resistance attributable to efflux has been reported in a number of gram-negative species, including *Salmonella* and *Pseudomonas*. Strains expressing efflux mechanisms leading to fluoroquinolone resistance are cross-resistant to a number of structurally unrelated antimicrobial agents, permitting multidrug resistance to develop (6). Therefore, inhibition of efflux systems as targets of therapeutic intervention would help prevent emergence of resistance to fluoroquinolones and associated drugs and would further potentiate drug activity. Bacteria exposed to concentrations near their MIC values readily undergo selection for resistance to ciprofloxacin (7). Hence, dosing regimens accounting for both treatment efficacy and susceptibility of clinical pathogens should help control drug resistance that causes frequent treatment failures (8).

Emerging resistance to antimicrobial agents by interacting pathogens is not solely responsible for treatment failures, since many other factors may be involved, e.g., inappropriate antibiotic regimen and dose selection, poor patient compliance, and drug-drug and drug-host interactions. One clinically important drug interaction involving fluoroquinolones is not only by coadministration with other drugs but also results from chelation to divalent and trivalent cations, such as in antacids, iron compounds, or dairy products; such chelation prevents most of the drugs from being absorbed (9).

Efforts should be aimed at shortening treatment duration by adopting efficacious drugs, since rapid, complete eradication of an infecting organism may limit the development of drug resistance. In addition, the rapid and sensitive detection by molecular methods of invasive disease due to *Salmonella* may help avoid overtreatment for fever of unknown origin (10). Finally, development of newer drugs offering similar activity against both enzyme targets (DNA gyrase and topoisomerase-IV), as well as an improved therapeutic index, will definitely strengthen clinical practice.

The challenge ahead is to further our understanding of newer antimicrobial resistance mechanism possibilities stemming from the recent development of structurally modified fluoroquinolones. Additional studies should assess the relevance of pharmacodynamic modeling in determining dosing or predicting efficacy and clinical management for various indications in different patient populations.

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Enteric Fever Treatment Failures—Reply to Drs. Chandel and Chaudhry

To the Editor: We are pleased that Drs. Chandel and Chaudhry support our concern that the development of low-level resistance to fluoroquinolone antimicrobial agents in *Salmonella enterica* serotype Typhi is a threat to health in both developing and developed countries. They cite their article (1) reporting the recent emergence in India of strains of *S.* Paratyphi A resistant to nalidixic acid and with low-level resistance to ciprofloxacin. This finding has also been observed in the United Kingdom, with >30% of *S.* Paratyphi A infections in 2000 being caused by strains with decreased susceptibility to ciprofloxacin. Of these strains, only one was also resistant to other antimicrobial agents.

Our findings and those of Chandel and Chaudhry clearly demonstrate the inadvisability of the use of ciprofloxacin in the Indian Subcontinent to treat many human infections, regardless of prescription. To maintain the efficacy of fluoroquinolones in both developing and developed countries, this class of antimicrobial agents must be reserved for treatment of invasive disease and not for prophylaxis. For travelers visiting developing countries, ciprofloxacin must be used only when absolutely necessary and not for treatment of uncomplicated gastroenteritis or for travelers' diarrhea syndromes.

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Mycobacterium tuberculosis Beijing Genotype, Thailand—Reply to Dr. Prodinger

To the Editor: We read with interest the report on the occurrence of *Mycobacterium tuberculosis* strains of the Beijing genotype in Thailand (1). In contrast to our findings in Vietnam (2), Prodinger et al. found no significant association between the Beijing genotype and either young age or drug resistance (1). However, we have some caveats regarding the comparison of these two studies. First, we restricted our analysis to newly diagnosed patients to avoid confounding by possible differences in relapse rates between

M. tuberculosis genotypes. Second, we excluded confounding by geographic collection site. Although this was not a problem in our study (with 58% of isolates in Hanoi and 53% in Ho Chi Minh City representing the Beijing genotype), it might be in Thailand in view of the reported difference between Thailand and Malaysia. Third, the statistical power of the study in Thailand was limited: a difference of 56% in the group <25 years versus 43% in the category >25 years is potentially important, even if not statistically significant with the given sample size. The power of the Thailand study to demonstrate an association with drug resistance is similarly limited.

Despite these caveats, we agree with Prodinger et al. that the epidemiology of the Beijing genotype strains may vary among Southeast Asian countries. For instance, in Hong Kong we found no association between the Beijing genotype and younger age and a weak association with isoniazid (INH) resistance (3).

Various explanations may account for these differences. For instance, if our hypothesis that the selective advantage of the Beijing genotype in Vietnam is due to its association with drug resistance is accurate, then no association with young age and recent transmission would be expected in situations where the Beijing genotype has not (yet) acquired these high levels of drug resistance. Moreover, if a strong program is in place to deal with drug-resistant tuberculosis, this selective advantage may disappear (4).

On the basis of the observation of Prodinger et al., we see no reason to dilute our previous message regarding the emergence of Beijing genotype strains. Ongoing research suggests that the Beijing genotype strains elicit a different immune response than other *M. tuberculosis* genotypes in particular human populations. For instance, in Jakarta, Indonesia, tuberculosis patients infected with Beijing genotype strains were significantly more likely to have febrile responses during the first 2 weeks of treatment (5). In this region we again also found a significant association with INH and streptomycin resistance.

Within the framework of a Concerted Action Project of the European Union, involving 32 institutes within and outside Europe, the worldwide spread of Beijing genotype strains will be examined. We strongly favor study of the genetic makeup of the Beijing genotype to gain insight into the success of this highly conserved family of strains, which appears to be responsible for a substantial part of the worldwide recurrence of tuberculosis, and in particular, of multidrug-resistant tuberculosis.

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