Rifampin and related rifamycins are the most important drugs in use for the treatment of tuberculosis (2). Rifamycins interfere with bacterial DNA-dependent RNA polymerase and are potent bactericidal agents. Rifampin and its analogues kill actively multiplying extracellular organisms, intracellular mycobacteria, and semidormant mycobacteria in tissues. The addition of rifampin to treatment regimens for tuberculosis can reduce the duration of therapy needed for active disease from 12 to 6 months and can reduce the duration of therapy needed for latent infection from 9 months to 2 to 3 months. Because of their potencies and sterilizing activities, rifamycins are the cornerstone of modern therapy for active tuberculosis and are extremely effective in the treatment of latent Mycobacterium tuberculosis infection (2, 3).

The emergence of resistance to rifampin has posed a serious problem in tuberculosis control in recent years (12). Resistance to rifampicins arises from mutations in the beta subunit of the ribosomal polymerase gene (rpoB) (18). Spontaneous mutations in an 81-bp region of the rpoB gene are associated with decreased susceptibility to the rifamycins; and antibiotic pressure, usually from rifampin monotherapy, during therapy can result in the selection of these mutants and the emergence of acquired drug resistance. It is noteworthy that the emergence of rifampicin resistance occurs during therapy of active tuberculosis disease and not during treatment of latent M. tuberculosis infection (3). The bacillary load found during active disease ensures the presence of a large population of innately resistant mutants that can predominate in the setting of selective pressure. Almost all rifampin-resistant M. tuberculosis clinical isolates are also resistant to isoniazid (by definition, these isolates are multidrug resistant [MDR]), and many are resistant to other first-line antituberculosis drugs as well (8). Cross-resistance among the rifamycins is considered complete, as isolates resistant to rifampicin have decreased susceptibilities to rifapentine, rifabutin, and other rifamycins (17).

The clinical impact of MDR tuberculosis is enormous: the rate of treatment failure with standard regimens is high; and treatment with second-line regimens is toxic, is expensive, and is associated with a substantial incidence of treatment failure and death (10). For this reason, efforts to “protect” rifampin have been promulgated by organizations such as the World Health Organization and the International Union against Tuberculosis and Lung Disease (7, 15). These measures include restriction of rifampin use to the treatment of active tuberculosis, promotion of the use of fixed-dose combinations to prevent monotherapy, use of non-rifamycin-containing regimens during the continuation phase of tuberculosis treatment, and supervision of administration of all rifamycin-based regimens. Use of rifampin for indications other than active tuberculosis and self-administration of rifampin are strongly discouraged by these organizations.

The antibacterial effects of rifamycins are not specific to mycobacteria; and rifampin and related drugs are active against a variety of gram-positive and gram-negative organisms, including streptococci, enterococci, staphylococci, Neisseria spp., and members of the family Enterobacteriaceae. Their mechanisms of action are the same: the inhibition of bacterial DNA-dependent RNA polymerase. Despite the broad spectra of activity of rifampin and related agents, however, their use is generally restricted to tuberculosis. Limited use of these agents occurs for prophylactic treatment for meningococcal exposure, combination oral and/or intravenous therapy for staphylococcal endocarditis or other severe skin and soft tissue infections, and, occasionally, treatment for other indications. Recent interest in the use of ciprofloxacin and rifampin to treat staphylococcal endocarditis in injection drug users has been dampened by the emergence of fluoroquinolone-resistant Staphylococcus aureus rather than any concern about rifampin use. Thus, as a class, the rifamycins are almost exclusively used for the treatment of active and latent tuberculosis or other mycobacterial infections.

The development of new rifamycins with increased potencies and enhanced pharmacokinetic features, such as increased absorption with food and longer half-lives that permit highly intermittent dosing, has renewed interest in this class and has spurred research on other potential uses for these potent agents (16). Research is under way to determine the activities of long-acting rifamycins in the treatment of Helicobacter pylori infections and chlamydial infections. The potencies of some rifamycins against both sexually transmitted Chlamydia trachomatis and Chlamydia pneumoniae, a potential agent of atherosclerotic coronary disease, are of particular interest. In addition, rifaximin, a poorly absorbed rifamycin, has recently been approved by the Food and Drug Administration for the treatment of traveler’s diarrhea.

An important, unresolved question regarding the use of rifamycins for indications other than tuberculosis is whether their use will result in the development of rifampin-resistant...
tuberculosis. With the current worldwide effort to control rifampin use by keeping it within tuberculosis control programs that use directly observed therapy and fixed-dose combinations, the extension of rifamycin use to nontuberculous infections might be perceived as inadvertently risking the selection of drug-resistant *M. tuberculosis*. It is important to consider the likelihood of this occurring in the context of the dynamics of tuberculosis drug resistance, the probable indications and uses of newer rifamycins, and the populations to which they will be directed.

As noted above, resistance to antituberculosis drugs arises from the emergence of innately drug-resistant clones under treatment pressure. The prevalence of rifamycin-resistant clones within a population of wild-type *M. tuberculosis* isolates is estimated to be approximately 1 per 10^9 organisms (6). In individuals with active tuberculosis, the total bacillary population is likely to range from 10^7 to 10^10 organisms, meaning that resistant clones are certain to be present in sufficient numbers to emerge during treatment if multidrug suppressive therapy is not given. Clinical trial and other experience confirms that monotherapy with antituberculosis agents results in the emergence of resistant organisms over a period of several weeks to months (14). Use of a rifamycin alone to treat patients for chlamydial or *Helicobacter* infections when they also have active tuberculosis would almost certainly result in the emergence of resistance if therapy extended beyond several weeks.

Conversely, prolonged treatment of patients with latent tuberculosis with a single agent virtually never results in the emergence of drug resistance (5). Several trials of rifampin for latent tuberculosis have been undertaken, and in none of these has rifampin-resistant tuberculosis developed in patients receiving monotherapy (9). For people with latent *M. tuberculosis* infections, the estimated bacillary burden is less than 10^4 organisms (4, 13); thus, innately resistant clones are not likely to be present, and monotherapy with a single antituberculosis drug will not lead to the selection of resistant organisms. In fact, rifamycin therapy for latent tuberculosis is highly effective and prevents the development of clinical tuberculosis. Individuals with latent tuberculosis who are treated with rifamycins for indications other than prophylaxis will still benefit with respect to the prevention of active tuberculosis. So, only individuals with active tuberculosis are at risk for the development of rifampin-resistant tuberculosis during therapy with a rifamycin alone.

Which patients are most likely to be treated with newer rifamycins for indications other than the prevention of tuberculosis? The most likely populations are patients in developed countries with atherosclerotic vascular disease, *Helicobacter* gastrointestinal infections, antibiotic-associated colitis caused by *Clostridium difficile* toxin, or sexually transmitted infections. These groups are at very low risk for active tuberculosis. Studies of patients attending sexually transmitted disease clinics in inner cities in the United States show that latent tuberculosis is not unusual, but active tuberculosis is extremely rare. Among patients with coronary heart disease receiving therapy to prevent myocardial infarction, tuberculosis is similarly rare, and almost all of these patients are screened with a chest X-ray, in which a potential active tuberculosis event could be detected. Thus, the target populations for rifamycin therapy are not as apt to have active tuberculosis and therefore are not at risk for developing drug resistance. Use of newer rifamycins in developing country settings, particularly in patients with human immunodeficiency (HIV) infection, would present a substantial risk of inadvertently treating active tuberculosis with a single agent; and efforts to rule out active tuberculosis in such patients would need to be intensive.

What can be done to prevent the emergence of rifamycin-resistant tuberculosis if long-acting drugs such as rifaluzil are introduced into regular use? Patients receiving prolonged rifamycin therapy (>7 days) should probably be screened for active tuberculosis with a symptom review and a chest X-ray. Studies of screening of large populations for tuberculosis suggest that the best predictor of active tuberculosis is the presence of cough for at least 3 weeks (1). When this is coupled with chest X-ray, the sensitivity is similar to that obtained by performing sputum cultures for the diagnosis of tuberculosis. Because the populations that will be targeted for rifamycin therapy are already at low risk, the addition of a sensitive and simple screening algorithm should be extremely effective for preventing inadvertent treatment of active tuberculosis with rifamycin monotherapy. In situations in which HIV infection and active tuberculosis are prevalent, however, additional measures, including culture of sputum and blood for mycobacteria, would be warranted because of the higher prevalence of undetected and extrapulmonary forms of tuberculosis in these patients (11). However, it is not likely that newer rifamycins would be introduced into clinical practice in such settings.

The rifamycins have transformed the treatment of tuberculosis over the past 25 years, and protecting their potencies and activities is critically important. Yet, this important drug class has the potential to benefit groups of patients other than those with *M. tuberculosis* infection or disease. Previous experience with treatment of latent tuberculosis strongly suggests that resistance is not acquired in the absence of active tuberculosis. Because of the dynamics of tuberculosis drug resistance and the low risk of disease in patients who will be treated with rifamycins for other indications, extension of the use of this class to other conditions is reasonable.

REFERENCES
The views expressed in this Commentary do not necessarily reflect the views of the journal or ASM.