with reference to programs a hundred years ago, when contemporary pesticides and biological and cultural controls did not exist and the tools of mosquito control were limited to such measures as deep-ditch draining of wetlands in New Jersey, clear-cutting, and use of arsenic compounds and crude petroleum for larval control. Deep-ditch draining was also practiced long ago in other states, such as Florida.

It was but half a century ago, after World War II, that chlorinated hydrocarbons such as DDT came into widespread use for mosquito control until they were banned, and organophosphates such as malathion and naled took their place. For cost and performance reasons, DDT continues to be used in several developing countries for mosquito control. Mr. Rupp refers to old reports of water management as a means of making land formerly considered useless into productive land capable of generating tax revenues. Today, this practice would be considered wetlands conversion and wildlife habitat destruction.

Robert Ward's article in the latest Florida Mosquito Control Association's Wing Beats reminisces about the venerable thermal fog machine, "those hot smelly 'smokers' belching up to eighty gallons of fog material per hour...fireballs, greasy streets and cars, or blinded drivers" (2). Back in those days, many children chased them on bicycles, ignorant of pesticide risks that are now known. Even in recent history, broad-spectrum organophosphates such as parathion and chlorpyrifos, which have potent nontarget effects, were used in aquatic habitats to control mosquito larvae.

Mr. Rupp's comments focus mainly on the mosquito control of a century ago, when the stakes were high because of malaria and yellow fever. The pioneers in mosquito control did marvelous work with the limited tools available to them and their limited knowledge of environmental consequences, but the history of mosquito control has had its time of pesticide reliance and has truly evolved to today's fully integrated mosquito management as briefly described in the article.

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Enteric Fever Treatment Failures: A Global Concern

To the Editor: We read with great interest the report by Threlfall et al. (1) of decreased susceptibility to ciprofloxacin in *Salmonella enterica* serotype Typhi from the United Kingdom. The authors indicate that nalidixic acid-resistant *S.* Typhi with decreased susceptibility to ciprofloxacin is now endemic in India and neighboring countries, constituting a threat to global health. The data are consistent with previous studies from India (2-4). Despite the wide applications and broad-spectrum efficacy of fluoroquinolones, resistance is increasingly observed in many species of gram-negative organisms, including *Salmonella*. Detection in any part of the world of even a few resistant strains with higher MICs to ciprofloxacin is of concern to clinicians and microbiologists. We report our recent observations in cases of treatment failure of enteric fever caused by *S. enterica* serotypes Typhi and Paratyphi A.

Fluoroquinolones have been in use for >15 years and have remained an extremely important weapon against infections. Ciprofloxacin is used widely in India to treat many human infections, even without prescription, although recommendations limit its use to enteric cases caused by multidrug-resistant (MDR) strains. However, concern is increasing that widespread use of these and newer drugs will result in development of resistance against them. Recently, reports have increased worldwide concerning reduced activity of ciprofloxacin and allied drugs against many infectious agents, including *Salmonella* (2-4).

In an ongoing study of drug susceptibility following E-test, >12% of recent isolates of *S*. typhi in our institution have shown increased MICs to ciprofloxacin (range 1.0 to 2.0 µg/mL), with 3% as high as 2.5 µg/mL (3-4). Of >100 strains screened recently, 4 of 18 MDR strains had increased resistance to ciprofloxacin. Of the rest, 9 of 82 had higher MICs to ciprofloxacin alone but were not MDR, and 2 were cases of double infection with *S.* Typhi and *S.* Paratyphi A, common serotypes causing enteric fever in our region. Because resistance to the quinolone group of drugs (caused by gene mutations) develops independent of that in other drugs, which are plasmid encoded, it also may develop in otherwise sensitive strains.

However, our recent observations differ from those of Dr. Threlfall, as well as from past data from India. We have observed that treatment failures did not always correlate with higher MICs to nalidixic acid and ciprofloxacin alone. We have also noted a declining rate of MDR in *S.* Typhi, reflecting increased sensitivity to chloramphenicol, amoxicillin, and trimethoprim. However, *S.* Paratyphi A showed relatively increased resistance to these drugs. The increasing resistance to ciprofloxacin, to which enteric fever treatment failures are often attributed, is now mainly caused by strains susceptible to other common drugs.

Drs. Threlfall and Ward stated that >50% of strains with decreased susceptibility to ciprofloxacin were MDR (1). In contrast, our findings suggest that, despite prolonged doses of ciprofloxacin, treatment failures are still common with isolates sensitive to ciprofloxacin and nalidixic acid. Drs. Threlfall and Ward also emphasized that MDR cases with reduced sensitivity to ciprofloxacin are mainly transmitted by travelers returning from India and Pakistan. This conclusion would be justified as long as phage type E1, comprising MDR strains with higher MICs to ciprofloxacin, is endemic in India. However, problems of reduced action by ciprofloxacin are now thought to be independent of MDR, to result from many other factors, and thus to be of global origin and incidence. Overall, we observe a much higher rate than in the past of reduced susceptibility in *S.* Typhi and *S.* Paratyphi A in our region, causing delayed response in enteric patients. The increasing enteric fever treatment failures noted by our clinicians indicate the need for careful screening of recent isolates.

Fluoroquinolone resistance usually results from mutations in genes for drug targets (gyrA and parC) or potential of the drug being marked as a substrate as a result of overexpression of drug-efflux pumps (5). Drug

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