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Scarlet Fever Outbreak, Hong Kong, 2011

To the Editor: Scarlet fever is a notifiable disease in Hong Kong, Guangdong Province, and Macau in the People's Republic of China. All 3 areas reported substantial increases in cases during 2011 (Figure, panel A). In Hong Kong, individual data, including age, geographic location, date of notification, and travel history within the incubation period, were collected from all locally notified scarlet fever case-patients. As of December 31, 2011, a total of 1,535 cases (21.7 cases/100,000 population) were reported, which was $\approx 10\times$ higher than the average number of annual cases reported during the preceding 10 years (1). Of those, 730 cases were laboratory confirmed; 46 cases were imported; and 2 cases, 1 each in a 7-year-old girl and a 5-year-old boy co-infected with chick-enpox, resulted in death (2).

Group A *Streptococcus* (GAS), the bacterium that causes scarlet fever,

is mainly transmitted by direct contact with saliva and nasal fluids from infected persons (3). Many children can also carry GAS or be asymptotically infected (4). A recent study in China showed that GAS is commonly resistant to macrolides and tetracycline but sensitive to penicillin, chloramphenicol, cefradine, and ofloxacin (5). In Hong Kong, GAS *emm* type 12 dominated among the isolates cultured during 2011 (6). Most of the cases reported were in children <10 years of age (range 1 month–51 years; median 6 years [interquartile range 4–7 years]). The age distribution is similar to that reported during previous years (data not shown).

In the United Kingdom during the mid-19th century, scarlet fever epidemics were found to follow a 5- to 6-year cycle, but this pattern disappeared as incidence decreased (7). Annual scarlet fever notifications in Hong Kong remained low during 2001–2010 (<4 cases/100,000 population) and did not demonstrate any apparent long-term pattern. The recent increase in scarlet fever notifications might be attributable to antigenic drift, increase in virulence of GAS (8), or increased circulation of GAS. However, other than mandatory notification of medically attended case-patients, systematic laboratory testing of GAS isolates was not conducted in Hong Kong, and these possibilities could not be further investigated.

Notifications of scarlet fever usually peak during December–March in Hong Kong, but the outbreak in 2011 peaked in June (Figure, panel B). The rise in scarlet fever cases in Guangdong Province and Macau slightly preceded that in Hong Kong; cases in Guangdong peaked in April (Figure, panel A). Maximum cross-correlations between spline-interpolated weekly scarlet fever notifications in Guangdong and Macau and those in Hong Kong were found at 1- and 2-week lags, respectively ($\rho = 0.45$ and 0.58) (online Technical Appendix, wwwnc.cdc.gov/EID/pdfs/12-0062-Techapp.pdf).

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In 2011, scarlet fever notification rates were elevated in all 4 regions of Hong Kong: New Territories East, New Territories West, Kowloon, and Hong Kong Island at 27.2, 21.7, 18.9, and 19.6 cases per 100,000 population, respectively. However, a distinctly higher proportion of imported cases before July 2011 (12 of 14, p value for exact binomial test = 0.01) were notified in New Territories East and New Territories West, where the main border crossings to mainland China are located. This finding suggests a link to the outbreak in Guangdong in these regions during the early phase of the local outbreak.

We estimated the instantaneous reproduction number (R_t), which measures the time-dependent frequency of transmission per single primary case (online Technical Appendix) (9). An R_t consistently >1 would indicate sustained local transmission. We estimated R_t on the basis of the daily scarlet fever notification data in different periods, adjusted for imported cases. For 19 cases (1.2% of all cases), we could not determine whether infection was local or imported. We estimated R_t in 2 different ways: either by assuming that all of these cases were local or by assuming that they all were imported, to represent possible extreme values of R_t . R_t fluctuated between 0.6 and 2.0 and was consistently >1 from mid-May through the end of June. R_t fell quickly to <1 beginning in early July after 2 fatal scarlet fever cases were reported on May 29 and June 21, which raised widespread concern in the community (Figure, panel C). Heightened surveillance, publicity, health education to the public (online Technical Appendix) were implemented by the Centre for Health Protection in early June and could have contributed to the reduction in transmissibility. The health education measures included guidance on pre-

vention and control measures, such as updates of antimicrobial drug resistance profile of GAS issued to all doctors and strengthening reporting of scarlet fever cases by child care centers and schools for prompt epidemiologic investigations,

In summary, we analyzed the notification data of scarlet fever and

investigated spatiotemporal spreading patterns of the disease with certain time lags in Hong Kong, Macau, and Guangdong. The estimated R_t in 2011 indicated the potential for local transmission and persistence. Such a borderless spread indicates a critical need to enhance cross-border communication and timely sharing of epidemic

information so that future disease control efforts can be made at multiple geographic levels.

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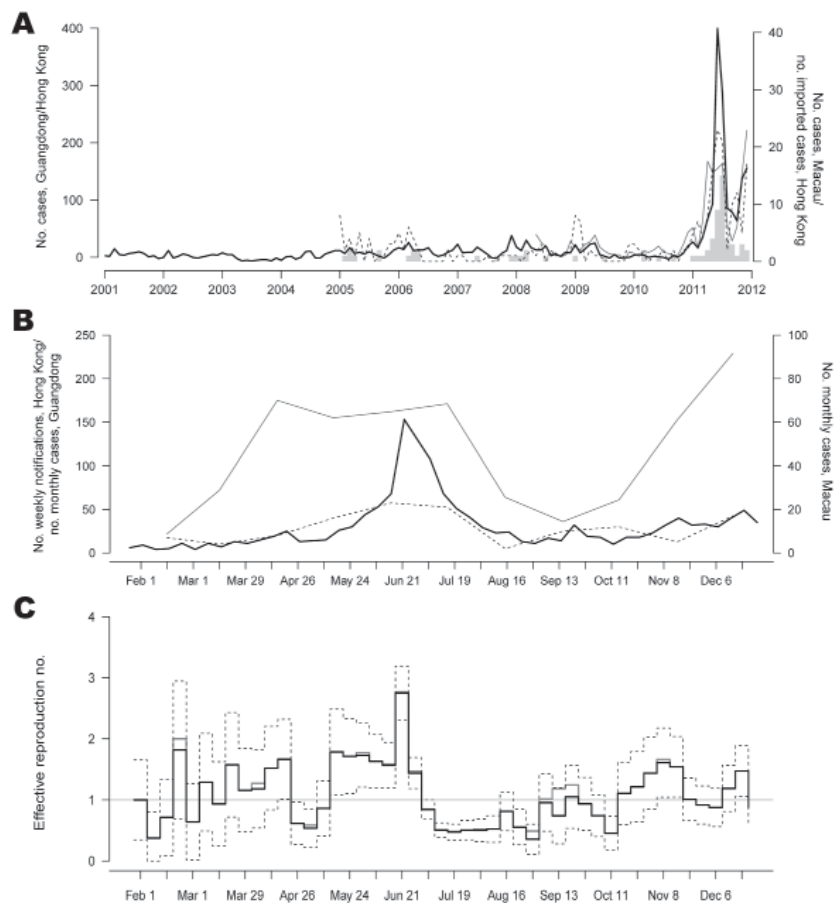


Figure. Trends in scarlet fever during outbreak in Hong Kong, Guangdong, and Macau, People's Republic of China, 2011. A) Monthly scarlet fever notifications in Hong Kong, Guangdong (data obtained from Department of Health Guangdong Province, www.gdwtst.gov.cn/a/yiqingxx), and Macau (data obtained from Health Bureau, Government of the Macau Special Administrative Region (www.ssm.gov.mo/news/content/ch/1005/statistic.aspx)). Vertical tick marks indicate January of each year. Data from Guangdong and Macau were available beginning in 2005. Black line indicates data from Hong Kong; gray line, data from Guangdong; broken line, data from Macau; gray bar, number of imported cases in Hong Kong, 2005-2011. B) Weekly notifications of scarlet fever cases in Hong Kong and monthly notifications in Guangdong and Macau. Black line indicates data from Hong Kong; gray line, data from Guangdong; broken line, data from Macau. C) Estimated instantaneous reproduction number (R_t) and 95% pointwise confidence intervals (CIs) based on scarlet fever notifications in Hong Kong, February–December, 2011. Black line indicates estimate calculated by grouping patients with unknown importation status with patients with imported cases; gray line, estimate calculated by grouping patients with unknown importation status with local case-patients; broken lines, the upper and lower limits of the 95% CIs for R_t . For better presentation, CIs are shown only for the former estimates. Horizontal line indicates the critical value of R_t , under which transmission of disease will not be sustainable.

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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. All letters should contain material not previously published and include a word count.

Hand, Foot, and Mouth Disease Caused by Coxsackievirus A6

To the Editor: Coxsackievirus A6 (CVA6) is a human enterovirus associated with herpangina in infants. In the winter of 2012, we evaluated a cluster of 8 patients, 4 months–3 years of age, who were brought for treatment at Boston Children's Hospital (Boston, MA, USA) with a variant of hand, foot, and mouth disease (HFMD) that has now been linked to CVA6 (Table, Appendix, wwwnc.cdc.gov/EID/article/18/10/12-0813-T1.htm). During this same period, the Boston Public Health Commission's syndromic surveillance system detected a 3.3-fold increase in emergency department discharge diagnoses of HFMD. In the United States, HFMD typically occurs in the summer and early autumn and is characterized by a febrile exanthem of oral ulcers and macular or vesicular lesions on the palms and soles; the etiologic agents are most often CVA16 and enterovirus 71.

In contrast to the typical manifestation, the patients in the Boston cluster exhibited symptoms in late winter (Table, Appendix) and had perioral (Figure, panel A) and perirectal (Figure, panel B) papules and vesicles on the dorsal aspects of the hands and feet (Figure, panel C). Patients experienced a prodrome lasting 1–3 days, consisting of fever (8 patients), upper respiratory tract symptoms (4 patients), and irritability (7 patients). This prodrome was followed by the development of a perioral papular rash (8 patients), which was often impetiginized with secondary crusting; a prominent papulovesicular rash on the dorsum of the hands and feet (6 patients); and a perirectal eruption (7 patients). Half of the patients had intraoral lesions. Fever abated in most of the patients within a day after onset of

the exanthem. The rash resolved over 7–14 days with no residual scarring. Samples from the oropharynx, rectum, and vesicles from these patients were sent to the Centers for Disease Control and Prevention (Atlanta, GA, USA) for analysis. Reverse transcription PCR and sequencing by using primers specific for a portion of the viral protein 1 coding region identified CVA6 (1) (Table, Appendix).

Outbreaks of HFMD caused by CVA6 have been described in Singapore, Finland, Taiwan, and most recently in Japan; most cases have occurred in the warmer months (2–6). Cases in the cluster described here are likely related to an emerging outbreak of CVA6-associated HFMD in the United States (7). The atypical seasonality of the outbreak, during the winter in Boston, could be related to the unusually mild temperatures in the winter of 2012.

Recent CVA6 outbreaks have been characterized by a febrile illness associated with an oral exanthem and lesions on the palms, soles, and buttocks. CVA6 infections in Taiwan during 2004–2009 were associated with HFMD in 13% of cases, with disease defined as oral ulcers on the tongue or buccal mucosa and vesicular rashes on the palms, soles, knees, or buttocks (2). In Singapore, where CVA6 accounted for 24% of HFMD cases, patients had oral lesions and <5 peripheral papules, placing them on a spectrum closer to the herpangina more typically observed in CVA6 infection (8).

The patients we report in this cluster most typically had perioral and perirectal papules in addition to vesicles on the dorsum of their hands. Two reports of CVA6-associated HFMD outbreaks describe cases that more closely resemble patients in the Boston outbreak. In a series from Finland in 2008, representative patients had both perioral lesions and vesicles on the dorsum of their hands (6). In a large series of patients with

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Technical Appendix

Statistical Methods and Discussion of Impact of Public Notification on Disease Transmission

Calculation of Cross-Correlation between Notification Data

Monthly scarlet fever notifications in Guangdong and Macau were cumulated from December 2010 to December 2011 and then smoothed using cubic spline assuming time points at 15th of each month. Weekly cumulative notifications was estimated by interpolation based on the spline function, which was then differenced to obtain weekly estimated number of notifications from week starting January 16, 2011, to week starting December 19, 2011. Cross-correlations were then calculated between estimated weekly number of notifications in Guangdong and Macau versus actual weekly notifications in Hong Kong. Maximum correlation among estimated weekly Guangdong and Macau scarlet fever notifications with different lags versus notifications in Hong Kong were identified.

Estimation of the Instantaneous Reproduction Number R_t

Let j_t be the incidence of infection within Hong Kong on day t (i.e., the number of new local cases), and similarly, let i_t be the incidence of imported cases on day t . We describe the evolution of the incidence within Hong Kong over time by employing the following renewal process (I):

$$j_t = R_t \sum_{\tau=1}^t (j_{t-\tau} + i_{t-\tau}) g_\tau \quad [\text{E1}]$$

where R_t is the instantaneous reproduction number, which is interpreted as the average number of secondary cases on day t produced by a single primary case, and g_τ is the probability mass function of the generation time of length τ days. The equation [E1] describes the process of secondary transmissions within Hong Kong that are caused by local and imported cases infected in the past. The right-hand side of [E1] uses the sum of local and imported cases, i.e., $(j_{t-\tau} + i_{t-\tau})$,

because their differential roles of secondary transmission are not explicitly separable. Using the cumulative distribution of a gamma-distributed generation time, $G(s)$, with the mean 14.0 days and standard deviation 4.9 days (2), and truncating the distribution at $s_{\max}=30$ days, the discrete function g_s was calculated as

$$g_s \Rightarrow \frac{G(s) - G(s-1)}{G(s_{\max})}$$

for $s > 0$.

Assuming that observation of j_t is sufficiently characterized by a Poisson distribution, the likelihood function, which is required to estimate R_t , is proportional to

$$\prod_t j_t^{Obs_t} \exp(-j_t) \quad [E2]$$

where Obs_t is the observed number of local cases on day t . When incorporating the influence of imported cases on the transmission dynamics in equation [E1], we ignored the time elapsed from infection of imported cases to their entry into Hong Kong due to the absence of additional datasets to support more realistic assumptions. To avoid spurious estimates of R_t due to noise, we employed a step function, especially a weekly constant model, to parameterize R_t . The maximum likelihood estimates of R_t were obtained by minimizing the negative logarithm of [E2].

Supplementary Discussion

In the main text, we have shown that the instantaneous reproduction number, R_t fluctuated below and above 1. This is not surprising, because scarlet fever has been, even at low frequency, continuously seen in Hong Kong. However, when there was a surge of notifications from February to April 2011, R_t still fluctuated, indicating that the local transmission may not have been so intense. Moreover, even though the estimates of R_t were above 1 from late May to June 2011, it should also be noted that this time period was accompanied by intense media coverage and the reporting coverage of scarlet fever is likely to have been greatly improved, which could plausibly explain the observed pattern and still suggests that R_t of scarlet fever in Hong Kong is around 1. Of course, $R_t > 1$ from late May to June 2011 indicates that the population in Hong Kong has been susceptible to the epidemic, but the disease may not be so transmissible. The publicity of the second death associated with scarlet fever in late June, along

with guidance on prevention and control measures to doctors, schools and institutions concerning updates of scarlet fever activity, suggested antibiotic treatment with respect to antibiotic resistance pattern and recommended sick leave duration for children, distribution of health education materials to the public concerning basic clinical and epidemiological knowledge and personal protection against scarlet fever, in various forms such as pamphlets, posters, stickers, TV and radio announcement further elevated concern and alert in the general population, which resulted in reduced transmission efficiency as reflected by the sharp drop of R_t in early July. There are two important implications for the epidemic which is likely fueled by continued importations. First, epidemiological monitoring at multi-geographic levels and its cross-border sharing are essential, as the epidemic dynamics are largely governed by large-scale spatial interactions. Second, public health control measures may be beneficial given that R_t declined below 1 in July 2011, but radical control measure may only reduce local transmissions instantaneously, and rather, long-term epidemic trend may be more likely regulated by introductions of cases from different locations.

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