Sexually Transmitted Infections

Editorials

Rapid and simple point of care diagnostics for STIs

The need for rapid diagnostic tests

The high prevalence of asymptomatic gonococcal and chlamydial infections is one of the greatest obstacles to STI control, especially in developing countries, where partner notification is difficult. A widely available diagnostic test which allowed prompt and effective treatment of asymptomatic patients could reduce the prevalence of these infections, prevent complications, and reduce the incidence of HIV infection, whose transmission they facilitate. Such a test could also play an important part in reducing unnecessary treatment of patients with STI syndromes that are not caused by these pathogens.

In 1994 the Rockefeller Foundation offered a prize of US$1 million for the development of a simple, rapid point of care test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection.[1] To be eligible for the prize, the test had to meet rather exacting performance specifications. It had to be 99% specific for both infections, and to have a sensitivity of >90% for *C trachomatis*, and >95% for *N gonorrhoeae*, using non-invasive samples such as urine. Moreover, it had to be cheap (less than $0.25 to manufacture simple (reliable results obtained by a primary healthcare worker after less than 2 hours' training), rapid (less than 20 minutes), require no equipment, and be stable for several months at high ambient temperatures.

Not surprisingly, the prize was never claimed, and the offer has since been quietly withdrawn. However, the need for such a test remains as pressing as ever, and a number of other funding agencies—for example, the Wellcome Trust, the National Institutes of Health (NIH), and the Sexually Transmitted Diseases Diagnostics Initiative (SDI) have supported rapid test development directly and through the provision of clinical samples and other research materials in recent years. Taking advantage of recent technological advances, the commercial sector has developed a number of rapid point of care tests for these infections.

A recent inventory carried out by the SDI, which is presently based in the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) at the World Health Organization, found that over 40 rapid tests for syphilis, *C trachomatis*, and *N gonorrhoeae* are on the market in 2001. Although most of these tests are manufactured in industrialised countries such as the United States, few of them have been approved for local sale by the US Food and Drug Administration (FDA). In most cases there has been no independent evaluation of their performance, and it is not clear whether any of the existing tests perform well enough to meet the needs of clinicians or disease control programmes in low income settings. Is it necessary that these tests meet the kind of performance goals laid out in the Rockefeller Prize, or even realistic to expect this?

How good do rapid tests need to be?

When calculated in terms of numbers of patients brought to treatment, rapid tests have a distinct advantage. In most healthcare settings, in both developed and developing countries, some patients do not return for the results of laboratory tests. The advantage of point of care tests is that they can enable treatment to be given on the spot, rather than hoping that the patient will return for treatment. Gift *et al* have drawn attention to what they call "the rapid test paradox," when fewer cases detected lead to more cases treated. Even if the sensitivity of a point of care test is less than that of the gold standard, if it is greater than the proportion of patients returning for their results it will lead to an increase in the number of infections treated.[2] Moreover, immediate treatment will reduce the risk of complications and prevent further transmission of the infection.

The sensitivity and specificity required of a diagnostic test depend on how it will be used. In general, if treatment is cheap and side effects rare, it is more important for tests to have a high sensitivity than a high specificity. The prevalence of infection in the target population must also be considered. If the prevalence is low, and the test is not highly specific, a high proportion of those treated will not have the infection. Mathematical modelling can help to predict the impact and cost effectiveness of rapid tests of varying sensitivity and specificity, and hence to determine the performance required for specific settings. This information will be valuable for those developing new tests, and for disease control programmes.

Priorities for diagnostic research and development

To address these issues an informal consultation, jointly sponsored by the SDI and the Wellcome Trust, was held in early 2001 between STI experts from developed and developing countries and major funding agencies including the NIH, the US Center for Disease Control and Prevention (CDC), and the US Agency for International Development (USAID). The aims of the meeting were to review STI diagnostic priorities; to identify biomedical and operational research needs; and to prepare for field trials of promising, rapid point of care diagnostic tests.

The meeting concluded that rapid point of care tests for *N gonorrhoea* and *C trachomatis* remained the highest priority, both for screening of asymptomatic patients and for reducing overtreatment among women with vaginal discharge; and that there was also an urgent need for a rapid point of care test for syphilis that uses whole blood and can distinguish active syphilis from previous infection. This would be of particular value for screening antenatal clinic attenders in high prevalence settings.

Evaluation of existing rapid tests

In view of the large number of rapid point of care tests now on the market, it was agreed that the main focus of SDI activities should shift from supporting the development of new tests to the evaluation of existing ones. A laboratory based evaluation of test performance and reproducibility will be used to identify the most promising candidates, which will then be evaluated in the field. In addition to performance evaluations measuring sensitivity and specificity, operational research is needed to determine the acceptability of new tests to patients and health workers, as well as their cost effectiveness and sustainability in primary healthcare settings. It is essential that these trials should be performed in the populations for which they are intended, using a standardised protocol, with adequate sample sizes; and precautions should be taken to avoid the many biases that may compromise trials to evaluate diagnostic tests.[3 4] Eventually, the impact of the introduction of rapid diagnostics on the prevalence and incidence of STIs and their complications needs to be measured.

New opportunities for rapid test development

Recent advances in immunology, molecular biology, materials science, nanotechnology, and DNA amplification techniques made the 1990s a fruitful decade for the development of new diagnostics.[5 6] At the start of the new millennium, we have the complete genome sequences of *C trachomatis* and *Treponema pallidum*,[7 8] and that of *N gonorrhoeae* will soon be available. The combination of genome sequence and the new microarray technology makes it possible to measure the expression of host and pathogen genes at every stage of the infection. This offers exciting possibilities for the identification of new diagnostic targets. To improve the performance of point of care tests, specimen collection and processing will need to be optimised. Biomedical research on the quantitation of infectious load in different biological samples and at different stages of the infection will ensure that the most appropriate sample can be collected. Improved methods for DNA extraction and for the concentration of pathogen in non-invasive samples, such as urine or saliva, will further increase sensitivity.

Conclusion

The rapid pace of scientific and technological progress, and pledges of support from major funding agencies for the development and evaluation of STI diagnostics makes it increasingly likely that within a few years we will have rapid diagnostic tests of proved value for specific indications. Perhaps the biggest challenge for the next decade will be to ensure that rapid tests of adequate quality are made accessible to the poor populations in developing countries that need them most, and that these tests can be used appropriately to guide therapy.

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