

## *Rapid Tests for Maternal Syphilis Screening: Effective and Cost-Effective*

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Congenital syphilis continues to exert a major toll on humanity. Current estimates suggest an annual congenital syphilis burden of up to 1.5 million cases annually, and the World Health Organization (WHO) has recently called for the global elimination of congenital syphilis.<sup>1</sup> The WHO action plan for congenital syphilis elimination is based upon four interconnected efforts of political advocacy, increased access to maternal and newborn health services, increased screening and treatment during pregnancy, and enhanced surveillance and monitoring systems.<sup>2</sup> Congenital syphilis elimination will directly contribute to the Millennium Development Goals, endorsed by all member states of the United Nations, by helping to reduce child mortality and improve maternal health. Yet despite sustained calls for action from the international health community, maternal syphilis seroprevalence remains high, exceeding 5 to 10% in some developing countries. Programs for screening and treatment of infected women during pregnancy are incompletely implemented, even though detection of syphilis during pregnancy and treatment of those infected can prevent adverse pregnancy outcomes.<sup>3</sup>

In this context, the report by Rydzak and Goldie<sup>4</sup> in this issue of *Sexually Transmitted Diseases* is a welcome contribution to global efforts to advance maternal syphilis screening in resource-poor settings, and stands to move the international health community one step closer to achieving the goal of universal screening during pregnancy. While the question of which syphilis test or tests to perform during pregnancy, and in what sequence, will continue to be debated, there should no longer be any debate over whether pregnant women should be tested. Indeed they should, and Rydzak and Goldie offer new evidence to support more extensive use of the new generation of rapid point-of-care treponemal tests. As these authors have shown, such tests are both effective in reducing congenital syphilis morbidity, and cost-effective relative to alternative testing strategies. The time is now to broaden our coverage of maternal syphilis screening, and rapid treponemal tests offer new hope for reaching heretofore inaccessible populations.

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### *Serologic Tests for Syphilis: Pros and Cons of Existing Approaches*

To a great degree, widespread implementation of maternal syphilis screening is hampered by the technical requirements of current testing methodologies, particularly the use of RPR (rapid plasma reagin) or other nontreponemal tests for screening, followed by a specific treponemal test for confirmation. This two-step algorithm has been the mainstay of syphilis testing for several decades. Nontreponemal tests, such as the RPR, detect antibody to reaginic antigen which is expressed by both *T. pallidum* as well as some human tissues. These tests have the advantage of being relatively inexpensive and sensitive, and they also can help clinicians distinguish current or recent infections from previously treated infections through serial analysis of nontreponemal test titers over time.

Yet nontreponemal tests are also subject to certain technical limitations which impede their ability to serve as a perfect diagnostic test for syphilis. Since test positivity is not specific, confirmation with a treponemal test is required to distinguish syphilis from other conditions which may cause of false-positive results. Moreover, the tests must be performed on serum rather than whole blood specimens, so clinical sites must cope with phlebotomy and a certain amount of laboratory processing of patient specimens. Also, nontreponemal tests generally use equipment that requires electrical power, making it difficult to perform the tests on-site in settings lacking electricity. And since test results are subjectively interpreted, they can be easily misread and misreported by inexperienced laboratory personnel.

In this context, rapid point-of-care treponemal tests present an attractive alternative for use in resource-poor field settings in order to identify pregnant women with syphilis during antenatal care visits. Rapid treponemal tests are relatively inexpensive, and allow immediate performance on whole blood specimens without special equipment or extensive staff training. They offer the opportunity for immediate detection, and immediate treatment, of infected pregnant women, and would therefore appear to serve congenital syphilis elimination goals if performance is adequate in field settings.

However, treponemal tests by their very nature also suffer some performance limitations. Since treponemal antibody persists for years, these tests cannot distinguish between active infection and

past, treated infection. Nor can they be used to monitor response to therapy, since the tests only provide a positive or negative test result rather than a quantitative antibody titer, and previously treated women will have persistently positive treponemal tests despite prior adequate treatment. Rapid tests therefore perform best in areas where screening and treatment have not been widely implemented. While experts maintain that a combination of the two types of tests is the best approach to syphilis screening, resource limitations in developing countries prevent this from occurring as routine clinical practice in many areas.<sup>2</sup>

#### *Rapid Treponemal Tests: New Hope for Underserved Populations*

Rydzak and Goldie<sup>4</sup> present an interesting, sophisticated modeling study of antenatal syphilis screening (and subsequent congenital syphilis prevention) in sub-Saharan Africa, focusing on the reduction in total discounted life years lost due to deaths of mothers and children. In this study, various model input parameters were based upon reasonable estimates from the published literature on fertility, as well as adverse outcomes of pregnancy associated with untreated maternal syphilis. These included rates of miscarriage, maternal death, low infant birthweight, stillbirth, neonatal death, and infant congenital syphilis. Four different screening strategies were examined: conventional two-step screening with a nontreponemal test (RPR) confirmed by a treponemal test, single-visit RPR with no confirmation, single-visit rapid treponemal screening using an immunochromatographic strip test, and no screening at all.

With regard to pregnancy outcomes, the rapid treponemal strip testing strategy proved superior to the other testing approaches, as measured by total healthy births and incremental gain in healthy births. That is to say, the model found that use of rapid treponemal tests was more effective in improving health outcomes for women in children when compared with alternative strategies. Moreover, rapid treponemal tests proved to be most cost-effective in the long term, saving a greater amount of money per 1,000 women screened than any of the other strategies. These findings hold great promise for congenital syphilis prevention, inasmuch as they may help justify the wider use of rapid treponemal tests in resource-poor settings. The study also provides useful data to support the growing contention that rapid treponemal tests, while more costly in the short run, are likely to be more effective as well as more cost-effective in the long run.<sup>5</sup>

Unfortunately, the fact that rapid point-of-care treponemal tests are currently more costly than RPR, even by a small amount, may also limit the ability of national STD programs to justify their use on a more widespread basis. Rydzak and Goldie estimated a cost of US\$ 3.18 for the treponemal strip test, compared with US\$ 1.97 for the RPR. This seemingly small difference in cost could represent a significant barrier to resource-limited control program managers, who will need to demonstrate to donors, politicians, and aid agencies that the higher initial costs will have greater long-term impact than current testing strategies.

Also, while rapid treponemal tests were best in this analysis, the authors showed that the single-visit RPR testing strategy (without confirmatory treponemal testing) performed better than the two-step confirmatory strategy in terms of adverse outcomes prevented. As well, while the single-visit RPR approach was less cost-effective when compared with the rapid treponemal test strategy, such an approach still generated a cost savings of US\$ 161,000 compared with no testing, and required less capital expenditure at the outset. These are important practical points which may permit

control programs to justify enhancement and solidification of existing RPR testing approaches if major capital expenditures on rapid treponemal tests are not financially feasible.

#### *Treponemal tests and the future of congenital syphilis elimination*

Moving forward, congenital syphilis prevention (and ultimately elimination) will depend on greater reliance on increasingly accurate and inexpensive point-of-care tests which can be implemented in field settings with minimal training. This point is a driving force behind the World Health Organization's Sexually Transmitted Disease Diagnostic Initiative (SDI), which supports the development and evaluation of rapid diagnostic tests for syphilis and other STDs. The ideal field tests will meet specific criteria which Peeling et al. have labeled by the acronym ASSURED: affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to the end-user.<sup>6</sup> Such tests will allow patients to be screened and treated during the same clinical encounter, and will be able to be performed in settings without access to a laboratory.

While rapid treponemal point-of-care tests may not meet all of these criteria, they do offer another weapon in the fight against congenital syphilis, and their use can and should be scaled up where finances and politics allow. Certainly, increasing reports of successful field implementation of rapid treponemal tests<sup>7,8</sup> need to be tempered with a realistic assessment of the drawbacks of such an approach - specifically, the potential for overdiagnosis and retreatment of previously treated syphilis. However, the realistic expectation is that in previously unscreened populations, the number of previously treated cases of syphilis will be low, and this confounder will be minimized. And weighed against the most realistic alternative, that populations of pregnant women will remain unscreened at all, the world is ready for moving forward with this new technological advance.

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