sistant; none of these strains were associated with adverse health effects. Within 30 days of the date of receipt of samples, the patients infected with a campylobacter isolate resistant to quinolone only had a 4.48 times (95% confidence interval [CI], 1.23–16.30 times) higher risk of invasive illness or death than did the patients infected with a quinolone- and erythromycin-susceptible isolate (table 1). This result is in the same range as that obtained when the DANMAP 27-mm breakpoint was used.

Macrolides bind irreversibly to the bacterial ribosome, which results in inhibition of protein synthesis. Chromosomal mutations in the gene encoding 23S rRNA are often responsible for erythromycin resistance [3]. These mutations result in substantial changes in erythromycin susceptibility, and, as is the case for quinolones, erythromycin-resistant and -susceptible isolates represent distinct populations of bacteria. As we did for quinolones, we reanalyzed our data in a model in which only isolates with an inhibition zone ≤20 mm (the CLSI breakpoint) were considered to be resistant to erythromycin, not those with an inhibition zone <27 mm (the DANMAP breakpoint). This resulted in reclassifying 77 (2.2%) isolates as susceptible; there were no isolates from patients with adverse health events in this group. Within 90 days of the date of receipt of samples, the patients infected with an erythromycin-resistant campylobacter strain had an 8.60 times (95% CI, 1.86–39.77 times) higher risk of invasive illness or death than did the patients infected with a quinolone- and erythromycin-susceptible strain (table 1).

In conclusion, we thank Shryock for his letter [7] and his interest in our work. We agree that it is important to use internationally recognized susceptibility standards, such as those of the CLSI. However, the classification of isolates was robust to the choice of breakpoints, because the conclusions of our study were not modified by a change from the DANMAP breakpoints to the Rosco recommendations for zone diameter interpretative criteria according to CLSI recommendations.

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or at what stage resistance was acquired, nor do we know whether there are, indeed, any excess adverse consequences.

Second, Varma et al. do not discuss which specific serotypes are involved in resistant infection. However, we calculate, on the basis of other National Antimicrobial Resistance Monitoring System data (available at: http://www.cdc.gov/narms/annual/2000/tables/table_8.htm), that it is probably that most of the resistant strains were, in fact, Salmonella serotype Typhimurium. Among several thousand nontyphoidal salmonella isolates examined in 2000, 56% of those resistant to >1 antibiotic—and 80% of those resistant to >5 antibiotics—belonged to the Typhimurium serotype. Varma et al. state that the association among resistance, bloodstream infection, and hospitalization was particularly strong for patients infected with Salmonella Typhimurium, but they provide no clear factual support for this or for their belief that this association is not fully explained by the fact that all 3 events are associated with Salmonella Typhimurium. Although a database including only 56 ascertained hospitalized patients (their table 4) with bloodstream salmonella infection is admittedly limited, we believe that what Varma et al. have probably shown is no more than that antimicrobial-resistant and possibly more virulent Salmonella Typhimurium is associated with excess bloodstream infections and hospitalizations for nontyphoidal salmonella infection. Thus, more general conclusions that “policies that reduce the antimicrobial resistance of Salmonella” (p. 561) are likely to have significant human health benefit or to help effectively control pandemic infection caused by related multidrug-resistant clones of this serotype do not appear to be warranted. To the contrary, a more sound understanding of the causal relationship among statistically associated outcomes is essential to the development of intervention strategies that have a high probability of being effective in producing intended results.

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Reference

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Reply to Cox and Phillips
To the Editor—In our study [1] analyzing data from 2 national surveillance systems, we found that patients with antimicrobial-resistant nontyphoidal Salmonella infection were more likely to have bloodstream infection and to be hospitalized than were patients with pansusceptible Salmonella infection. Furthermore, among patients with the most common serotype, Salmonella serotype Typhimurium, the association among resistance, bloodstream infection, and hospitalization was particularly strong.

Cox and Phillips [2] apparently do not dispute these findings but object to the assumption that the emergence of resistance in nontyphoidal Salmonella is primarily a consequence of selective pressure associated with the use of antimicrobial agents in food animals. Despite the widespread endorsement of this assumption by the scientific community [3, 4], Cox and Phillips offer an alternative hypothesis for the emergence of resistance in nontyphoidal Salmonella: the use of antimicrobial agents in humans. Cox and Phillips suggest that the observed association between increased antimicrobial resistance and the increased frequency of bloodstream infection is a result of patients with bloodstream infection being more likely to receive antimicrobial therapy, and this putative increased use of antimicrobial therapy results in increased resistance. In this scenario, patients are first infected with a susceptible nontyphoidal Salmonella strain, then treated with antimicrobial agents; the strain becomes resistant as a consequence of the antimicrobial therapy in the patients, and then the resistant strain is further transmitted nosocomially, primarily person to person.

Although events comparable to the Cox and Phillips scenario have been occasionally described as a source of resistant strains, it is a rare occurrence with nontyphoidal Salmonella; the emergence of resistance in Salmonella during treatment in humans does not occur frequently [5, 6], and nosocomial transmission of nontyphoidal Salmonella is rare in the United States [7]. Investigations of outbreaks have found that, when patients are infected with antimicrobial-resistant Salmonella, the strain of Salmonella is already resistant when it infects the patients. In foodborne disease-outbreak investigations involving antimicrobial-resistant nontyphoidal Salmonella, for example, the antimicrobial resistance patterns of Salmonella isolated from patients and contaminated food that caused the outbreak typically match [8].

Furthermore, because antimicrobial therapy is common for patients with Salmonella who seek medical attention, patients with severe (i.e., bloodstream) infection may not be more likely than other patients with laboratory-confi med infection to receive antimicrobial therapy. In a recent case-control study of 215 patients with sporadic laboratory-confi med Salmonella serotype Newport infection, for example, more than two-thirds of patients were treated with antimicrobial