

Adventitious Viruses and Smallpox Vaccine

To the Editor: Recently, Murphy and Osburn (1) strongly argued for testing old smallpox vaccine stocks made in animal skin for adventitious infectious agents such as viruses, mycoplasmas, and eventually, prions. Their argument appears clearly justified after unexpected cases of myopericarditis occurred during recent campaigns of smallpox vaccinations in the United States (2).

To the long list of bovine viruses cited in this paper, it seems necessary to add another, the pseudocowpox virus, a widespread parapoxvirus that may infect humans. During the 1960s, this virus was identified in vaccine lymph from a heifer at the Institut Pasteur, Paris (3).

In humans, this virus is responsible for limited skin lesions, more frequently in immunocompromised patients. Mainly farmers and butchers are affected. Pseudocowpox virus is easily differentiated from orthopoxviruses such as vaccinia virus by the virus's peculiar form on transmission electron microscopy scan, but polymerase chain reaction is probably the best detection method (4). In fact, many other more hazardous viruses may be found in the oldest stocks of smallpox vaccine and deserve more attention than previously considered.

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Fluoroquinolone Use in Food Animals

To the Editor: Two recent articles (1,2) show that fluoroquinolone use in food animals is associated with infections by antimicrobial drug-resistant strains of *Campylobacter* in humans. These infections cause problems in treating illnesses as well as increased rates of illness and death (3). Despite a large body of scientific evidence and a judicial review (1-3) that show harmful results in many persons, some members of the poultry and pharmaceutical industries argue that fluoroquinolone use in food animals has no adverse effects in humans (4) and continue to supply these drugs for use in poultry (2,5). The use of these drugs has caused rapidly increasing resistance rates in most countries. In the United States, 19% of *Campylobacter* isolates from humans are now ciprofloxacin resistant (2), and resistance rates >80% are seen in Spain (5). By contrast, in Australia, where fluoroquinolones were never approved for use in food animals, domestically acquired infections with fluoroquinolone-resistant *Campylobacter* spp. are rarely found in humans (6). Drug-resistant *Escherichia coli* is also of concern. In Spain, humans frequently acquire fluoroquinolone-

resistant *E. coli* associated with fluoroquinolone use in poultry (7).

In the United States, better controls in meat and poultry slaughter and processing, as well as improved food-safety education campaigns, have resulted in 28% fewer *Campylobacter* infections annually since 1996 (8). However, ≈1.8 million persons (600 per 100,000) are likely to contract symptomatic *Campylobacter* infections per year (3,8), and fluoroquinolone resistance is now 19% (2). Thus, the risk of a person's contracting fluoroquinolone-resistant *Campylobacter* infection is 114 per 100,000 per year. If 80% of *Campylobacter* infections are foodborne (3), and 90% of these infections are acquired from poultry (9), then ≈82 of 100,000 persons per will contract ciprofloxacin-resistant *Campylobacter* infections from poultry each year. Most persons with *Campylobacter* infections would not benefit from antimicrobial drug therapy. However, if only 10% of infected persons would benefit from antimicrobial drug therapy, fluoroquinolone use in poultry could cause ≈82 persons per million to have a compromised response to therapy. In the United States (population 300 million), this number translates to >24,000 persons annually.

Data on the number of animals that receive fluoroquinolones are difficult to find. Bayer (manufacturer of the only fluoroquinolone used in poultry in the United States) states that Baytril (enrofloxacin) is used in <1% of US broiler flocks (4). This statistic allows us to estimate how many persons will potentially have an adverse outcome compared to the number of animals receiving fluoroquinolones. If 24,000 persons in the United States have an adverse outcome annually after <84 million chickens (1% of 8.4 billion) are treated with enrofloxacin, then ≈285 persons are at risk of having an adverse outcome for every 1 million chickens treated.

This risk seems needless. In Australia, consequences from not using these agents in food animals (i.e., neither therapeutic nor prophylactic use is approved) have not been seen. Thus, I do not agree with Iovine and Blaser (1), who would allow fluoroquinolones to be used to treat sick food production animals. Bayer claims that “Baytril is used for therapeutic purposes only...” (4). Thus, continuation of fluoroquinolone use for these therapeutic purposes will allow the consequent development of resistant bacteria in humans, which will include resistant strains of *Campylobacter*, *E. coli*, and *Salmonella*. Discontinuing fluoroquinolone use by mass dosing (the current practice for poultry [10]) would decrease the amount of the drug used. However, why use fluoroquinolones at all? Narrower spectrum antimicrobial drugs (e.g., sulfonamides, amoxicillin) could be used to adequately treat sick animals. Surely *E. coli* drug resistance in food animals in the United States cannot be at a level that makes fluoroquinolones indispensable. If resistance levels to narrower spectrum antimicrobial drugs are at high levels, does this finding not imply that major changes concerning antimicrobial drug use in food animals are needed?

Better methods are needed to accurately estimate how many persons are negatively affected annually because of the misuse of antimicrobial drugs in food animals. Compromised therapeutic outcomes occur in many persons throughout the world because of fluoroquinolone-resistant *Campylobacter* infections (10). Fluoroquinolone use is not essential for food animal production or the welfare of animals. Many ways to keep animals healthy and productive exist other than treating or trying to prevent infections with the mass use of antimicrobial drugs such as fluoroquinolones.

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In response: We agree with Dr Collignon’s view that using fluoroquinolones in the poultry industry imposes a “needless risk” of harm to humans by promoting the emergence of fluoroquinolone-resistant *Campylobacter* infections and consequent increased illness in humans (1). We support the therapeutic use of fluoroquinolones in poultry if only animals that are ill are treated (2). The widespread practice of adding fluoroquinolones to the drinking water of a hen house with thousands of birds, or of an entire flock, promotes the emergence of resistant *Campylobacter* strains. Unless veterinary practices limit fluoroquinolone use exclusively to sick birds, the only responsible recourse is to ban the use of fluoroquinolones in the poultry industry altogether, in agreement with the Food and Drug Administration’s decision (3).

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In response: We thank Dr Collignon for his comments regarding the human health impact after fluoroquinolone use in food animals (1). Similar conclusions concerning the human health consequence of using fluoroquinolones in poultry in the United States were reached by the US Food and Drug Administration (FDA) in a quantitative risk assessment in 2000 (1). FDA concluded that fluoroquinolone use in poultry has resulted in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter* that infects thousands of persons each year in the United States. Therefore, since 2000, FDA has sought to discontinue the use of fluoroquinolones in poultry. On July 25, 2005, FDA announced the withdrawal of fluoroquinolones for use in poultry effective as of September 12, 2005.

The debate regarding the use of antimicrobial agents in food animals and their impact on human health has been longstanding. For many years, public health officials have raised concern regarding the use of antimicrobial drugs in food animals that are of importance to human health. Industry representatives have stated that these concerns are unfounded. In our study, we found no fluoroquinolone resistance among a sample of *Campylobacter jejuni* strains collected from persons in 1990 (2). In 1995, fluoroquinolone use was approved in the United States for food animal use, specifically for poultry. Between 1997 and 2001, we noted a significant increase in fluoroquinolone resistance among human *Campylobacter* strains in the United States, monitored through Centers for Disease Control and Prevention surveillance (13%–19%, logistic regression odds ratio 2.4, 95% confidence interval 1.4–4.1). This finding means that despite a 31% decline in the overall incidence of *Campylobacter* infections from 1997 to 2001, the incidence of fluoroquinolone-resistant

Campylobacter infections increased (3,4). More recently published data show that persons with fluoroquinolone-resistant infection have a longer duration of diarrhea and are more likely to have invasive disease or die than persons with fluoroquinolone-susceptible infections (5,6). These data demonstrate, as Dr Collignon indicates, the human health consequences of increasing fluoroquinolone resistance among *Campylobacter*.

Campylobacter is a zoonotic pathogen and most often associated with consumption of poultry. Our study found that in 1999, 10% of grocery store–purchased chickens yielded fluoroquinolone-resistant *Campylobacter* (2). More recently, retail food testing in 2002 performed by FDA found that 14% of retail chicken samples were contaminated by fluoroquinolone-resistant *Campylobacter* (7). Studies of commercial poultry flocks before, during, and after fluoroquinolone treatment found that only a small proportion of flocks had fluoroquinolone-resistant *Campylobacter* infections before fluoroquinolone treatment, but that fluoroquinolone-resistant strains quickly emerged during treatment and often persisted after treatment (8,9). As Dr Collignon describes, in Australia, fluoroquinolone-resistant *Campylobacter* strains have not been detected in domestically acquired human infections; this finding has been attributed to the fact that fluoroquinolones are not licensed for use in food animals (10). We agree with Dr Collignon that convincing data indicate that use of antimicrobial agents that are of human importance among food animals has an adverse human health impact and that the time has come to find alternatives that promote food-animal health while minimizing the induction of antimicrobial resistance.

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Ehrlichia ruminantium, Sudan

To the Editor: *Ehrlichia ruminantium*, the causative agent of heartwater, is transmitted by *Amblyomma* spp. ticks. *Amblyomma variegatum* ticks, which are found in the Caribbean and sub-Saharan Africa, except in certain areas of southern Africa, are major vectors of *E. ruminantium* (1–3). *A. lepidum* is also an important vector of heartwater, especially in eastern Sudan (4). However, few epidemiologic data exist on infection rates of *Amblyomma* spp. ticks and distribution of *E. ruminantium* in Sudan. A polymerase chain reaction (PCR) assay that uses DNA probe pCS20 has been developed for detecting *E. ruminantium* (5). Another PCR assay for the major antigen protein 1 gene (*map1*) has been used to differentiate strains of *E. ruminantium* (6,7). These PCR assays have high sensitivity and specificity for the amplification of *E. ruminantium* DNA (6,8). For epidemiologic study of *E. ruminantium* in Sudan, we used PCR to detect *E. ruminantium* DNA in ticks. We also sequenced PCR products to identify the genotype of *E. ruminantium*.

The pCS20 DNA fragment of *E. ruminantium* was detected in 8 (8.2%) of 97 *A. variegatum* ticks and 2 (1.9%) of 106 *A. lepidum* ticks ($\chi^2 =$

3.123, by Yates correction). The nucleotide sequences (279 bp) obtained from 5 *A. variegatum* ticks and 1 *A. lepidum* tick were identical (GenBank accession no. AB218277). The sequences were similar to those of Welgevonden, Vosloo, and Ball3 strains from southern Africa and Gardel strain from the Caribbean islands (similarity = 99.64%). The pCS20 sequences obtained in this study were different from those of strains from western Africa.

An 855-bp *map1* nucleotide sequence obtained from 1 *A. lepidum* tick was provisionally named Gedaref (GenBank accession no. AB218278). The nucleotide sequence of Gedaref

was found to be closely related to those of Senegal and Pokoase strains from western Africa and to South Africa Canine and Kümml strains from southern Africa (similarity = 90.53%–97.43%). Gedaref clustered with these 4 strains and with 6 other strains, including Kiswani from eastern Africa and Antigua from the Caribbean islands (Figure). In contrast, the nucleotide sequence of Gedaref showed 84.8% similarity with that of Um Banein, which has been known as the only strain of *E. ruminantium* in Sudan. Um Banein formed another cluster with Gardel, Lutale, and Umpala strains from southern Africa (Figure). The *map1*

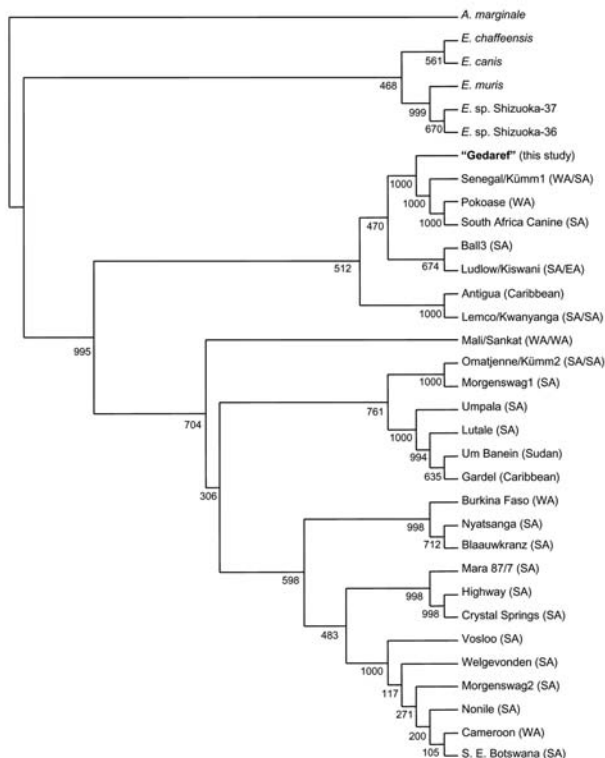


Figure. Neighbor-joining phylogram based on *map1* nucleotide sequences of *Ehrlichia ruminantium* strains. Ninety-seven *Amblyomma variegatum* ticks were obtained from cattle in the suburbs of Juba in southern Sudan, and 106 *A. lepidum* ticks were obtained from camels in the suburbs of Gedaref in eastern Sudan in 2000. The amplicon used included all 3 variable regions in the *map1* sequence (nucleotide positions 472–1377) (7). The nucleotide position refers to GenBank accession no. X74250. The amplicon without primer sequences (855 bp) was subjected to sequencing analysis. Sequence homogeneity was determined and multiple alignment analyses were conducted as previously described (9). *A. marginale* strain Pawhuska major surface protein 4 (GenBank accession no. AY127078) was used as an outgroup. WA, western Africa; SA, southern Africa; EA; eastern Africa. Kiswani is identical to Ludlow, Kümml1 is identical to Senegal, Kümml2 is identical to Omatjenne, Kwanyanga is identical to Lemco, and Sankat is identical to Mali (6).