NEAR-PATIENT TESTING

Near-patient testing will not improve the control of sexually transmitted infections

G L Dean

Debate

The definition of a near-patient, or ''point-of-care'' test (POCT), is an investigation carried out in a clinical or non-clinical setting, or in the patient's home, for which the result is available without reference to a laboratory, perhaps rapidly enough to affect immediate patient management.

The characteristics of an ideal POCT, as outlined by the World Health Organisation Sexually Transmitted Diseases Diagnostics Initiative in 2001 (http://www.who.int/std_diagnostics/about_SDI/priorities.htm), should fulfil the ASSURED guidelines; it should be *affordable* by those at risk of infection; *sensitive*, with few false negatives; *specific*, with few false positives; *user* friendly or simple to perform, with minimal training; *rapid*, to enable treatment at the first visit; *robust*, not requiring refrigeration or heating; *equipment-free*; and *delivered* to those who need it. Unfortunately, for most sexually transmitted infections (STIs), such tests do not yet exist, and our perception of what is currently available or possible is often overambitious. Six years ago, Professor Peter Borrelio, Director of the Public Health Laboratory Services at the Central Public Health Laboratory, Cardiff, UK, suggested that ''a single microchip could be programmed to perform a range of tests for different organisms on a single pinprick blood specimen taken from a patient. The chip could then tell the GP [general practitioner], or the patient themselves, what sort of organism is causing their infection''.[1] Unfortunately, technology has not advanced sufficiently to make this a reality. Currently available tests are not as rapid, or as simple as, for example, a pregnancy test or urine dipstick. Much of the published literature focuses on theoretical utility rather than providing data to support integration into routine clinical practice. Of course if a POCT existed that fulfilled the World Health Organisation recommendations outlined above, genitourinary medicine services could benefit enormously; however, currently these tests are not sufficiently accurate, simple or cheap to affect STI control. There are several issues to consider.

Accuracy

Many POCTs use immunochromatography, based on ELISA methods, to detect a range of antigens or antibodies, with the generation of a visual read-out. For infections such as syphilis, however, where antibodies persist long-term, a positive result fails to distinguish between new and previously treated infection; laboratory confirmation in these cases is essential. This decreases their utility in moderate to high prevalence populations, the very populations where near-patient testing is likely to be considered. A rigorous worldwide evaluation of the performance of POCTs for syphilis was conducted by the Sexually Transmitted Diseases Diagnostics Initiative in 2003. For one of the better performing tests, the Abbott Determine Syphilis TP, the mean sensitivity was 97.2% and the specificity was 94.1% (http://www.who.int/std_diagnostics/publications/ meetings/SDI_Report.pdf). Nonetheless, if this test was used on a population with, for example, 1.8% prevalence (the prevalence found during the Brighton syphilis outbreak among men who have sex with men), the expected positive predictive value would be only 0.23—that is, of all people receiving a positive result by that method, 77% would be false, with all the attendant health and social ramifications this would entail. Decisions regarding more widespread use of POCTs must consider the performance of the individual test *and* the prevalence of the infection in the target population.

For many of the more common STIs, such as chlamydia, ELISA tests have long been considered substandard. Commercially available tests are hyped by producers as highly accurate and reliable, but with limited independent evaluation of their performance. Compared with nucleic acid amplification testing (NAAT), where sensitivities of 96% and specificities of 99.5% are expected, those reported for POCTs are considerably inferior. The manufacturers' advertising information and package insert data can be misleading. Many use cell culture as the comparative gold standard, and others report sensitivities or specificities based on test performance in the research setting in controlled clinical trials. Many trials are conducted on symptomatic, high-prevalence populations, with testing performed by experienced laboratory technicians. These populations are not necessarily representative of populations that may be targeted for subsequent screening; neither are the testing conditions necessarily transferable to outreach settings. The literature confirms this disparity, with reported sensitivities for chlamydia of 62–72% in head-to-head laboratory comparison trials,[2] compared with only 32–74% in clinics for the treatment of sexually transmitted diseases and outpatient settings.[3 4] When a test routinely misses 26–68% of people with an infection such as chlamydia, its value must be called into question. It is essential that the performance of POCTs in the field setting, and utility in disease control programmes is more carefully evaluated before further implementation.

What must not be forgotten is that most laboratories will report only a specimen as truly positive, if on re-testing using a different platform, the second result is *also* positive. This ensures that false-positive results are minimised.

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This approach is essential when testing for low-prevalence infections such as HIV. Even using a test with a high specificity (99%) in a population with only 1% prevalence, as would be the case in many UK testing sites, the probability that a person has the disease, given a positive test result, is only 50%. If, however, a second test is also positive, this markedly improves the positive predictive value to 99% (http://www.who.int/hiv/pub/vct/e/Rapid%20Test%20Guide%20-%20FINAL.pdf). To consider this issue in the outreach setting, some authors have suggested using a combination of rapid tests to confirm positive results, but with consequent increases in complexity, time and cost. A further drawback of the rapid HIV tests is that they are analogous to the third-generation laboratory-based tests and do not detect the p24 antigen. There is a danger therefore, when compared with the superior fourth-generation laboratory tests, that some cases of very early HIV infection may be missed. Considering that, in a population of men who have sex with men, 54% of those whose infection was first diagnosed at the Brighton clinic during 2004 had evidence of recent infection, the introduction of POCTs may, by missing people at a highly infectious stage of their illness, actually worsen HIV infection control rather than improve it.

Currently, there is general consensus[5–8] that for most STIs, the sensitivities of rapid methods are too low to be recommended for use in screening programmes, the setting most likely to substantially affect the control of STIs.

Simplicity

In reality, in the past 5 years, it is the NAAT that has revolutionised the diagnosis of common STIs such as chlamydia, and is likely to have the largest effect on STI control. The NAAT has permitted the launch of large-scale screening programmes, the introduction of non-invasive testing and the possibility of testing specimens taken for other indications such as liquid-based cytology. The NAAT permits the large-volume laboratory throughput that is required for widespread STI screening and control. By contrast, the test material required for POCTs using ELISA methods often demands invasive sampling (eg endocervical swab for women using the Clearview chlamydia test (Unipath, Basingstoke, UK)), or major manipulation (eg, centrifugation to produce a urine pellet for men). To extract the lipopolysaccharide antigens, the samples must be heated to 80℃ for 10 min, requiring a heated workstation and electricity. For trained personnel in the laboratory setting this is a simple procedure; for busy clinic staff seeing numerous patients in the outreach setting, it poses more of a challenge. Hopwood *et al*[9] found reduced sensitivity of the rapid chlamydia test compared with current gold standards (74% *v* 96%) and they also concluded that, owing to priorities of care, it was impossible for a POCT to be carried out by the designated nurse. It was therefore necessary for a biomedical scientist to be employed, who needed to batch test the samples, resulting in 24% of patients not receiving their test results on the same day. In this setting, the authors concluded that rapid chlamydia testing ''was not a desktop procedure'', and in fact required both extra time and personnel.

When a test is performed in the outreach setting, as opposed to the laboratory, it is essential that the same clinical governance and minimum standards are met. This includes formal training for the staff performing the tests: how to collect specimens, principles of the analysis, use of the machine, calibration and quality assessment, expected values in health and disease, and the safe disposal of samples. Users need to show competence at regular intervals, should have well-defined user manuals, and apparatus and associated equipment must be adequately maintained and regularly cleaned.

Testing in multiple, unregulated, outreach environments runs the risk of quality lapses compared with a centralised, well-functioning laboratory environment. The opportunities for error are undoubtedly greater. This is highlighted by the Determine HIV-1/2 test (Abbott Laboratories, Berkshire, UK), which uses whole blood taken from a finger prick. The sample is collected using a glass capillary tube, which is easily broken, with risk to the operator if training is inadequate. Furthermore, the test is not suitable for large-volume testing, with no immediate plans by the company to make it more suitable for general use in the field.

Whether the advantages of POCTs outweigh the disadvantages outlined so far largely depends on the level of access to high-quality laboratory services, as well as reliable transport links. Although in theory a rapid test may purport to improve health outcomes, real-life experiences are often different. A randomised controlled trial comparing the effect of POCTs for maternal syphilis screening in rural South Africa[10] found that on-site testing was too complex, the reading of results was subjective, and testing created high workloads given the limited staffing available. Staff found it difficult to conduct the test, as well as inform the women of their infection and initiate treatment. The maintenance of a regular supply of testing materials, reagents and batteries was difficult. Even when the results were available, some women had left the testing site before receiving their results. The authors observed no benefit in implementing an on-site testing service in this setting, principally because they had a well-functioning laboratory service in place already. Most clinical settings in the UK will have similarly good laboratory links. Our own experience in a busy genitourinary medicine clinic running at full capacity, with excellent laboratory backup, is that we have chosen not to use the POCT routinely but only in situations where the usual laboratory service is unavailable—for example, out of hours.

Loss to follow-up

One of the potential advantages of POCTs is with the possibility of diagnosis and treatment at a single visit to the clinic and the theoretical reduction in patients being ''lost to follow-up''. It is estimated that if 20% of patients subsequently fail to attend for treatment, and 50%

transmit their infection in the interim, the lower sensitivities obtained with the current POCTs may be acceptable.[11] Although historical data suggest that patient return rates are low, a combination of clinic process modernisation (eg, automated generation of positive infection lists), more acceptable treatment regimens and improvement in methods of communication (eg, mobile phones, text messaging) have improved matters. Not only is the interval between testing and notification shorter, but the treatment completion rates have also improved substantially. For example, the treatment completion rate for the National Chlamydia Screening Programme is 98% (http://www.dh.gov.uk/assetRoot/04/09/30/91/04093091.pdf), with a local rate of 99% in Brighton. Similarly, since the introduction of the measures outlined above, the rates of loss to follow-up in our own clinic is <1% for all the major STIs, including HIV, syphilis, chlamydia and gonorrhoea, with patients informed of their infection within 3–5 working days (M Ottewill, Senior Health Adviser, personal communication, 2005).

Cost and cost effectiveness

For traditional laboratory-based testing, large-scale automation is associated with considerable efficiency gains. By contrast, POCTs are often more expensive in real terms (eg, £12.07 and £6.13, respectively, for rapid HIV and syphilis kits, compared with £2.22 for standard laboratory consumables) and are also time consuming and labour intensive. Testing in outreach settings may have further hidden costs such as transport of specimens, publicity, venue hire, etc. For STI control, high-volume testing is essential if a major effect on the overall population prevalence is to be achieved. Our own experience of coordinating outreach testing projects is that high testing throughput is unfeasible, even when there is a team dedicated solely to testing. Other issues that should not be underestimated in the outreach setting include lack of clinical backup, health and safety issues related to testing in an uncontrolled environment, cross-contamination of specimens, intraobserver variation, and difficulty with consent and confidentiality. Similarly, in the clinical setting, attempts to integrate rapid testing into overburdened services, such as sexual health or termination of pregnancy clinics, will pose even greater challenges. It is essential that before the widespread introduction of POCTs, rigorous evaluation is performed, considering both cost effectiveness and acceptability to the individual patient and healthcare provider.

Reduction of anxiety

For many people, the support available in traditional testing services is a fundamental aspect of their overall care. Duncan *et al*[12] explore the psychosocial implications of receiving a positive chlamydia diagnosis, highlighting three main areas of concern for women: perceived stigma, anxiety surrounding future fertility and fear of notifying partners. These people were unable to access their usual support networks of friends and family, given the sensitive nature of the diagnosis. For them, the importance of the clinic support structure, particularly the role of the health adviser, was crucial.

There is concern that HIV testing outside the clinical setting, particularly in the patient's home, in the absence of expert explanation and discussion, may lead to misinterpretation of the meaning of positive and negative results. Without adequate pre-test discussion, testers may not fully understand the consequences of testing positive or may be tested without giving consent. Rapid testing in these circumstances will not be as effective in promoting strategies for HIV risk reduction. Undoubtedly, a proportion of people would prefer to have an interval between testing and receiving the result, to reflect on the pretest discussion and involve family or other support mechanisms.

Diagnosis of STIs differs from other disciplines of medicine in that the results have direct consequences for people other than the index patient. For this reason, we should offer the best available test to our patients. For people receiving false-negative results, consequences are untreated infection; for those with false-positive results, there is potential for psychosocial upheaval. Certainly, the legal fall-out of giving inaccurate results can be substantial.

Loss of surveillance data

Finally, there is considerable concern that the widespread introduction of POCTs may jeopardise the high-quality surveillance data for which we are renowned in this country. Testing in the outreach setting, in the patient's home or at the general practitioner surgery will all run the risk of losing precious epidemiological information or early warnings of potential outbreaks, as well as preventing the characterisation of pathogens in terms of treatment susceptibility, virulence or mechanisms of antibiotic resistance.

Conclusion

In summary, in sexual health care, where accurate diagnosis and confirmation are paramount, the best available testing method should be offered, which currently involves traditional laboratory facilities. Little evidence is available to support the introduction of POCTs in preference to existing laboratory services. Their application is limited by either poor performance or doubtful utility in low-prevalence populations. Implementation in the outreach setting is complex and costly, and for most common STIs, POCTs are not yet sufficiently advanced for STI screening at a population level, and therefore will have little effect on the overall control of STIs.

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This is a transcription of a verbal debate given at the HPA conference 2005 between GD and PW. Both authors argued from extreme angles in the interest of a lively debate.

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