Correspondence

Safety of the Rifampin and Pyrazinamide Short-Course Regimen for Treating Latent Tuberculosis Infection

To the Editor—The recent article by Cook et al. [1], wherein they compared the outcomes of treating latent tuberculosis infection with short-course regimens of either rifampin and pyrazinamide (RZ) or rifampin alone versus isoniazid, deserves further comment. The investigators' careful monitoring of the Pitt County Health Department (Greenville, NC) patients treated with these 3 regimens, plus their analysis of 5 years of treatment-outcome data, complements our previous reports [2–4].

First, although not specifically calculated in their article, the rate of hospitalization for liver injury among the patients receiving RZ was 1 in 291 persons (3.4 cases per 1000 patients), in spite of preselecting away from the RZ regimen those patients who might have been at greater risk for liver injury. This rate is similar to our reported point estimate of 3.7 cases per 1000 patients initiating RZ, which was determined from a national survey that included a larger denominator of initiations of RZ treatment ($n = 8087$) [3]. No hospitalizations occurred among the Pitt County patients treated with rifampin or isoniazid. Also, although the authors detected no RZ-associated fatalities among the 291 patients who initiated RZ in their study, the study lacked sufficient sample size to measure a fatality rate if it was in the range of the reported rate of 0.9 cases per 1000 patients [3].

Cook et al. [1] found indistinguishable rates of liver injury for patients receiving either of 2 short-course regimens (RZ or rifampin) and patients receiving isoniazid. Given the history of RZ-associated hepatotoxicity and the estimated low rate of liver injury for rifampin [5–9], a more specific analysis would be to estimate the liver-injury rate only for persons who received RZ. Calculated from the data in the report, the observation of alanine aminotransferase levels that were >5 times the upper level of normal occurred 19 times among 291 persons who initiated RZ therapy (65 cases per 1000 patients [6.5%]). This rate for the group receiving RZ is not only greater than the rate for the group receiving isoniazid (6.5% versus 2.0%; $P = .04$, by χ^2 test), but it is also greater than a previous estimate of 25.6 cases per 1000 initiations of RZ [3].

We agree that the study by Cook et al. "provides a more realistic picture of the true toxicity of this regimen" [1, p. 274]. Thus, we question advocating the use of RZ despite the high observed rates of adverse events, even with intensive monitoring. Surveillance data indicate that RZ-associated fatalities continued despite revised recommendations for increased monitoring of patients [4]. Given the treatment options, the risk of liver injury outweighs the benefits of the RZ regimen.

The 2003 recommendation to generally not use RZ for the treatment of latent tuberculosis infection [2] reflected a consensus recommendation by a panel of experts. The data-driven guidance from the Centers for Disease Control and Prevention and the American Thoracic Society was endorsed by the Infectious Diseases Society of America [2–4]. The preferred regimen is 9 months of daily or biweekly isoniazid therapy, with an alternative of 4 months of daily rifampin therapy [2]. Contrary to the authors' interpretation, their findings reinforce the Centers for Disease Control and Prevention and the American Thoracic Society's recommendation that RZ should generally not be offered to persons with latent tuberculosis infection [2].

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Reply to Ijaz et al.

To the Editor—The hepatotoxicity of the 2-month pyrazinamide and rifampin (PZA-RIF) regimen for the treatment of latent tuberculosis infection (LTBI) is well described [1, 2]. Our article [3] confirmed that the toxicity of the PZA-RIF regimen was greater than the isoniazid (INH) regimen. However, before we throw the baby out with the bathwater, we should reexamine the purpose of treatment of LTBI and look with an unjaundiced eye at the efficacy of the "gold standard" of the 9-month regimen of INH.

Numerous studies have determined that certain high-risk populations are at increased risk for reactivation of dormant tuberculosis [4]. The efficacy of a 9-month regimen of INH in preventing reactivation of LTBI is well known. What is also known is that only 30%–60% of persons who begin treatment with INH actually complete therapy [4–6]. A recent study from Johns Hopkins [7] revealed that only 52.6% of 770 patients who were treated with INH took at least 80% of their medications over the 9-month period. Treatment with INH, although less toxic than PZA-RIF, still carries a significant risk of serious adverse effects, particularly among the elderly population and in patients who are treated with immunosuppressive agents for rheumatoid arthritis [8, 9]. Severe hepatotoxicity resulting in liver transplantation and death have been reported for many years in patients treated with INH for LTBI [10, 11]. There have been 3 INH-associated deaths in North Carolina in the past 4 years (unpublished data). Unlike it is for patients receiving PZA-RIF regimen, monitoring of liver functions is not routinely performed in patients who are treated with INH. This policy may lead to an underestimation of the actual incidence of hepatotoxicity in patients treated with INH.

In our cohort, none of the patients who developed hepatotoxicity because of PZA-RIF died. In fact, liver functions returned to normal in all patients when either PZA alone or both drugs were discontinued. We are increasingly using the 4-month regimen of rifampin to treat our patients with LTBI, because the hepatotoxicity is low and the completion rates are high for this regimen [7].

The authors from the Centers for Disease Control and Prevention would have us believe that treatment of LTBI is a choice between good (INH) and evil (PZA-RIF). Would that the argument were that simple. Our goal is for patients to complete therapy with whatever regimen is chosen. Given the greater likelihood of completing the short-course regimens (PZA-RIF for 2 months and RIF for 4 months) and the self-limited hepatotoxicity (in our hands) of the PZA-RIF regimen, we will continue to use both regimens in selected patients.

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Prevalence of Antibodies against Rubella Virus in Spain

To the Editor—Hyde et al. [1] report the results of a prevalence study of rubella immunity levels in the US population. In relation to their findings, we present our experience in a European country. The importance of the strategy of anticipating rubella revaccination, improved surveillance, and the implementation of specific vaccination programs against rubella addressing susceptible groups needs no emphasis [2, 3]. Recommendations by committees of experts and the prevailing childhood immunization schedules are unanimous in including the above-mentioned strategies [4]. In this context, ser-

oepidemiological survey studies allow for the assessment of humoral immunologic response against viral structural antigens [5], despite the assumed potential bias attached to their design. Because we were aware of the importance of describing the real prevalence of rubella seropositivity in our community, we decided to document such a situation in a cohort of children receiving vaccination as part of a routine immunization schedule. Our report relies on data from a cross-sectional study performed during 2001 and 2002 involving children from an autonomous region of Spain (Castilla y León, the largest region in the European Economic Community). The chosen framework was restricted to serum samples received by the microbiology laboratory of a university hospital (Hospital Clínico Universitario de Valladolid, Valladolid, Spain) which were to be analyzed for infectious markers other than rubella antibodies. According to demographic features, a double stratification was made, and we evaluated samples from 323 children aged 1–5 years and 1166 children aged 6–14 years. All samples were aliquoted and frozen at −20°C until the moment of processing. Antibodies to proteic antigens on the rubella viral envelope were determined by means of an indirect EIA (Bio-Whittaker). Results were validated in accordance with the manufacturer's instructions, and samples that showed a neat absorbance greater than the cut-off value plus 15% were considered to be positive.

Our findings revealed that 309 (95.7%) of the samples obtained from children aged 1–5 years had antibodies to rubella virus (95% CI, 93.2%–98.2%); the rest of the samples were seronegative for rubella virus antibodies at the time of our study. Rubella antibodies were detected in 1055 (90.5%) of 1166 samples obtained from children aged 6–14 years (95% CI, 88.6%–92.5%), indicating a lower prevalence than that observed in the group of children aged 1–5 years; the difference was statistically significant ($P = .003$). The rate of seropositivity for rubella antibodies was 5.2% lower in the older age group than in the younger age group. An additional finding was that, in the 6–14-year-old age group, female subjects had a significantly higher percentage of seroprotection than male subjects; 534 (94.4%) of 568 female subjects had positive resutls, compared with 521 (87.1%) of 598 male subjects ($P < .001$).

Although we are conscious of the caution that should be exercised in this kind of study, we believe that, assuming internal validity for the evaluated population, our results indicate an age-dependent loss of seroprotection against rubella virus. Among the potential causes that support this conclusion are, on the one hand, differences in the level of vaccine coverage reached by the 2 groups of children [6] and, on the other hand, limitations inherent in the vaccine itself [7]. Moreover, it is true, of course, that in our country—as in all developed countries—systematic vaccination of girls before puberty is highly efficient in preventing congenital rubella syndrome [8]; all the same, it is certain that there are still small proportions of unprotected persons. The growing importance of immigration in developed countries is of particular interest because of the introduction of clusters of unprotected individuals [9]. The efficiency of new strategies of anticipating combined vaccines needs to be evaluated, and seroepidemiological studies seem to be a good tool for such a purpose [10].

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Efficacy of Nitazoxanide for Cyclosporiasis in Patients with Sulfa Allergy

To the Editor—*Cyclospora cayetanensis* is a human parasite thought to largely af-

fect children and immunocompromised patients who live in developing countries. However, since the mid-1990s, several foodborne outbreaks of *C. cayetanensis* infection have been recognized in North America, and cyclosporiasis has emerged as an important and underdiagnosed cause of diarrhea in immunocompetent persons [1]. We report a case of cyclosporiasis in an individual with a history of severe sulfa allergy who did not respond to therapy with ciprofloxacin and who was then successfully treated with nitazoxanide (Alinia; Romark Laboratories).

A 40-year-old woman with a past medical history significant only for hypothyroidism and asthma presented with complaints of profuse, watery diarrhea of several days' duration. She did not complain of having fever, bloating, nausea, or vomiting. She denied having made any recent travel or having sick contacts. Although the patient noted a recent household dietary change to include more fresh fruits and vegetables, no other family members reported illness. The findings of her physical examination were normal. Stool specimens were sent for culture and examination for ova and parasites. The patient was sent home receiving ciprofloxacin.

Although *Cyclospora* species are often missed in clinical laboratories, modified acid-fast staining of the patient's stool specimen revealed the multiple oocysts of *C. cayetanensis*. When her diarrhea did not improve several days later, she was seen in the infectious diseases clinic, where, because of a severe sulfa allergy, she commenced a regimen of nitazoxanide treatment [2]. After 7 days of treatment, her symptoms improved. The findings of follow-up stool examinations were normal. A food source of cyclosporiasis was not determined for our patient, and no other cases were reported related to her infection; however, she did comment on a recent change in her diet: incorporation of large amounts of fresh produce, including berries.

Diarrheal illness due to *C. cayetanensis* is usually self-limited in immunocompetent people, but it may cause prolonged symptoms if it is untreated, as occurred in our patient. The treatment of choice is trimethoprim-sulfamethoxazole [3], and ciprofloxacin has been suggested as an alternative agent. This latter recommendation stems from a randomized trial that compared ciprofloxacin treatment with trimethoprim-sulfamethoxazole treatment in HIV-infected patients who had *Isospora belli* or *Cyclospora* infection, and both agents were found to be effective [4]. However, there is significant anecdotal evidence of treatment failure with ciprofloxacin.

Nitazoxanide, a newer agent used primarily to treat cryptosporidiosis in patients with HIV infection, has been suggested as a potential alternative treatment. Nitazoxanide is a well-tolerated thiazolide compound with activity against many intestinal parasites [5]. It was first introduced in Central America in 1996 and has been available in the United States since 2002 [6]. In addition to its activity against a wide variety of intestinal parasites, including *C. cayetanensis*, nitazoxanide also has activity against *Clostridium* and *Bacteroides* species. The exact mechanism of action for the drug is unknown, but it is thought to act through inhibition of the organism's pyruvate ferredoxin oxidoreductase enzyme [6]. Successful treatment of patients with *C. cayetanensis* infection using nitazoxanide has only been reported for a small number of patients [7].

Although *C. cayetanensis* is an unusual cause of diarrhea in the United States, it has emerged as an important cause of outbreaks of foodborne disease and can be found sporadically in immunocompetent people, such as our patient. Nitazoxanide represents an important treatment option for patients who have a sulfa allergy or for whom treatment with a sulfa or ciprofloxacin has failed.

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