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## Syphilis Control — A Continuing Challenge

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Syphilis. The name of this widespread and ancient disease is familiar to health care providers worldwide. This name recognition, however, belies the complexity of the disease, as well as the diagnostic and therapeutic challenges that continue to affect global efforts to control syphilis. Early (primary or secondary) syphilis is typically marked by ulcerative lesions that occur initially at the site of inoculation, followed several months later by widespread cutaneous, mucosal, and even systemic manifestations of the dissemination of the causal agent, *Treponema pallidum* (see Figure 1). Even without treatment, both primary and secondary lesions resolve, and the infection enters a “latent” stage. During this stage, there are no clinical manifestations of disease, yet the infection may still be passed to children born to infected mothers; it may also progress, resulting in late (tertiary) manifestations, including late neurosyphilis, cardiovascular disease, and space-occupying inflammatory lesions (gumma). The ill effects of syphilis, however, go far beyond the disease’s effect on individual infected persons. Early syphilis is associated with the infection of sexual partners and an increased risk of acquisition or transmission of human immunodeficiency virus (HIV). The transmission of syphilis to infants of untreated mothers may occur at any stage of infection.

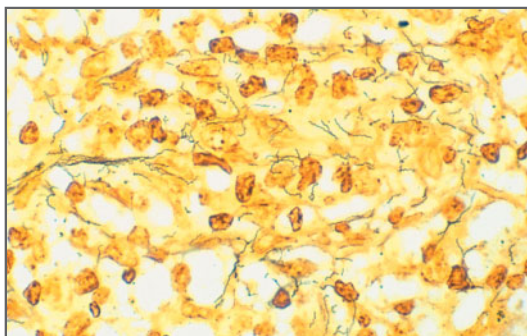
The disease remains a public health problem worldwide. The World Health Organization (WHO) estimates that there are 12 million new cases of syphilis each year, with more than 90 percent oc-

curing in developing nations (see Figure 2). Congenital syphilis remains a leading cause of stillbirths and death among neonates in many developing countries. In Russia and much of Eastern Europe, the reemergence of syphilis is contributing to burgeoning HIV epidemics. In North America and Western Europe, where the disease is less common, the epidemiology of syphilis has shifted so that the infection is disproportionately common among men who have sex with men and persons who use cocaine or other illicit drugs; in these regions, the rates of infection are again rapidly increasing.

Despite dramatic advances in other biomedical fields, the tools for the management and control of syphilis have changed little in the past 60 years. Although they are effective for many infected persons, these tools — serologic testing, penicillin therapy, and a clinic-based infrastructure for the control of sexually transmitted diseases — have limitations. Addressing these limitations could enhance syphilis-control efforts.

It is not practical to cultivate *T. pallidum* for diagnostic purposes. Dark-field microscopy is not widely available and can be performed only in the small proportion of infected persons who have lesions. Consequently, serologic testing, used both in screening for asymptomatic infections and as an adjunct to clinical diagnosis, remains the principal tool for the diagnosis of syphilis, as it has been since the 1930s. Although relatively simple, inexpensive, and sensitive tests are commercially available, a major limitation is the inability to perform serologic testing easily on site and provide treatment during the same clinic visit. Furthermore, serologic diagnosis and follow-up may be confounded by false positive tests and a slow serologic response to therapy; it has been observed that one year after the receipt of recommended penicillin therapy, more than 15 percent of patients with early syphilis do not have serologic evidence of a therapeutic response, despite the resolution of clinical manifestations of infection.

The Sexually Transmitted Diseases Diagnostics Initiative of the WHO is currently conducting field evaluation of four rapid, point-of-care serologic tests for syphilis that were found to provide



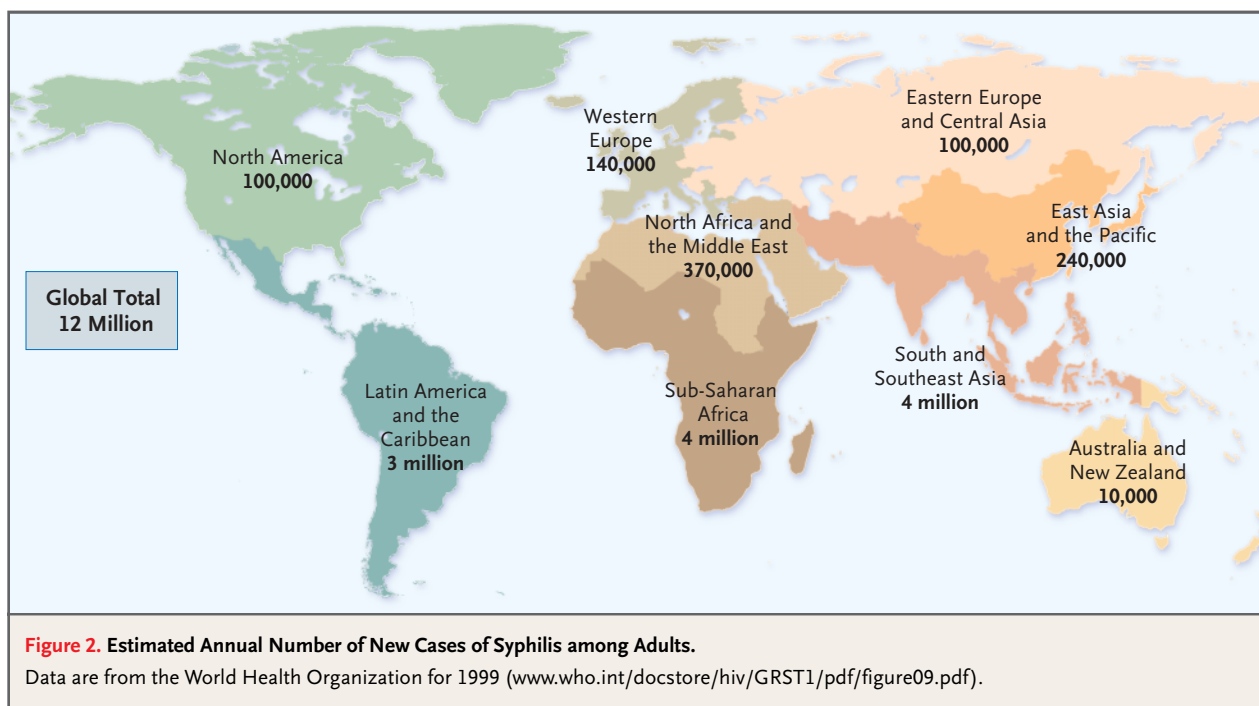
**Figure 1.** *Treponema pallidum* in a Skin-Biopsy Specimen (Steiner Silver Stain).

reproducible and accurate results with the use of whole-blood specimens. These tests cost less than \$1 apiece, are simple to perform, and require minimal training and no equipment. Effective point-of-care tests of this sort could substantially enhance control efforts in many settings by improving the screening of pregnant women before childbirth and the on-site testing of patients with suspicious clinical lesions, and thereby facilitating the timely treatment of infected persons.

Few of the newer antibiotics have been studied extensively as possible syphilis therapies. In the early 1940s, syphilis was among the first infections to be treated with penicillin. At present, long-acting (benzathine) penicillin remains the best-studied drug and is the only medication that is routinely recommended for patients with syphilis who are not allergic to penicillin. Effective single-dose oral therapy could enhance syphilis control, particularly if it were used in combination with accurate, rapid, point-of-care diagnostic tests. The pharmacologic properties of azithromycin and data from small case series suggest that this drug may be a promising alternative for syphilis therapy. However, as described by Lukehart and coworkers in this issue of the *Journal* (pages 154–158), there are case reports of treatment failures, and a genetic muta-

tion of *T. pallidum* has been associated with resistance to macrolides and related antibiotics. Therefore, azithromycin use is not recommended unless careful follow-up can be ensured. The National Institute of Allergy and Infectious Diseases is sponsoring an ongoing randomized clinical trial comparing azithromycin with benzathine penicillin for the treatment of early syphilis; the trial will provide data on the usefulness of this new drug for syphilis therapy.

Finally, clinic-based efforts to eliminate the disease have not succeeded. Syphilis persists in developing nations and is resurging in parts of the world where the rates of disease were once lower. Simple, affordable tools for diagnosis and curative therapy are already available. The absence of a sound health care infrastructure has been cited as another missing link in syphilis-control efforts. Many infants in developing nations still die of congenital syphilis, despite the fact that current serologic tests cost less than 50 cents and one dose of benzathine penicillin costs 23 cents. The combination of rapid on-site testing and oral treatment may offer a viable solution for decentralized, primary care-based syphilis-control programs. Point-of-care serologic tests could be provided for at-risk persons wherever they might be found. A single-dose oral regimen will be



preferable to one that requires injection. This combined approach could be considered for use in outbreaks as well.

Syphilis remains a worthy target for biomedical research. There are still important unanswered questions about the organism, the disease, and appropriate management strategies. Modern approaches to the understanding of the pathogenesis of syphilis, the development of improved diagnostic tests, and the implementation of decentralized management strategies offer the promise of improving syphilis control. Although some progress

has been made, questions remain about the management of long-standing latent infections, central nervous system involvement, and the interaction between syphilis and HIV. Answers and solutions are urgently needed.

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