is likely to be the cause of bacterial vaginosis and that Koch's postulates for disease causation are inadequate for describing potential causal relationships in this syndrome. Bacterial vaginosis probably results from infection with complex communities of bacteria that consist of metabolically interdependent (syntrophic) species. Diseases caused by uncultivated microbes or communities of microbes are not amenable to the application of Koch's postulates in their original formulation[2]; therefore, we must build a case for causation on the basis of a concordance of scientific evidence.[3]

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Azithromycin versus Penicillin for Early Syphilis

TO THE EDITOR: In their study on the treatment of early syphilis, Riedner et al. (Sept. 22 issue)[1] concluded that the wider use of oral azithromycin should be encouraged as part of syphilis-control programs in developing countries. Whereas this conclusion would appear to be rational on the basis of the authors' results, we believe that there are other factors that should be considered before opting for such a strategy.

Although the authors acknowledged the potential for the emergence of azithromycin-resistant *Treponema pallidum*, ongoing monitoring for such resistance, as they suggested, requires molecular-sequencing techniques,[2] which are unavailable in most developing countries. More important, the inability of azithromycin to cross the placenta[3] limits its use in the prevention of congenital disease. Treatment of seropositive mothers with oral azithromycin, after routine antenatal screening, could result in declining maternal titers on the rapid plasma reagin test without affecting the potential for fetal infection.

Since the prevention of congenital syphilis remains a major objective of control programs and is a current focus for global elimination activities,[4] we believe that azithromycin has only a limited role in the management of syphilis in resource-constrained settings.

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TO THE EDITOR: Riedner and colleagues report that azithromycin is equivalent to penicillin G benzathine in treating early syphilis and may be useful in developing countries in which use of penicillin G benzathine is problematic, and they alert us about the cases of azithromycin-resistant *T. pallidum*. In Brazil, we struggle even with inexpensive drugs, such as penicillin G benzathine; azithromycin is not widely available and can be 10 times as expensive as penicillin G benzathine. We believe that it is not wise to change from a known, inexpensive drug with few cases of resistance after a half century of use[1] to a more expensive, unfamiliar drug that has already shown resistance after a few years of use.[2] Thus, the implementation of azithromycin in developing countries remains prohibitive because of the cost and because of the possibility of resistance, and this drug should not be used as a first choice yet.

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TO THE EDITOR: Riedner and colleagues demonstrated the successful treatment of early syphilis with azithromycin. Holmes's accompanying editorial laments the absence of prospective data on patients treated for early syphilis with azithromycin and the influence of molecularly defined azithromycin-resistant *T. pallidum* on treatment outcomes.[1]

In San Francisco, where an estimated 56 percent of circulating strains of *T. pallidum* were resistant to azithromycin in 2004,[2] we conducted a randomized, controlled trial of azithromycin (1 g given orally as a single dose) as compared with penicillin G benzathine (2.4 million units intramuscularly) in sexual contacts of persons with infectious syphilis; our aim was to compare the efficacy of the two drugs for the treatment of incubating syphilis. A data safety monitoring board (DSMB) supervised the study.

After two treatment failures in the 12 patients receiving azithromycin as compared with none in 13 patients receiving penicillin, the DSMB terminated the study (P=0.18, by Fisher's exact test). Although it was a small study sample (n=25), our data suggest that azithromycin was inferior to penicillin in the presence of high community levels of azithromycin-resistant *T. pallidum*. Although we have feasible methods to monitor macrolide resistance in *T. pallidum*, routine surveillance is not currently supported by federal agencies.

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THE AUTHORS REPLY: We agree with Ballard et al. that further studies are needed before azithromycin can be recommended for the treatment of syphilis in pregnancy, although studies in women undergoing cesarean section have shown that azithromycin does cross the placenta.[1]

Resistance is clearly a concern in view of the high proportion of strains of *T. pallidum* found among men who have sex with men in the United States and Ireland that contain mutations that may confer resistance to macrolides. The clinical significance of this mutation has not been definitively established, although the small study by Klausner et al.[2] provides some support for such a link. The results of our trial suggest that azithromycin resistance is not currently a clinically significant problem among heterosexual patients in Tanzania. We recognize that most laboratories in Africa do not have the facilities to identify mutations in local strains of *T. pallidum*. In view of the considerable advantages that would be conferred by a single-dose oral treatment for syphilis, however, we believe further studies are warranted to study the geographic distribution and clinical significance of strains bearing this mutation.

We do not agree with Savaris and Abeche that azithromycin is too expensive to be used for the treatment of syphilis in developing countries. Generic supplies of the drug, made in India, have been available for some years at a cost of approximately $1.20 for a 2-g dose.[3] Azithromycin came off patent in the United States in November 2005. Although penicillin G benzathine is an inexpensive drug, the cost of administering it has to include the cost of the needle and syringe.

Despite the issues raised by the correspondents, we consider that single-dose azithromycin may have a place in the treatment of early syphilis and in the management of genital-ulcer disease at the primary health care level in developing countries.

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THE EDITORIALIST REPLIES: It is striking that the first randomized trial demonstrating azithromycin's efficacy for early syphilis in Africa was conducted virtually simultaneously with the emergence of azithromycin-resistance mutations in *T. pallidum* in all five cities where such mutations were sought in the United States and Ireland. This may represent a world record for the adaptation of a pathogen to an antimicrobial agent newly proved effective to treat it — and this by an organism not previously known for its propensity to develop resistance to other antimicrobial agents. Reservations about the use of azithromycin for the treatment of early syphilis are clearly warranted.

Fortunately, *T. pallidum* remains fully susceptible to penicillin G benzathine worldwide, and the forthcoming 2006 Sexually Transmitted Disease Guidelines from the Centers for Disease Control and Prevention will correctly recommend that "penicillin G, administered parenterally, is the preferred drug for treatment of all stages of syphilis" and that the recommended regimen for adults with primary, secondary, or early latent syphilis is "benzathine penicillin G 2.4 million units IM [intramuscular] in a single intramuscular dose."

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Cost-Effectiveness of ICDs

TO THE EDITOR: The cost-effectiveness of implantable cardioverter–defibrillator (ICD) therapy reported by Sanders et al. (Oct. 6 issue)[1] is overly optimistic, because it does not fully account for several factors that raise the costs and lower the effectiveness of this therapy. The authors assumed a constant benefit of the ICD during the patient's lifetime, whereas in previous investigations, the benefit declined, with a convergence of survival curves by seven to eight years.[2] The assumed probability of lead-related complications (2.4 percent over 20 months) underestimates the spectrum and frequency of serious complications (up to 14 percent in the Sudden Cardiac Death in Heart Failure Trial [SCD-HeFT]).[3] The high frequency of recalls of devices and the consequent interventions are not accounted for.[4] The base-case assumption of an equivalent quality of life among patients who received an ICD and the control patients does not account for the adverse effect of ICD shocks (31 percent in SCD-HeFT)[3] or for the discomfort, inconvenience, and the loss of time and income due to the implantation procedure and the need for replacement of the device, the checking and programming of the device before and after many forms of surgery, and, because of the presence of the device, the exclusion of several types of diagnostic procedures, treatments, employment, and recreation. The inclusion of these factors, in addition to those noted by Goldman in his editorial,[5] would unfavorably affect the cost-effectiveness of ICDs.

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TO THE EDITOR: The study by Sanders et al. of the cost-effectiveness of ICDs exemplifies the skilled analyses that are crucial as the choices become