University (Atlanta, GA, USA) and the National Center for Disease Control and Public Health approved the study.

Medical chart abstraction was conducted for all infants with BCG lymphadenitis either reported to the NCTLD or found by inquiry of pediatricians at the largest children's hospital in the country during January 2012–July 2013. We used national surveillance data to obtain the number of live-born infants.

BCG vaccine is given intradermally over the deltoid muscle on the left arm to infants within 5 days after birth at the maternity hospital. BCG lymphadenitis was clinically

defined as ipsilateral axillary lymph node enlargement developing within 2 years after vaccination. If the patient was brought for care to the NCTLD, a sample was obtained through aspiration for acid-fast bacilli smear; culture; and, if necessary, drug-susceptibility testing (*3*). Although treatment was at the discretion of clinicians, national TB program treatment guidelines did not include management of BCG-related adverse events.

During 2007–2011, six cases of BCG lymphadenitis were reported to the NCTLD. During the 19-month study period, we found 23 cases of BCG lymphadenitis: 15 reported to the NCTLD and 8 diagnosed at the Tbilisi children's hospital and ascertained by inquiry (Table). In all cases, a 0.05-mL dose of Danish SSI BCG vaccine (series 111003A and 111021A) was used. The 15 infants from the NCTLD were vaccinated at 8 maternity hospitals: 6 in Tbilisi and 2 in outside regions. A total of 14,230 live-born infants were registered at hospitals reporting BCG lymphadenitis in 2012. Based on the following calculation—16 cases/(14,230 live-born infants × 96% vaccination coverage)—the estimated prevalence of BCG-related suppurative lymphadenitis in 2012 was 1.12 cases per 1,000 infants.

Median time from BCG vaccination to onset of lymphadenitis was 5 months (range 1–15 months). No patients had systemic signs or symptoms.

After a change in BCG vaccine strains in Georgia to the exclusive use of BCG SSI vaccine, we found a substantial increase in the known prevalence of BCG-associated lymphadenitis. We found 23 cases of BCG-associated lymphadenitis during a 19-month period, ≈4 times the number of reported cases during the prior 5 years, when multiple vaccine strains were used. The estimated prevalence of suppurative lymphadenitis (1.12 cases/1,000 infants) was higher than the expected rate of <1/1,000 given by the manufacturer (*4*). Our rate is probably an underestimation, given a mainly passive system of surveillance. Prior studies in various countries have similarly shown increased BCG lymphadenitis with the introduction of the BCG SSI vaccine (*5*–*7*).

We found different approaches to treatment of BCG-associated lymphadenitis depending on where care was received. Physicians at the NCTLD prescribed first-line anti-TB medications, including pyrazinamide, whereas patients managed at the children's hospital were treated with either surgical excision or a conservative watch-and-wait approach. Although no official treatment guideline exist for suppurative BCG-associated lymphadenitis, a recent meta-analysis found no benefit to using anti-TB medications (*8*). Furthermore, *Mycobacterium bovis* is inherently resistant to pyrazinamide. A randomized controlled trial found needle aspiration to improve rates and speed

Table. Characteristics of 23 infants with BCG lymphadenitis, Georgia, January 2012–July 2013*

	Characteristic†							
Hospital, infant no.	Sex	Date of birth	Age at presentation, mo	Size of axillary lymph node, mm	Culture	Surgery	Drugs used	Treatment outcome‡
NCTLD, n = 15								
1	F	2012 Jan 9	5	20	Pos	No	R, I, P	Completed
2	M	2012 Dec 19	5	14	ND	No	R, I, P	Completed
3	F	2012 Jul 2	9	40	NA	No	R, I, P	Completed
4	F	2012 May 31	12	28	NA	No	R, I, P	Completed
5	M	2012 Jul 25	4	15	NA	No	R, I, P	Computed
6	F	2012 Aug 16	1	15	NA	No	R, I, P	Defaulted
7	M	2012 Feb 7	2	22	NA	No	R, I, P	Completed
8	M	2011 Nov 28	3	24	NA	No	R, I, P	Defaulted
9	M	2012 Jul 9	2	18	NA	No	R, I, P	Defaulted
10	M	2012 Aug 7	7	23	NA	Yes	R, I, E	Unknown
11	M	2012 May 10	4	56	NA	No	R, I, P	Completed
12	M	2012 Nov 13	6	60	NA	No	R, I, P	Completed
13	M	2012 Oct 1	2	11	Pos	Yes	R, I	Completed
14	M	2012 Feb 22	9	24	NA	No	R, I, P, E	Completed
15	F	2012 Feb 24	5	15	NA	Yes	R, I, P	Complete
Pediatric hospital, n = 8								
1	F	2013 Jan 28	4	25	ND	Yes	None	Unknown
2	M	2012 Jun 15	8	20	ND	Yes	None	Unknown
3	M	2012 Mar 25	15	17	ND	Yes	None	Unknown
4	M	2012 Jan 28	6	21	ND	Yes	None	Unknown
5	M	2013 Jan 28	4	21	ND	Yes	None	Cured
6	M	2012 Jun 28	8	25	ND	Yes	None	Unknown
7	M	2013 Mar 28	5	15	ND	No	None	Cured
8	F	2013 Jun 8	1	17	ND	No	None	Cured

*BCG, bacillus Calmette-Guérin vaccine; Pos, positive; E, ethambutol; I, isoniazid; P, pyrazinamide; R, rifampin; NA, not available; ND, not done; NCTLD, National Center for Tuberculosis and Lung Diseases.
†For all patients, type of BCG strain used was Danish SSI (Statens Serum Institute, Copenhagen, Denmark).
‡Defaulted is an outcome definition applied by the tuberculosis program when a patient misses treatment for 2 consecutive months and is considered lost to follow-up.

of healing of suppurative nodes and is the only evidence-based effective treatment (*9*). Surgical excision remains controversial because of potentially high rates of significant scarring (*10*). For nonsuppurative lymphadenitis, a watch-and-wait approach is recommended because most resolve rapidly (*8*).

Given our findings, the National TB Program in Georgia subsequently created a management protocol. This protocol recommends no intervention for nonsuppurative lymphadenitis and needle aspiration for suppurative local lymphadenitis.

In summary, we found an increasing rate of BCG-associated lymphadenitis after a shift to exclusive BCG SSI vaccine use in Georgia. Countries with a BCG vaccination policy should have a clear protocol on management of BCG vaccine–related adverse events to avoid inappropriate treatment in children.

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Fatal Accelerated Cirrhosis after Imported HEV Genotype 4 Infection

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To the Editor: Hepatitis E is a viral hepatitide that is endemic in many developing countries. In its classic form, it results from ingesting fecally contaminated water that carries hepatitis E virus (HEV), and it frequently resolves without treatment. When hepatitis E is imported to the United States, it originates mainly from persons who have acquired HEV genotype 1 infection from South Asia (*1*). We report imported HEV genotype 4 infection (Technical Appendix Figure, panel A) in a patient during which cirrhosis and fatal hepatic decompensation ensued.

The patient was a 68-year-old man of Chinese ethnicity who had been a California resident since 1985. He sought treatment for mild jaundice in April 2013 in Hong Kong, where he had been staying for 7 weeks. Sixteen years before, he had undergone orthotopic liver transplantation at Stanford University Medical Center (Palo Alto, California, USA) for hepatitis B cirrhosis. Since then, he had received entecavir and tacrolimus for maintenance and had been vaccinated against hepatitis A virus. Until his current illness, routine liver function tests had not indicated hepatic dysfunction (values in November 2012: alanine aminotransferase 2 IU/L, aspartate aminotransferase 24 IU/L, alkaline phosphatase 67 IU/L, total bilirubin 0.5 mg/dL).

When the patient returned to the United States, 3 weeks after onset of jaundice, the initial work-up showed the following values: alanine aminotransferase 149 IU/L, aspartate aminotransferase 59 IU/L, alkaline phosphatase 193 IU/L, total bilirubin 2.8 mg/dL (online Technical Appendix Figure, panel B, http://wwwnc.cdc.gov/EID/article/21/9/15-0300-Techapp1.pdf). Hepatitis B virus DNA and antinuclear antibodies were not detected, and the tacrolimus level was stable. Ultrasound revealed a normal transplanted liver. A liver biopsy specimen showed mild portal, biliary, and lobular inflammation and early biliary injury (Figure,

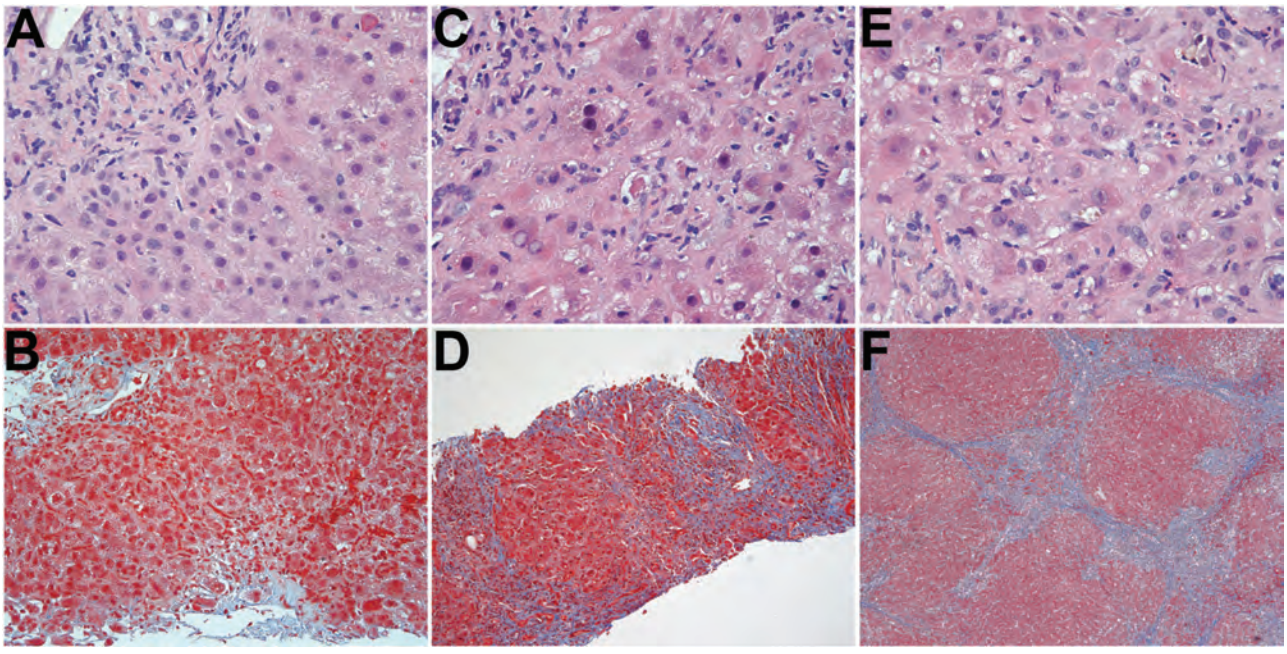

Figure. Serial histologic changes in liver of the patient who received a diagnosis of hepatitis E after a visit to Hong Kong in 2013 (A and B: at first biopsy; C and D: second biopsy; E and F: third biopsy. A) Mild mixed portal infiltration; minimal lobular inflammation; acidophil body present at upper right; and bile duct showing injury with lymphocytic infiltration (original magnification ×400). b) Mild portal inflammation; some interface activity; and portal tracts not showing increased fibrosity (original magnification ×200). C) Mononuclear infiltration of portal tract at upper right with bile duct/ductular infiltration and injury; lobular changes more severe, showing more inflammation, acidophil bodies and reactive nuclear change in hepatocytes with ballooning of some hepatocytes (original magnification ×400). d) Portal and lobular inflammation; and marked increase in fibrosis with bridging and regenerative nodule formation (original magnification ×100). E) Extensive lobular inflammation and reactive hepatocytic changes with nuclear enlargement, prominent nucleoli, and ballooning (original magnification ×400). F) Well-developed cirrhosis (original magnification ×40). Hematoxylin and eosin staining (A, C, E); Masson trichrome staining. (B, D, F).

panels A, B; a color version of this figure is available online [http://wwwnc.cdc.gov/EID/article/21/9/15-0300-F.htm]). Prednisone was initiated and the dosage escalated, and mycophenolate mofetil was added. Liver enzyme activity showed some improvement, but the bilirubin level continued to rise (online Technical Appendix Figure, panel B).

A biopsy specimen taken 3 months later showed grade 3 hepatitis with bile ductular reaction, bridging hepatocytic necrosis and fibrosis, and regenerative nodule formation (Figure, panels C, D). A blood sample taken about this time tested positive for HEV RNA. The patient was then given ribavirin (1,000 mg/d). Before hepatitis E was diagnosed, tacrolimus was given (1 mg 2×/d); when the diagnosis was confirmed, the tacrolimus dose was reduced to 0.5 mg every other day. Four months after the patient sought treatment, ascites was noted. Ribavirin was stopped because of pancytopenia. Blood samples subsequently tested negative for HEV RNA, but HEV IgM and IgG were found. Hepatic function did not improve.

Eight months after onset of the patient's condition, marked hepatic decompensation occurred (online Technical Appendix Figure), culminating in esophageal variceal hemorrhage. The patient was placed on a waiting list and then underwent liver transplantation, but he died during the operation from complications of hemorrhage. Biopsy of the liver explant revealed intense lobular inflammation with the hepatocellular reactive changes persisting and stage IV fibrosis (Figure, panels E, F).

The patient had lived and worked in Hong Kong before he became a resident of the United States. He had not visited Hong Kong in the 3 years preceding his most recent trip, nor had he traveled to Europe. Review of his medical records revealed no evidence of hepatic dysfunction after his previous travels. Considering that his most recent visit to Hong Kong coincided with the incubation period of hepatitis E (*2*), he most likely acquired HEV genotype 4 infection during that visit.

In China over the past decade, national notifications of HEV infection have risen, with 28,232 cases reported in 2013 (*3*). In Hong Kong, where a rising trend in hepatitis E notifications also has been observed (150 cases reported in 2012 [*4*]), HEV infections are almost all associated with HEV genotype 4 (*5*).

This patient's HEV subgenomic sequence was closely related to human and porcine HEV genotype 4 sequences

reported from mainland China and Hong Kong (online Technical Appendix Figure, panel A). Porcine liver has been implicated as a possible HEV transmission vehicle in that region (*6*); although we do not know whether the patient ate food that carried HEV, the possibility underscores the importance of avoiding eating inadequately cooked animal-derived food products during international travel (*2*).

Chronic hepatitis with accelerated cirrhosis has been reported in solid-organ transplant recipients infected with HEV genotype 3, but not with genotype 4 (*7*). Serial liver biopsy specimens from the patient showed persistent and worsening hepatitis and rapid onset of fibrosis that intensified (online Technical Appendix Figure, panel B).

Testing for HEV infection is recommended during initial assessments of posttransplant hepatic dysfunction because histologic appearances in liver biopsy specimens may not clearly distinguish between graft rejection and acute viral hepatitis (Figure, panels A, B). Early diagnosis of hepatitis E should lead to prompt administration of antiviral therapy and appropriate adjustments to the immunosuppressant drug regimen, particularly because some drugs can exert opposing effects on HEV replication (*8*).

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Measles Reemergence in Ceará, Northeast Brazil, 15 Years after Elimination

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To the Editor: Measles was endemic in Brazil before 2000 and caused large outbreaks every 2 or 3 years (*1*). Although measles was eliminated in Brazil in 2000, cases have continued to be imported (*2*,*3*). During 2001–2014, the median annual number of measles cases reported in Brazil was 50 (range 2–712). The median annual number of Brazilian states with reported cases was 2.5 (range 1–7). Since elimination, the highest numbers of cases reported in Brazil occurred in 2013 (220) and in 2014 (712) (*3*–*5*). According to the Pan American Health Organization, endemic transmission is reestablished when epidemiologic and laboratory evidence indicate that a chain of transmission of a virus strain has continued uninterrupted for ≥12 months in a defined geographic area (*6*).

From December 2, 2013, through December 31, 2014, in the state of Ceará, Brazil, 681 measles cases were reported. A measles case was considered confirmed when a patient exhibited fever, rash, and ≥1 of 3 symptoms and signs (i.e., cough, runny nose, conjunctivitis); was positive for IgM and negative for IgG against measles virus; and had not been vaccinated in the previous 21 days. D8 genotype, the same virus genotype that was circulating in Europe, was the only genotype identified, and how the virus was introduced into the region was not clear (*4*,*5*). From 2000 to 2013, vaccine coverage among children 12 months of age remained >95% in Ceará, although that coverage was not homogeneous for the whole state. In 14.7% (27/184) of municipalities, the vaccination coverage was much lower

(*4*). Pernambuco, the state that borders southern Ceará, reported a measles outbreak with 222 confirmed cases from March 2013 through March 2014 (*4*,*5*,*7*). Thus, the timing of the 2 outbreaks overlapped.

During December 2013–December 2014, Ceará's outbreak seemed to evolve in 2 waves: the first from epidemiologic weeks 3 through 6 (mainly in Fortaleza, the capital of Ceará) and the second from epidemiologic weeks 27 through 53 (mainly on the northwest side of Ceará, an economically disadvantaged region, which also included the capital). Cases were confirmed in 15.8% (29/184) of all municipalities. Most patients (47.3%; 322) were from Fortaleza, followed by Massapê (18.6%; 127) and Sobral (12.2%; 83) (Figure).

Children <12 months of age were the most affected group (27.5%; 187), followed by patients 20–29 years (19.2%; 131) and those 15–19 years (14.4%; 98). The age distribution was significantly different between Fortaleza and the 2 inner cities (together), with more cases reported among those <12 months of age (37.6% [121/322] vs. 14.3% [30/210], respectively) and for those 15–29 years (25.2% [81/322] vs. 43.8% [92/210], respectively) (p<0.001 for both comparisons) (*5*). Vaccination status of affected patients (data through August 8, 2014) was the following: unvaccinated, 22.2% (55/252) <1 year of age and 31.3% (79/252) ≥1 year of age; unknown vaccination status, 27.4% (69/252); and received only 1 dose of vaccine, 18.7% (47/252) (*8*). No deaths were reported (*4*). The main reported symptoms were rash (100%), fever (100%), cough (84.5%), runny nose (68.2%), and conjunctivitis (60.3%) (*8*).

Response vaccination activities have taken 10–20 weeks to be initiated in some municipalities after the first cases were recognized. Vaccination campaigns involving children 6–60 months of age are being intensified and surveillance for suspected cases has increased, but as of January 1, 2015, the chain of transmission appeared ongoing (*4*,*5*). In addition, one cannot underestimate the fact that health professionals in Ceará had not seen cases of measles for 15 years. Younger health professionals had never seen even 1 case, and this lack of familiarity may have had some effect on surveillance, rapid recognition of new cases, and adoption of control measures. This difficulty of recognition should be taken into account in regions that have been free of endemic measles transmission for many years.

In conclusion, the measles outbreak in Ceará was probably imported directly from Europe or from there

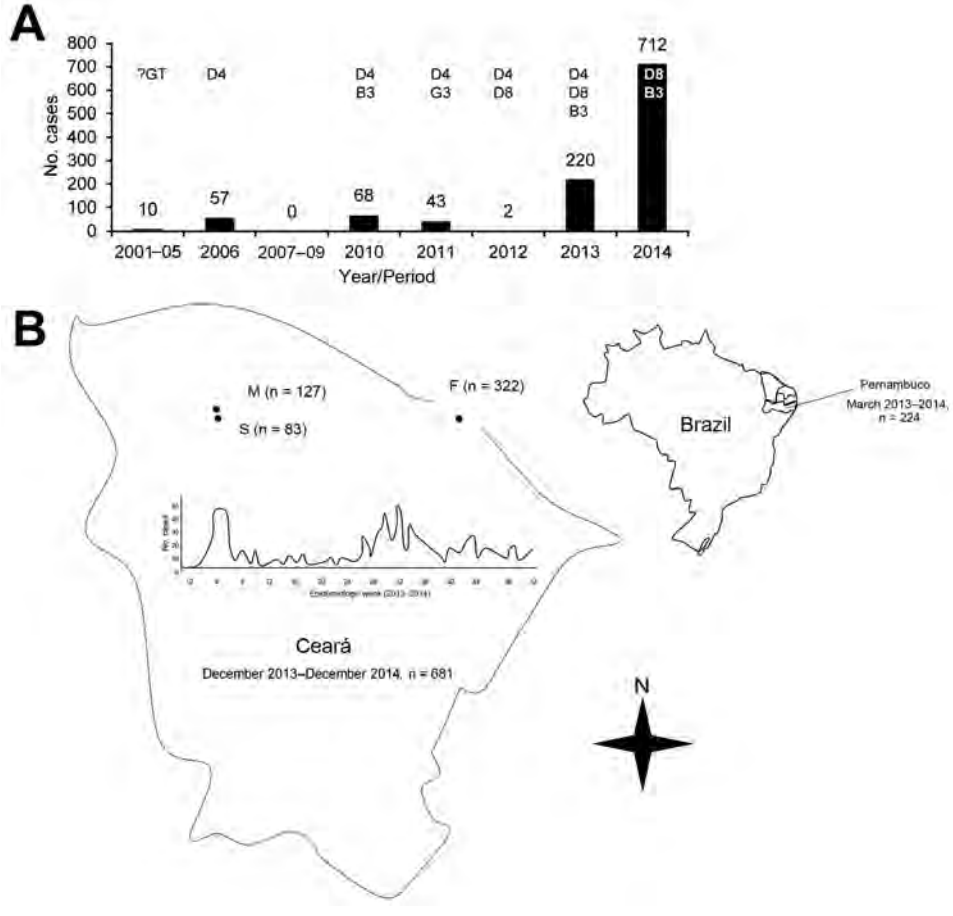

Figure. Measles cases reported in Brazil after elimination, 2001–2014. A) Cases and genotypes identified, by year. B) Spatial distribution of measles outbreaks in the states of Pernambuco and Ceará during 2013–2014, in which only genotype D8 was identified. Genotypes B3 and D4, observed during 2013–2014, were reported in other Brazilian states. The cities with the highest number of cases are highlighted on the map, as well as the evolution of its outbreak, which had 2 waves with peaks in the first and second halves of 2014. Data through December 31, 2014. F, Fortaleza; M, Massapê; S, Sobral; B3 , genotype B3; D4, genotype D4; D8, genotype D8; G3, genotype G3; ?GT, unknown genotype. Sources: (*3*,*5*,*7*).

through the bordering state of Pernambuco (*4*,*5*,*9*). Cases were concentrated in Fortaleza and the northwest region of the state. Patient age distribution was significantly different between the capital, where the infection most affected children <12 months of age, and the inner cities, where it most affected persons 15–29 years of age. Current heterogeneous measles vaccine coverage (*4*,*5*); a delayed response and insufficient vaccination coverage in the past, particularly in socially disadvantaged populations from the inner cities; and difficulties in the prompt recognition and surveillance of suspected cases may explain why this outbreak occurred in a population with a vaccine coverage historically >95%. In addition, vaccination campaigns directed at children <5 years of age may not have been sufficient to interrupt the outbreak because a substantial number of older persons were susceptible. Most notably, because it has lasted >12 months, Ceará's current outbreak may represent the reestablishment of endemic transmission of measles in the Americas.

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Chikungunya Virus in Macaques, Malaysia

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To the Editor: In the past 10 years, chikungunya virus (CHIKV) has caused global epidemics of fever, rash, and arthralgia affecting millions of humans, most recently in the Americas (*1*). CHIKV is an alphavirus transmitted by *Aedes* spp. mosquitoes. This virus has been isolated from wild vertebrates, particularly nonhuman primates (NHPs), in Africa (*2*). This sylvatic cycle might maintain the virus during interepidemic periods. The role of sylvatic cycles in Asia is less clear.

Encroachment of human settlements into forests has caused increased conflict between humans and macaques for space and resources in urban and rural areas. This interface exposes humans to zoonotic pathogens found in monkeys, such as CHIKV, dengue virus, and *Plasmodium knowlesi*. The most common macaque species in Peninsular Malaysia is the long-tailed macaque (*Macaca fascicularis*); an estimated population of >130,000 monkeys live in human-populated areas (*3*). We determined the potential role of long-tailed macaques in conflict with humans as a reservoir of CHIKV in Malaysia.

In response to reports of long-tailed macaques in human-populated areas, the Malaysian Department of Wildlife and National Parks traps monkeys in these areas and relocates them to forest areas. As part of the Wildlife Disease Surveillance Program conducted by Outbreak Response Team of this department, with assistance from the EcoHealth Alliance, serum samples were collected from 147 long-tailed macaques at >20 sites in the states of Selangor (88 monkeys), Negeri Sembilan (21), Perak (18), Pahang (17), and Penang (3) (Figure). Samples were collected in October–November 2009 and October 2010, just after a nationwide outbreak of CHIKV that affected >13,000 persons in 2008–2009 (*4*). These samples represent 0.05%–0.29% of estimated populations of long-tailed macaques in human-populated areas in these 5 states (*3*).

A seroneutralization assay was performed by using baby hamster kidney cells to screen for neutralizing antibodies against CHIKV in heat-inactivated monkey serum

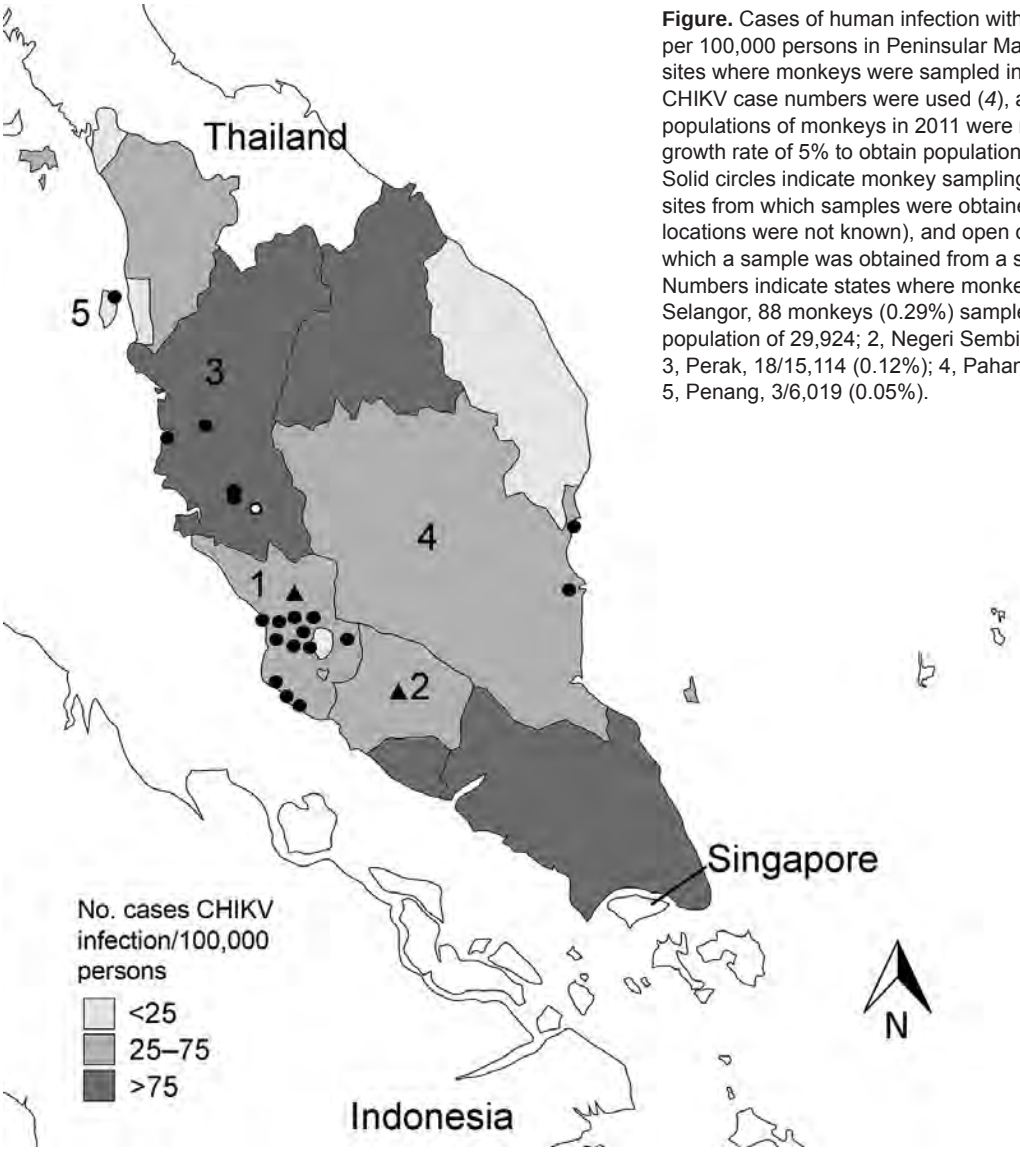

Figure. Cases of human infection with chikungunya virus (CHIKV) per 100,000 persons in Peninsular Malaysia, 2008–2009, and sites where monkeys were sampled in 2009–2010. Published CHIKV case numbers were used (*4*), and published estimated populations of monkeys in 2011 were reduced by an annual growth rate of 5% to obtain population estimates for 2010 (*3*). Solid circles indicate monkey sampling sites, triangles indicates sites from which samples were obtained (where the specific locations were not known), and open circle indicates site from which a sample was obtained from a seropositive macaque. Numbers indicate states where monkeys were sampled. 1, Selangor, 88 monkeys (0.29%) sampled of an estimated population of 29,924; 2, Negeri Sembilan, 21/10,133 (0.21%); 3, Perak, 18/15,114 (0.12%); 4, Pahang, 17/12,590 (0.14%); 5, Penang, 3/6,019 (0.05%).

samples. Samples at a 1:20 dilution that neutralized CHIKV in ≤2 days were confirmed as positive by using a described immunofluorescence-based cell infection assay (*5*) with modifications. Serially diluted serum samples were mixed with equal volumes of CHIKV suspensions at a multiplicity of infection of 10 and inoculated into baby hamster kidney cells. After incubation for 6 h at 37°C, cells were fixed, processed, and immunostained with a monoclonal antibody. Fluorescence was determined by using the Cellomics High Content Screening ArrayScan VTI imaging system (ThermoFisher Scientific, Waltham, MA, USA).

Despite the recent widespread CHIKV outbreak in humans and proximity of sampled macaques to humans in Malaysia, CHIKV neutralizing antibodies were detected in only 1 (0.7%) of 147 macaques. This seropositive macaque was captured in Kampung Jeram Mengkuang (4.06°N, 101.24°E) in Perak, one of the most affected states during the 2008–2009 outbreak (*4*). All serum samples tested showed negative PCR results for the CHIKV envelope 1 protein gene.

CHIKV neutralizing antibodies have also been detected in NHPs in Thailand (*6*) and Malaysia (*7*). In the study in Malaysia, 6 (1.5%) of 393 long-tailed macaques were seropositive (*7*). A recent study in Mauritius reported neutralizing antibodies in just 1 (0.7%) of 134 long-tailed macaques after a large human outbreak in 2006 (*8*). In another study in Malaysia, 105 wild long-tailed macaques were sampled from several sites in 3 states during 2007–2008; CHIKV was isolated from 4 (3.8%) samples from 1 site (Kuala Lipis in Pahang) (*9*). This site is 90 km from the village where the 1 seropositive monkey was trapped in our study. In addition, a variety of domestic and wild vertebrates, including

horses, cattle, pigs, rats, squirrels, bats, and chickens, have been reported to be seropositive for CHIKV (*2*,*6*–*8*).

These results indicate that CHIKV infects long-tailed macaques in Malaysia, but seroprevalence rates are low, and there is little evidence of viremia, except at the 1 specific site in Kuala Lipis. Although experimental infection of long-tailed macaques resulted in detectable CHIKV antigen in macrophages for ≥3 months, infectious CHIKV is not detectable beyond 44 days (*10*), and long-term neutralizing immunity is present for ≥180 days (*5*). However, there is no evidence for long-term active CHIKV infection and its recrudescence in macaques or humans.

A limitation of our study was the relatively small number of monkeys sampled. Although we found no overall significant correlation between incidence of human cases of infection with CHIKV and estimated number of long-tailed macaques per 100,000 persons in each state ($r^2 = 0.05$, $p = 0.49$), we cannot exclude the involvement of long-tailed macaques in a local outbreak at a specific site. Long-term dynamics of antibodies against CHIKV in long-tailed macaques are not known, which might affect sensitivity of detection assays.

We conclude that long-tailed macaques in conflict with humans in specific areas probably played a small part in transmission of CHIKV during recent large outbreaks in humans in Malaysia. Human–mosquito–human transmission and travel by infected humans were probably the major factors involved in spread of this virus. If a true sylvatic reservoir that effectively maintains CHIKV is present in Malaysia, long-tailed macaques might play only a minor role. In addition, involvement of other NHPs and mammals remains to be elucidated.

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Functional Immune Reconstitution by Interleukin-2 Adjunctive Therapy for HIV/Mycobacterial Co-infection

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To the Editor: We describe a case of an immunocompromised patient with AIDS who sought treatment for immunotolerance to an invasive, systemic mycobacterial infection that was unresponsive to antimycobacterial therapy alone. The 41-year old man sought treatment in November 2006 for fatigue, dyspnea, and epigastric pain of 4 weeks' duration and weight loss of 10 kg. HIV-1 infection (20 cells/mL CD4+ T-cells, viral load 230,000 genome equivalents/mL) was diagnosed. Antiretroviral therapy (ART) and *Pneumocystis* pneumonia prophylaxis were initiated.

In June 2007, acid-fast bacilli (AFB) were detected on mediastinal lymph node specimens obtained by endobronchial-ultrasound-guided biopsy during a bronchoscopy; empiric antituberculosis treatment was initiated. *Mycobacterium tuberculosis* DNA was not detected by nucleic acid amplification on these specimens. At the time of referral to our clinic, the physical examination revealed

generalized lymphadenopathy and oral leukoplakia. The patient's bodyweight was 63 kg. Computed tomography showed extensive mediastinal and abdominal lymphadenopathy without other abnormalities. Serologic investigations showed negative results for hepatitis A, B, C, and syphilis. Esophageal-gastro duodenoscopy showed a cottage cheese–like appearance of the duodenal mucosa, and histopathological examination of biopsies documented massive numbers of AFB (online Technical Appendix Figure, panel A, http://wwwnc.cdc.gov/EID/article/21/9/15-0461-Techapp1.pdf). Nucleic acid amplification of 16S rRNA from biopsies was performed, and sequence comparison to the National Center for Biotechnology Information database identified the presence of *M. tilburgii*. In July 2007, specific treatment against infection with *M. tilburgii* was initiated with rifabutin, ethambutol, and azithromycin (*1*).

Despite nondetectable levels of viral replication while the patient was receiving ART, CD4+ T cell count did not rise above 73 cells/mL (Figure). In November 2007, he reported diarrhea and weight loss of 6 kg (total weight 57 kg); testing showed hypochromic-microcytic anemia (hemoglobin 8.2 g/dL). Bone marrow biopsy showed infiltration of AFB, and 16S rRNA amplification confirmed *M. tilburgii* infection. Macroscopic and microscopic appearance of the duodenal mucosa was unchanged.

During the next 10 months, antimycobacterial therapy had to be altered as a consequence of adverse drug events (Figure). In November 2007, treatment with linezolid resulted in an allergic reaction with generalized rash and fever. In March 2008, treatment with rifabutin was discontinued after pancytopenia developed. Treatment with amikacin between March and November 2008 resulted in hearing loss. During this time, the patient's symptoms improved, and he gained 16 kg (total weight: 73 kg) when he received pulsed doses of prednisolone (20 mg/dL), but he had diarrhea when steroids were tapered to 10 mg/dL. By August 2008, after >1 year of antimycobacterial therapy, there were no improvements of clinical findings.

Adjunctive treatment with interleukin-2 (IL-2 [Proleukin S, Novartis Pharma GmbH, Nuremberg, Germany]) was administered subcutaneously (4.5×10^6 IU) on 3 occasions in September, October, and November 2008. The mean post–IL-2 treatment CD4+ cell count was 242/mL, an improvement over 64/mL before the intervention (Figure). In November 2009, the duodenal mucosa appeared normal on inspection, and no bacteria were found on histopathological examinations (online Technical Appendix Figure, panel B). Antimycobacterial therapy (Figure) was discontinued, steroid administration was gradually reduced, and measured bodyweight stabilized (72–74 kg). At the last examination in December 2014, the patient remained free of signs and symptoms of recurrence of *M. tilburgii* infection.

M. tilburgii is an uncultivable nontuberculous mycobacterium related to *M. simiae* and *M. genavense* (*2*). Fewer than 10 clinically relevant cases of *M. tilburgii* infections have been described in the literature (*2*–*7*); most were intestinal infections in immunocompromised hosts (*3*). Successful treatment has been achieved with combination

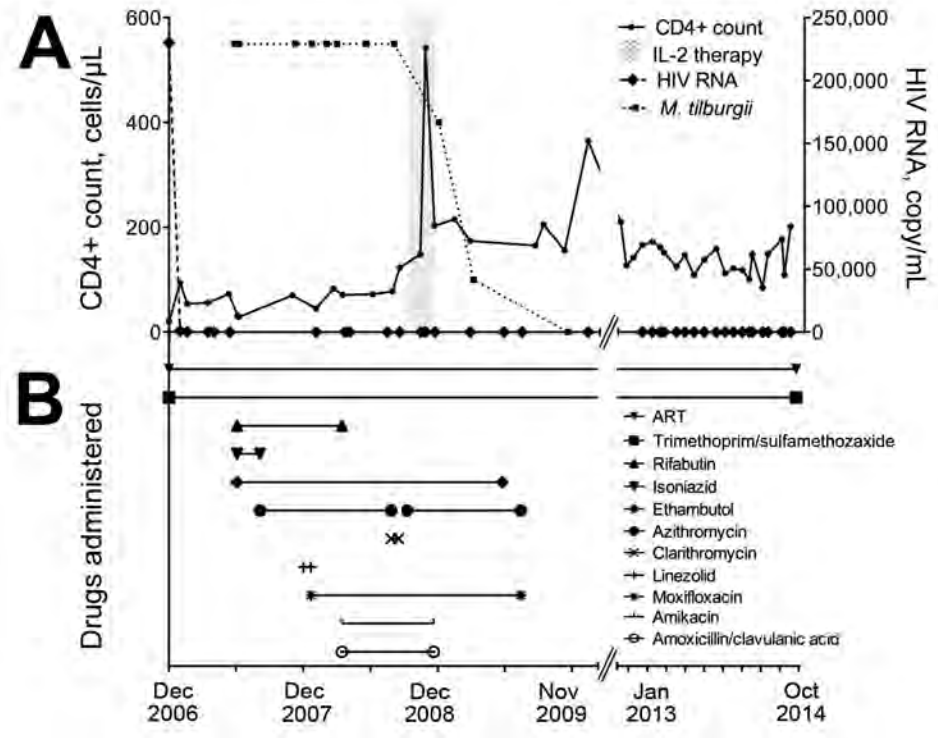

Figure. Laboratory findings and drug treatment regimen over time for an HIV-infected patient with disseminated *Mycobacterium tilburgii* infection, December 2006–October 2014. A) CD4+ T cell count, HIV viral load, and use of interleukin-2 (IL-2; gray shading). B) Antimycobacterial drug combinations, antiretroviral therapy (ART), and trimethoprim/sulfamethoxazole prophylaxis.

regimens of antimycobacterial drugs that are also effective against *M. avium* complex (*4*).

In 2 studies that evaluated the effect of adjunctive IL-2 therapy in addition to ART for previously treatment-naive patients with HIV infection, baseline median numbers of circulating CD4+ cells increased significantly, but expansion of CD4+ T cells was not associated with the reduction in the risk for opportunistic diseases or death (*8*). In contrast to these results, in a study of HIV-positive patients who had low circulating CD4+ T cell counts, the participants experienced fewer AIDS-defining events and fewer deaths occurred when they were treated with adjunctive IL-2 immunotherapy (*9*).

This case report provides lessons for the understanding of mycobacterial diseases. First, despite massive infiltration of duodenal mucosa, mesenterial lymph nodes, and bone marrow, the lack of inflammatory responses in this patient prevented tissue destruction. Second, in the absence of a sufficient immune response and an increase in the number of circulating CD4+ T cells, antimycobacterial therapy without adjunctive immunotherapy did not clear the systemic bacterial infection.

Host responses to pathogens are not always beneficial. Intense immune reactions experienced during episodes of sepsis or HIV immune reconstitution inflammatory syndrome are frequently associated with patient death. Alternately, in the absence of inflammatory responses to pathogens, the patient is unprotected, and even microbiota that are harmless to an immunocompetent person can adversely invade. In an optimal immune response setting, a balance between proinflammatory and anti-inflammatory factors in response to pathogens is maintained (*10*).

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Corynebacterium bovis Eye Infections, Washington, USA, 2013

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To the Editor: *Corynebacterium bovis* is well known as a normal bovine microbiota and is a common cause of bovine mastitis (*1*). *C. bovis* infections in humans are rare, and identification of the organism by biochemical methods is challenging (*2*). Although 9 cases of *C. bovis* infections in humans have been reported (*3*–*6*), only the most recent case, which involved prosthetic joint infection, used 16S rRNA gene sequencing to identify the bacterium with certainty (*6*).

During February–July 2013, four adult patients (Table) were seen at Veterans Administration Puget Sound Health Care System in Seattle, Washington, USA, for eye swelling, pain, and purulent discharge. All 4 cases were

Table. Characteristics and test results for 4 isolates of *Corynebacterium bovis* from patients with eye infections, Washington, USA, 2013*

Characteristic	Isolates from this study				Reference strains		
	F7181	F7545	F7275	F7551	*C. bovis* type strain ATCC 7751	Animal isolates,† n = 115	Human isolates,† n = 6
Patient no.	1	2	3	4			
Age, y/sex	49/M	25/M	33/M	90/M			
Date isolated	2013 Feb 4	2013 Jul 2	2013 Feb 27	2013 Jul 12			
Location where specimen was collected	VAPSHCS urgent care	VAPSHCS urgent care	VAPSHCS ED	Bellevue clinic			
API Coryne test code	2001004	0001004	0001105	0001004			
Test results							
Production of							
Catalase	+	+	+	+	+	100	100
Urease	+	+	+	+	–	44–68	17
Pyrazinamidase	+	–	–	–	+	ND	ND
Acid production from							
Glucose	–	–	+	–	+	56–98	50
Galactose	–	–	–	–	+	11–31	33
Mannose	–	–	–	–	+	5–33	33
Lactose	–	–	–	–	+	11–26	17
Sucrose	–	–	+	–	ND	ND	ND
GenBank accession no.	KJ769199	KJ769200	KJ769201	KJ769202			
16S rRNA gene sequence identity to type strain ATCC 7751, %	100	100	100	100			
Length of 16S rRNA gene sequence, nt	465	424	465	436			

*Phenotypic characteristics of *C. bovis* isolates from this study (*2*) were obtained by using API Coryne system v3.0 and Vitek2 (bioMérieux, Marcy l'Etoile, France). +, positive; –, negative; ED, emergency department; ND, not determined; VAPSHCS, Veterans Administration Puget Sound Health Care System.
†% strains positive.

associated with isolation of *C. bovis* from essentially pure culture. We investigated these 4 cases after obtaining approval from the Puget Sound Veterans Administration Medical Center Institutional Review Board (MIRB #01012).

Patient 1 was a 49-year-old man with swelling of the right eyelid with discharge and pain after an episode of itching. Before this visit, the patient had 3 similar episodes and received incision and drainage of the eyelid. On examination, the inverted lower palpebrum revealed a purulent cyst (diameter 1–2 mm); pus was collected from the cyst for culture. The patient was prescribed tobramycin ophthalmic drops and amoxicillin/clavulanic acid. No follow-up information was available.

Patient 2 was a 25-year-old man with bilateral eye infection that started on the left eye a week before the patient sought care. The eye had redness, swelling, blurred vision with loss of acuity, and irritation. The right eye had the same symptoms on the day of visit. Examination found bilateral keratoconjunctivitis and a 3-mm cyst with drainage on the lower palpebrum. The patient was treated with ofloxacin ophthalmic drops for 4 months but did not improve. A specimen was then collected from his right eye for culture. In 2014, he was given a diagnosis of chronic conjunctivitis.

Patient 3 was a 33-year-old man with severe pain, erythema, and swelling on his left eyelid. His symptoms started 1 week before he sought care and included swelling, increased cyst size, and disturbed vision. The pustular exudate was aspirated and sent to the laboratory. The patient was prescribed erythromycin ointment and oral trimethoprim/sulfamethoxazole. The patient's eye had improved at 3 weeks.

Patient 4 was a 90-year-old man who fell at home 2 days before his visit. He landed on his cheek, causing an abrasion, and his eye was swollen shut a few hours after the fall. On the second day, his cheek was swollen and reddened, and yellowish purulent matter was present on the skin. A swab specimen was collected from the wound and sent for culture. The patient was treated with doxycycline for 14 days, and the wound healed by day 12.

The aerobic cultures of 3 eye and 1 cheek wound specimens from these patients grew gram-positive bacilli (Table). The organism was initially identified by the API Coryne system (biomérieux, Marcy l'Etoile, France) as *C. urealyticum* or *Corynebacterium* group F-1. However, given the difficulty of phenotypic identification and the lack of literature to support eye infections associated with *C. urealyticum*, we performed 16S rRNA gene sequence analysis of the first ≈500 bp to confirm the identity. Using the MicroSeq 500 database version 0023b (Applied Biosystems, Foster City, CA, USA), we identified all 4 isolates as *C. bovis* (100% identical to ATCC 7715; sequence length

424–465 nt). According to the MicroSeq 500 and GenBank databases, the next 2 closest matches were *C. confusum* (96.1% similarity) and *C. macginleyi* (95.9% similarity), making the identification unambiguous.

C. bovis has not been described as part of the human microbiota, nor has it been associated with eye infections, in contrast to other *Corynebacterium* spp. known to colonize the human conjunctiva and skin (*7*) and cause eye infections (*8*,*9*). We found *C. bovis* associated with each of these eye and facial soft-tissue infections, but whether this lipophilic organism colonizes in the oily glands of eyelids in healthy individuals is unclear. What is certain is that *C. bovis* can exist on the human facial skin, has pathogenic potential, and is difficult to identify.

Because human and animal strains of *C. bovis* vary in biochemical properties (*2*), phenotypic identification is unreliable. All our isolates were urease positive, contrary to most isolates reported in the literature (*2*). This phenotype may result in underreporting of the organism because it is not described in some databases (*10*). An epidemiologic investigation revealed no overlap among any of the specimens regarding date of collection, clinic location where patients were seen, or date of clinical work-up. From results of our investigation, we believe that cross-contamination was unlikely and that these cases are probably independent of each other.

The pathogenicity of *Corynebacterium* spp. can be easily overlooked, especially because some species are common skin colonizers. Speciation should be prompted when *Corynebacterium* spp. are isolated in large quantity or from a pure culture. Unexpected phenotypic identifications such as *C. urealyticum* from eye specimens should be confirmed with 16S rRNA gene sequencing.

Acknowledgments

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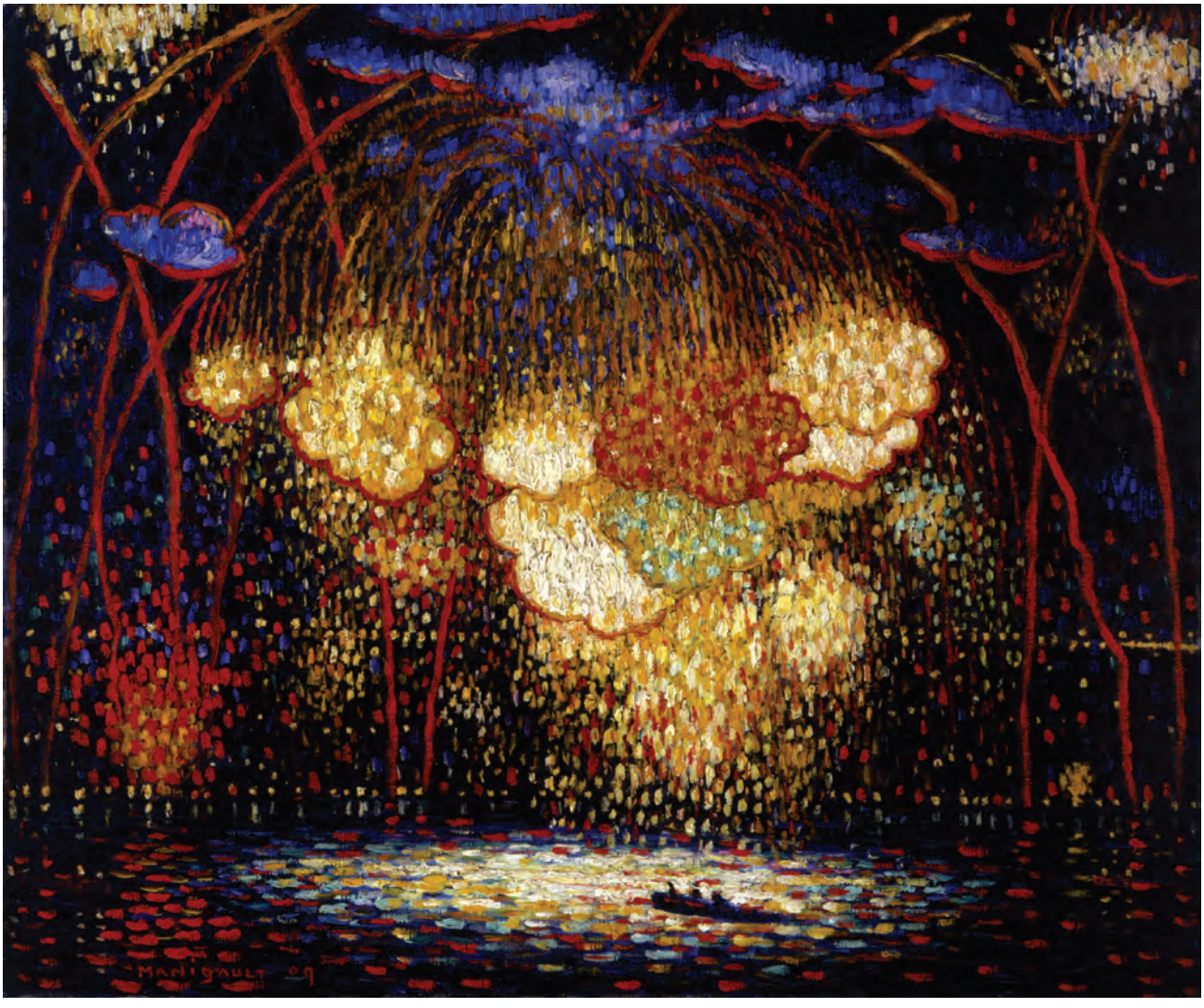

Ceaseless Experimentation Sparks Fireworks, Art, and Science

Byron Breedlove

Fireworks and festivities have long been linked. The earliest documentation of the genesis of fireworks points to the 7th century Tang Dynasty in China. Subsequently, these celebratory practices fanned out to other cultures and countries. Some speculate that Marco Polo or returning Crusaders introduced fireworks to the West, though fireworks probably trickled in over the course of many years, tucked among the belongings of various missionaries, traders, or explorers returning from sojourns to the East. Regardless of how knowledge of fireworks seeped into Europe, once there, it took root and flourished. During the Renaissance, two European schools of pyrotechnics emerged and thrived: Italians stressed intricate fireworks displays, and Germans focused on the science behind the spectacle.

For centuries, fireworks displays were marvels of sound, fury, and smoke, as pyrotechnicians had far more success mastering the formulas for the oxidations and reductions that ensured successful ascensions and explosions than those that would consistently yield color.

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Experimentation during the 19th century finally yielded the formulas for mixing the various metal salts and metal oxides required to produce the brilliant colors associated with modern fireworks. A flamboyant lexicon categorizes the varieties of explosions: a peony expands outward to form a sphere of stars; fish wriggle away from the central explosion before dissolving into points of light; falling leaves are colored stars that briefly hang in the sky before drifting down slowly; kamuro are the willow-like tendrils of light that radiate out and down, a favored effect for finales. The militaristic names for the chambered vessels that streak skyward toward a brief, spectacular end are less poetic: shells, rockets, and mortars figure prominently.

Radiating and dazzling, a wonderful confluence of science, art, and skill, fireworks celebrations attract crowds around the world. This month's cover image, "The Rocket," by the American Modernist artist Edward Middleton Manigault, vividly portrays an evening's fireworks show during the state of New York's 1909 Hudson-Fulton Celebration. This civic event commemorated the 300th anniversary of Henry Hudson's discovery of the river now bearing his last name and the 100th anniversary of Robert Fulton's inauguration of steamboat travel on the Hudson River (although the actual centennial was in 1907).

"The Rocket" bristles with energy; it is a dramatic, imaginative, and colorful reckoning of the celebration. Fireworks streak into the night sky, their explosions rendered by bold red, orange, and yellows brush strokes dabbled against the black night and blue clouds. Glowing ribbons of red light streak skyward and rim the blue clouds and the glowing fireworks clustered in the center of the painting, adding structure and symmetry like the lead cames in a stained glass window. The water refracts and reflects the spectacle, as a lone small boat sits on the river, nearly overwhelmed by the radiant display showering down. Myriad reflected splotches of color coat the surface of the river, like a vividly colored array of water lilies.

Manigault relied on Impressionistic style and technique in creating "The Rocket," during what is considered the peak of his career. Manigault restlessly and persistently explored new styles and influences in his personal quest to fathom the power and intensity of color. He would focus intently on specific styles and methods for several years and then shift to mastering a new approach—one of his admirers has dubbed Manigault's artistic focus as "ceaseless experimentation."

The notion of "ceaseless experimentation" also resonates well within the sciences, where the collaborative power of networks allows programs the chance to investigate and broadly test and evaluate ideas and approaches. It has been 20 years since the Centers for Disease Control and Prevention launched the Emerging Infections Program. This national resource for surveillance, prevention, and control of emerging infectious diseases expands the routine activities of participating state health departments by joining with academic partners and strives to translate surveillance and research activities into public health policy and practice.

The Emerging Infections Program—which debuted in 1995—traces its genesis in part to the Institute of Medicine's 1992 report *Emerging Infections: Microbial Threats to Health in the United States* and more specifically to the Centers for Disease Control and Prevention's 1994 report *Addressing Emerging Infectious Disease Threats: a Prevention Strategy for the United States*. This special-themed issue of the *Emerging Infectious Diseases* journal offers a wide-ranging perspective of the Emerging Infections Program's activities and accomplishments, and Manigault's dynamic painting helps us celebrate those two decades of research, collaboration, and publication with the appropriate flare.

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Another Dimension

Emerging Infectious Diseases accepts thoughtful essays, short stories, or poems on philosophical issues related to science, medical practice, and human health. Topics may include science and the human condition, the unanticipated side of epidemic investigations, or how people perceive and cope with infection and illness. This section is intended to evoke compassion for human suffering and to expand the science reader's literary scope. Manuscripts are selected for publication as much for their content (the experiences they describe) as for their literary merit.

EMERGING INFECTIOUS DISEASES®

Upcoming Issue

- Evolutionary and Ecologic Characterization of Mayaro Virus Strains Isolated during an Outbreak, Venezuela, 2010
- Delayed Disease Progression in Cynomolgus Macaques Infected with Ebola Virus Makona Strain
- Decreased Ebola Transmission after Rapid Response to Outbreaks in Remote Areas, Liberia, 2014
- Methicillin-Susceptible, Vancomycin-Resistant *Staphylococcus aureus*
- Public Health Response to *Aedes aegypti* and *Ae. albopictus* Mosquitoes Invading California, USA
- Acute Flaccid Paralysis Associated with Novel Enterovirus C105
- Utility of Oral Swab Sampling for Ebola Virus Detection in Guinea Pig Model
- Local and International Implications of Schistosomiasis Acquired in Corsica, France
- Detection of Mixed Infections with *Plasmodium* spp. by PCR, India
- Zika Virus Outbreak, Bahia, Brazil
- Bloody Diarrhea Associated with Hookworm Infection in French Tourist, Myanmar
- Schistosomiasis Screening of Travelers from Italy with Possible Exposure in Corsica, France
- Nonhuman Primate–to-Human Transmission of *Entamoeba nuttalli* and *Trichuris trichiura*

Complete list of articles in the October issue at http://www.cdc.gov/eid/upcoming.htm

Upcoming Infectious Disease Activities

September 17–21, 2015
ICAAC
Interscience Conference on Antimicrobial Agents and Chemotherapy
San Diego, CA, USA

October 25–29, 2015
ASTMH
American Society of Tropical Medicine and Hygiene
64th Annual Meeting
Philadelphia, Pennsylvania, USA
info@astmh.org

December 6–9, 2015
2015 National HIV Prevention Conference
Atlanta, GA, USA
http://www.cdc.gov/nhpc/index.html

February 8–10, 2016
ASM Biodefense and Emerging Diseases Research Meeting
Arlington, VA, USA
biodefense@asmusa.org

March 2–5, 2016
ISID
17th International Congress on Infectious Diseases
Hyderabad, India

Announcements

To submit an announcement, send an email message to EIDEditor (eideditor@cdc.gov). Include the date of the event, the location, the sponsoring organization(s), and a website that readers may visit or a telephone number or email address that readers may contact for more information.

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Article Title

Encephalitis Surveillance through the Emerging Infections Program, 1997–2010

CME Questions

1. Which of the following statements regarding the clinical profiles of different forms of encephalitis and their respective etiologic agents is most accurate?

A. The case-fatality ratio of encephalitis is approximately 0.2%
B. Temporal lobe abnormalities are almost exclusively associated with West Nile virus
C. Visual disturbances are pathognomonic for herpes simplex encephalitis
D. The etiologic agent associated with febrile infection-related epilepsy syndrome is unknown

2. Which of the following statements regarding challenges of testing for the cause of encephalitis is most accurate?

A. An underlying cause was found for more than 90% of cases
B. Antibody testing was associated with more rapid diagnoses vs. PCR
C. The high sensitivity of PCR resulted in detection of viruses that were probably not clinically significant
D. Autoimmune encephalitis has been demonstrated to play a very small role in disease

3. Which of the following agents appears to be the most common cause of sporadic infectious encephalitis in the United States?

A. Herpes simplex virus
B. West Nile virus
C. Enterovirus
D. Mycoplasma pneumoniae

4. Which of the following statements regarding anti-N-methyl-D-aspartate (NMDAR) encephalitis is most accurate?

A. It was first reported as a rare adverse event associated with the measles-mumps-rubella vaccine
B. It remains exclusively a neoplastic disorder
C. It is more common than many forms of infectious encephalitis among people 30 years old or younger
D. Varicella virus may serve as an antigenic trigger for anti-NMDAR

Activity Evaluation

1. The activity supported the learning objectives.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly Disagree				Strongly Agree
1	2	3	4	5

Earning CME Credit

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Article Title

Mycobacterium abscessus Complex Infections in Humans

CME Questions

1. Your patient is a 22-year-old woman with cystic fibrosis in whom you suspect *Mycobacterium abscessus* infection. According to the literature review by Meng-Rui Lee and colleagues, which of the following statements about clinical and nosocomial aspects of *M. abscessus* infections is correct?

A. These infections only involve the lungs, skin, and soft tissue
B. Persons with underlying structural lung disease such as cystic fibrosis, bronchiectasis, and previous tuberculosis are at increased risk for lung infections with *M. abscessus*
C. Isolation of *M. abscessus* complex from respiratory samples is, in and of itself, diagnostic of pulmonary disease
D. *M. abscessus* complex is highly sensitive to disinfectants

2. According to the literature review by Meng-Rui Lee and colleagues, which of the following statements about clinical and treatment aspects of infections with *M. abscessus*, subspecies is correct?

A. Five subspecies are currently identified, with *M. abscessus* subspecies *bolletii* being the most common
B. Subspecies identification among *M. abscessus* complex is readily available and easy to perform in most laboratories
C. Treatment response is best among patients with infections resulting from *M. abscessus* subspecies *abscessus*
D. *M. abscessus* subspecies *abscessus* and *massiliense* differ in the pattern of the erm(41) gene, which provides intrinsic resistance to macrolides

3. According to the literature review by Meng-Rui Lee and colleagues, which of the following statements about treatment of *M. abscessus* infections would most likely be correct?

A. Infections from *M. abscessus* complex are much easier to treat than those resulting from species comprising *M. avium* complex
B. Treatment regimens usually involve only oral therapy
C. Clarithromycin, amikacin, and cefoxitin are currently considered to be the drugs of choice
D. Treatment is usually complete in 10 days

Activity Evaluation

1. The activity supported the learning objectives.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly Disagree				Strongly Agree
1	2	3	4	5

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Biographical Sketch. Include a short biographical sketch of the first author—both authors if only two. Include affiliations and the author's primary research interests.

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Tables. Provide tables within the manuscript file, not as separate files. Use the MS Word table tool, no columns, tabs, spaces, or other programs. Footnote any use of boldface. Tables should be no wider than 17 cm. Condense or divide larger tables. Extensive tables may be made available online only.

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Perspectives. Articles should not exceed 3,500 words and 40 references. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), 1-sentence summary, and biographical sketch. Articles should provide insightful analysis and commentary about new and reemerging infectious diseases and related issues. Perspectives may address factors known to influence the emergence of diseases, including microbial adaptation and change, human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, and the breakdown of public health measures.

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Research. Articles should not exceed 3,500 words and 40 references. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), 1-sentence summary, and biographical sketch. Report laboratory and epidemiologic results within a public health perspective. Explain the value of the research in public health terms and place the findings in a larger perspective (i.e., "Here is what we found, and here is what the findings mean").

Policy and Historical Reviews. Articles should not exceed 3,500 words and 40 references. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), 1-sentence summary, and biographical sketch. Articles in this section include public health policy or historical reports that are based on research and analysis of emerging disease issues.

Dispatches. Articles should be no more than 1,200 words and need not be divided into sections. If subheadings are used, they should be general, e.g., "The Study" and "Conclusions." Provide a brief abstract (50 words); references (not to exceed 15); figures or illustrations (not to exceed 2); tables (not to exceed 2); and biographical sketch. Dispatches are updates on infectious disease trends and research that include descriptions of new methods for detecting, characterizing, or subtyping new or reemerging pathogens. Developments in antimicrobial drugs, vaccines, or infectious disease prevention or elimination programs are appropriate. Case reports are also welcome.

Another Dimension. Thoughtful essays, short stories, or poems on philosophical issues related to science, medical practice, and human health. Topics may include science and the human condition, the unanticipated side of epidemic investigations, or how people perceive and cope with infection and illness. This section is intended to evoke compassion for human suffering and to expand the science reader's literary scope. Manuscripts are selected for publication as much for their content (the experiences they describe) as for their literary merit. Include biographical sketch.

Letters. Letters commenting on recent articles as well as letters reporting cases, outbreaks, or original research, are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have 1 figure or table and should not be divided into sections. No biographical sketch is needed.

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Conference Summaries. Summaries of emerging infectious disease conference activities (500–1,000 words) are published online only. They should be submitted no later than 6 months after the conference and focus on content rather than process. Provide illustrations, references, and links to full reports of conference activities.

Online Reports. Reports on consensus group meetings, workshops, and other activities in which suggestions for diagnostic, treatment, or reporting methods related to infectious disease topics are formulated may be published online only. These should not exceed 3,500 words and should be authored by the group. We do not publish official guidelines or policy recommendations.

Photo Quiz. The photo quiz (1,200 words) highlights a person who made notable contributions to public health and medicine. Provide a photo of the subject, a brief clue to the person's identity, and five possible answers, followed by an essay describing the person's life and his or her significance to public health, science, and infectious disease.

Etymologia. Etymologia (100 words, 5 references). We welcome thoroughly researched derivations of emerging disease terms. Historical and other context could be included.

Announcements. We welcome brief announcements of timely events of interest to our readers. Announcements may be posted online only, depending on the event date. Email to eideditor@cdc.gov.

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