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Not surprisingly, the prize was never claimed, and the offer has since been quietly withdrawn.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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GRASP: a new national sentinel surveillance initiative for monitoring gonococcal antimicrobial resistance in England and Wales

Antimicrobial resistance is a major public health problem. Two recent publications have drawn attention to the growing nature of this problem, and the potential impact on the National Health Service. A report by the House of Lords[1] highlighted the alarming increase in antibiotic resistance and concluded that the problem "ought to be considered much more widely than it is at present." This was further supported by the Standing Medical Advisory Committee's report *The Path of Least Resistance*,[2] which underscored the need to urgently prioritise antimicrobial resistance on the national agenda and recommended the creation of a national strategy for minimising the development of antimicrobial resistance. Increasing antibiotic resistance is likely to be related to the increased use of broad spectrum agents, "over the counter" use of antibiotics, and inappropriate prescribing practices. Antibiotic resistant *Neisseria gonorrhoeae* may be also imported into England and Wales if infections are acquired in areas where such practices are common.

In the light of these growing concerns, there is a need to evaluate current strategies for monitoring *N gonorrhoeae* antimicrobial susceptibility. This article takes an evidence based approach to consider the justification for and methodology of a new national surveillance system for monitoring *N gonorrhoeae* antimicrobial resistance in England and Wales.

The problem

N gonorrhoeae is the second most common bacterial sexually transmitted infection (STI) in England and Wales, with over 20 000 new infections being diagnosed in genitourinary medicine (GUM) clinics in 2000.[3] This figure does not include infections diagnosed outside of the GUM clinic sector or undiagnosed prevalent infections in the community. Diagnoses of uncomplicated gonorrhoea in England and Wales have continued to rise since 1994,[3] with substantial annual increases as large as 20% (1995 to

1996) and 30% (1998 to 1999) being observed over recent years.[4 5] The reasons for the increasing incidence are unclear. However, given the correlation between gonococcal infection and high risk sexual behaviours,[6] failure to maintain safer sex at the population level may be a contributing factor. Young people are most commonly affected with current rates being highest in men aged 20–24 years and women aged 16–19 years. A recent estimate suggests that of those reattending an STD clinic, 28% of men and 58% of women with gonorrhoea have unrecognised infections.[7] This is worrying, given the complications of untreated infection which include pelvic inflammatory disease, infertility, ectopic pregnancy, and chronic pelvic pain.[8] Further, gonococcal infection during pregnancy may lead to spontaneous abortion, stillbirth, or neonatal complications.[9]

Treatment failure due to antibiotic resistance, exacerbates both the transmission and the sequelae of gonococcal infections and may also be driving the increases. Antibiotic resistance in *N gonorrhoeae* is acquired by two different mechanisms: firstly, by plasmid transfer for penicillinase producing strains (PPNG) and high level tetracycline resistance (TRNG) and, secondly, by chromosomal mutation for penicillin and tetracycline (CMRNG), fluoroquinolones (CRNG), and other antibiotics. Antibiotic treatment should be expected to eradicate 95% of infections of uncomplicated gonorrhoea in the community.[10] UK point estimates of the prevalence of PPNG include 2.6% in Scotland[11] and 4%[12] and 1.8%[13] in London. The current UK guidelines for the treatment of uncomplicated gonorrhoea now recommend the first line use of fluoroquinolones (either ciprofloxacin or ofloxacin).[14] However, ciprofloxacin resistance was first seen in the United Kingdom in the early 1990s[15] and has been increasingly reported over recent years.[16 17] Quinolone resistant gonococci are more prevalent in countries in the Western Pacific region. Initially, most such infections seen in the United Kingdom were acquired abroad but recent data show that more than half are now acquired through heterosexual contact within England and Wales.

Key questions

Thus, a number of key questions remain. Is gonococcal antibiotic resistance a problem in England and Wales? If so, what is the burden of disease, who is affected, and how does it vary across geographic regions? What antibiotic resistance patterns of *N gonorrhoeae* are most prevalent and how are these changing over time? How can we best advise national prescribing policy for disease control?

Evidence

Surveillance data on antibiotic resistance in *N gonorrhoeae* are currently provided through two main systems in England and Wales. Ongoing laboratory surveillance of resistant gonococcal isolates is provided, without charge, by the Public Health Laboratory Service (PHLS) Genitourinary Infections Reference Laboratory (GUIRL) at Bristol. Annually, approximately 3000 isolates are sent for diagnostic confirmation and quantitative antibiotic susceptibility testing from over 200 microbiological laboratories in England, Wales, and Ireland. The GUIRL provides a largely reference service and collects additional behavioural and demographic data only on resistance isolates therefore, detailed comparisons between resistant and susceptible isolates cannot be made. Overall trends observed in the GUIRL data suggest a decline in the number of PPNG isolates during the early 1990s. A large rise, however, was observed between 1997 and 1998. Moreover, the number of PP/TRNG and CMRNG isolates referred to GUIRL have been rising throughout the 1990s. During 1998, the GUIRL received 532 antibiotic resistant isolates of *N gonorrhoeae*, 68% occurred in men. Men aged 25–34 years and women aged 16–19 years were most likely to be infected (modal groups). Ethnic origin was available for 365 (67%) cases; 66% were in white patients, 16% black Caribbean, 4% black African, and 5% Asian; 62% reported having acquired their infections in the United Kingdom and 23% in the Far East. The distribution of resistant isolates was PPNG (17%), PP/TRNG (28%), CRNG (26%), and CMRNG (29%).[18]

The Gonococcal Surveillance Project at Imperial College, London, was established in 1996, and by 1999 had 13 of the larger London GUM clinics participating in a sentinel surveillance programme. Annually, over 1500 specimens were obtained during a 3 month collection period and quantitative antibiotic susceptibility testing was performed on all isolates. The Gonococcal Surveillance Project provided robust point and trend prevalence estimates of antibiotic resistance among tested isolates.[13] However, this active surveillance was restricted to the London region, and the project collected relatively few behavioural and demographic data on patients. Nevertheless, prevalence estimates indicated that 4.2% of isolates showed plasmid mediated resistance with 2.4% being high level tetracycline resistant (TRNG), 1.3% both penicillinase producing and tetracycline resistant (PP/TRNG), and 0.5% penicillinase producing resistant (PPNG) only. Eight per cent of samples showed chromosomally mediated resistance (CMRNG). Ciprofloxacin resistance was found in less than 1% of samples.[13]

The true prevalence of gonococcal antibiotic resistance in England and Wales is unknown. However, routine surveillance and ad hoc surveys suggest that there are considerable variations between geographic locations, demographic, and behavioural risk groups. A national, cross sectional study examining the recent rise in *N gonorrhoeae* suggested that, during 1996, almost one in five homosexual men and about one in 16 heterosexuals presenting with gonorrhoea at GUM clinics in England had a penicillin resistant strain.[19] In Scotland, isolates from men accounted for 90% of resistant isolates, with throat and rectal infections more likely than genital infections to be caused by resistant organisms.[11] A London survey found an association between ethnicity and the isolation of TRNG and PPNG, highlighting the importance of different population subgroups.[20]

The contribution of active national surveillance programmes

A number of industrialised countries have developed gonococcal resistance surveillance programmes including the United States, Canada, Australia, and the Netherlands. In 1986 in the United States, the Centre for Disease Control and Prevention (CDC) established the Gonococcal Isolate Surveillance Project (GISP). Data from GISP have documented important patterns of antimicrobial resistance, and have steered CDC national guidelines for gonorrhoea treatment. GISP data have highlighted the decline in PPNG and TRNG since 1991 following the implementation of recommendations for the routine use of ceftriaxone for gonorrhoea treatment[21] and later the detection of fluoroquinolone resistance.[22] The Australian Gonococcal Surveillance Programme 1998 annual report highlights regional differences in antibiotic susceptibility patterns—for example, the continued suitability of penicillins for use in many parts of rural Australia and high level tetracycline resistance in New South Wales.[23] Surveillance initiatives in the Netherlands have highlighted the importance of commercial sex in the establishment and spread of

PP/TRNG in the community.[24] These existing systems demonstrate the benefits of monitoring not only resistance but also geographical, behavioural, and demographic characteristics.

The advantages of monitoring antimicrobial resistance are not restricted to national surveillance and planning. Knowledge of antimicrobial resistance patterns is important to rationalise prescribing practice and inform strategic policy development. Many centres have used resistance monitoring data to inform their local treatment regimens. Ciprofloxacin is a highly active antimicrobial agent for the treatment of gonorrhoea and its increasing use as first line therapy will produce an additional need to monitor the emergence of antibiotic resistance in this country.

GRASP: establishing national surveillance in England and Wales

In June 2000, the PHLS Communicable Disease Surveillance Centre (CDSC), the Genitourinary Infections Reference Laboratory, and Imperial College launched a new national sentinel surveillance programme: the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP). Funded by the Department of Health until 2003, GRASP is supported by the MSSVD and the Scottish *N gonorrhoeae* Reference Laboratory. It aims to establish a sustainable, cost effective, national sentinel surveillance system for monitoring antimicrobial resistance to *N gonorrhoeae* in England and Wales. Key objectives include providing prevalence estimates for *N gonorrhoeae* antimicrobial resistance; to determine drifts in susceptibility to specific antibiotics; and to identify relevant clinical and epidemiological associations with gonococcal resistance in order to inform a rational and cost effective approach to antibiotic therapy for *N gonorrhoeae*.

The system combines laboratory and clinical data on gonococcal isolates obtained from purposely selected laboratories, and covers two distinct geographical regions: London and outside London. In the first year of collection, 13 London laboratories (previously collaborators in the London Gonococcal Working Group) and 17 outside London were selected to enable good geographical coverage with representation of all NHS regions and to maximise the number of isolates collected. All consecutive gonococcal isolates identified in participating laboratories during the months of June, July, and August were sent to either the GUIRL (outside London) or Imperial College (London) for susceptibility testing. Minimum inhibitory concentrations (MICs) of all isolates were been determined for the following antibiotics and at concentrations including (as a minimum): penicillin (0.03–4.0 mg/l), ciprofloxacin (0.002–0.125 mg/l) extended range 0.125–32 mg/l tested as necessary, spectinomycin (2–64 mg/l), tetracycline (1–32 mg/l), and ceftriaxone (0.12 mg/l, single concentration). GUM clinics provided demographic and behavioural data for each patient included in the GRASP collection. Data were obtained from routinely collected information in the case notes including sex, age, ethnic background, sexual orientation, postal area, travel history, previous infections, symptom presence, concurrent STIs, number of partners, and therapy received. Multicentre (MREC) and local (LREC) research ethics committee approval has been obtained.

CDSC collects, collates, and links the behavioural (from GUM clinics) and susceptibility data (from reference laboratories) in order to determine the distribution and determinants of gonococcal disease and antimicrobial resistance, temporal trends in both clinical and low level antibiotic resistance, and to identify potentially linked clusters (using phenotypic and genotypic methods). Although isolates obtained from sites outside GUM clinics are also collected, detailed behavioural data will only be collected from participating GUM clinics. Results from the first year's collection have now been published[25] and disseminated locally (through participating centres) and nationally.

Conclusions

GRASP is a unique collaboration which has brought together key areas of the GUM specialty, clinical laboratories, public health medicine, communicable disease surveillance, and health policy. The initiative has also raised the possibility of creating a UK-wide network for the prospective monitoring of gonococcal antimicrobial resistance, by establishing collaborative networks with colleagues in Scotland. Through this process it is hoped that a more robust understanding of the distribution and transmission dynamics of gonococcal antimicrobial resistance will be possible.

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