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From Bench to Bedside: Setting a Path for the Translation of Improved STI Diagnostics into Health Care Delivery in the Developing World

An informal consultation jointly organised and sponsored by WHO/TDR and the Wellcome Trust

Geneva, Switzerland- 29-30 January 2001

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Executive Summary

A meeting was held in Geneva in January 2001, co-sponsored by the Wellcome Trust and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR), to discuss diagnostics needs for STI in developing countries and to establish mechanisms for bringing affordable rapid point-of-care STI diagnostics to primary health care settings in developing countries. This consultation was planned in response to the urgent global need for improved STI diagnostics and planned in response to the urgent global need for improved STI diagnostics and followed on from the meeting convened by the Trust in Durban in February 2000 on STD Diagnostics in the Developing World. The meeting was attended by STI experts from both developed and developing countries as well as representatives of CDC, NIH and USAID. The specific aims of this meeting were:

- To review priorities for rapid STI diagnostics and define the STIs, indications and populations in which improved diagnostics would have the greatest impact on disease control

- To prepare for field trials of promising rapid, point-of-care STI diagnostic tests

- To identify biomedical and operational research needs for rapid test development and deployment

Priorities

Syndromic management of genital ulcer disease and urethral discharge in males has been shown to be a cost effective method for the control of STIs and HIV infection. For women, symptoms of vaginal discharge are poor predictors of STIs, resulting in over treatment. Moreover, a high proportion of STIs are asymptomatic in both men and women. The highest priority is for simple, rapid diagnostic tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, that could be used in support of syndromic management of symptomatic women, and for screening asymptomatic men and women at high to moderate risk of infection.

The second priority is for a rapid test for screening syphilis in pregnant women. The test should be used with whole blood, and should be able to distinguish active syphilis from previous infection.

Preparation for field trials in developing countries

More than 40 rapid diagnostic tests for syphilis, chlamydial infection and gonorrhoea are now on the market in developing countries. Although many are manufactured in the USA, none has FDA approval, and there is little reliable information on their performance. A two-step strategy was devised for the evaluation of these tests:

1. A laboratory-based evaluation of analytical test performance and reproducibility using archived specimens to identify promising candidates for field evaluations.

2. Field trials of test performance, acceptability and sustainability at primary health care settings in developing countries. It is essential that the evaluations be performed in the populations for which they are intended, using a standardised protocol, with adequate sample sizes.

Operational research needs

Operation research is needed to assess the cost effectiveness and impact of rapid STI diagnostics on disease prevalence and cases of HIV and sequelae averted. It was recognised that a rapid point of care test could result in the treatment of a higher proportion of infected individuals than a "gold standard" test, even if it were less sensitive, since many patients fail to return for their results. Mathematical modelling to evaluate the impact and cost-effectiveness of rapid tests was recommended, and modelling may also help to determine the sensitivity and specificity required.

New opportunities for test development

Private-public sector partnerships are critical for new tool development. While industry is making steady advances in material sciences and nanotechnologies to improve product development, a joint public-private sector effort on test development could also be made along 2 fronts: understanding specimen heterogeneity by geography, anatomical site and symptomatic status, and the search for novel diagnostic targets. Since the human genome sequence and that for *Chlamydia trachomatis, Treponema pallidum* and *Neisseria gonorrhoeae* are known, DNA chip or microarray technology can be exploited to examine host and pathogen gene expression at different stage of disease and offer exciting opportunities for the discovery of novel diagnostic targets for these infections.

Introduction

1.1. Background

Sexually transmitted infections (STI) are a major global cause of reproductive illness. WHO estimated that 340 million new cases of syphilis, gonorrhoea, chlamydia and trichomoniasis occurred throughout the world in 1999 in men and women aged 15-49 years (1). This figure only represents 4 of the curable STIs out of 20 or more pathogens that are sexually transmitted. There is now strong evidence that STIs facilitate the transmission of the Human Immunodeficiency Virus (HIV) by increasing both susceptibility and infectiousness (2). Strengthening STD control capacity is therefore an important priority worldwide.

Early and accurate laboratory diagnosis is an essential component of an effective STI control programme. Rapid technologcical advances in the last decades have resulted in availability of highly sensitive and specific laboratory diagnostic tests for many STIs. However, 90% of STIs occur in settings where access to these tools for disease control is limited. Simple STI diagnostic tests such as microscopy and the Rapid Plasma Reagin (RPR) tests still require technical expertise and equipment. At primary health care settings, the ideal STI diagnostic is a simple, rapid test which requires minimal training and no equipment, and which can be stored at room temperature for long periods. In 1999, the Wellcome Trust sponsored a meeting in Durban, South Africa, on STI Diagnostics in the Developing World. The objectives of the meetings were to review state-of-the-art diagnostics for STIs and to identify STI diagnostic needs for developing world settings, with special reference to rapid point-of-care tests, which allow non-invasive sampling (3). This joint consultation by TDR and the Wellcome Trust was held as a follow-up to the Durban meeting to define a path for the translation of rapid STI diagnostics into primary health care settings in the developing world.

1.2. Meeting objectives

- **To review rapid STI diagnostic priorities**
- **To identify biomedical and operational research needs for test development and deployment**
- **To prepare for field trials of promising rapid STI diagnostics**

2. Priorities for Rapid STI Diagnostics

Rapid STI diagnostics are useful for two reasons. By identification of infection at the bedside, the patient can be given immediate treatment to reduce the risk of developing complications and of further transmission of infection. Rapid diagnostics also have the added advantage of being useful at non-traditional settings such as pharmacies or schools for screening adolescents who are especially vulnerable to STIs and long term adverse reproductive complications.

2.1. Who benefits from rapid point-of-care tests?

Patients who will benefit most from rapid point-of-care diagnostics are infected individuals with no other indication for therapy. This is particularly important for STIs that cause mild or no symptoms in which infection is associated with severe long term complications such as pelvic inflammatory disease (PID), ectopic pregnancy, infertility in the case of genital *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection, or with neonatal morbidity and mortality in the case of syphilis. The success of screening for asymptomatic infections using laboratory-based tests is dependent not only on test performance but also on the rate of patient return for test results and therapy. For example, in a study to determine the cost-effectiveness of screening strategies for chlamydial infection in women, it was shown that a point-of-care test with a lower sensitivity than a laboratory-based test led to more patients being treated when the patient return rate fell below 65% (4).

2.2. STI diagnostic priorities for screening

Screening for genital chlamydial and gonococcal infections:

At least 50% of women with these infections are asymptomatic. Asymptomatic infections are also common in men. A dipstick type test, which can be used with urine or vaginal swab specimens, will be useful. The target populations should include high-risk populations such as commercial sex workers as well as bridging populations such as clients of commercial sex workers and migrant labourers. Adolescents are a vulnerable group and young women are at particular risk of developing adverse reproductive sequelae.

Screening for syphilis:

Syphilis is a major cause of perinatal morbidity and mortality. Most cases of syphilis are asymptomatic in women. Therefore screening of pregnant women for syphilis an important priority. The RPR test is a cheap, sensitive and simple antibody detection test, but biological false positive results can occur as the antigen is cardiolipin and not specific for *Treponema pallidum*, the causative agent of syphilis. Results are difficult to interpret. Treatment rates are poor when testing is centralised due to low return rates and delay in obtaining results. A rapid, simple, antibody detection test based on specific treponemal antigens would be useful for screening for syphilis in pregnant women. As treponemal specific antibodies tend to persist for long periods, there is a need for the development of a syphilis test which distinguishes active, untreated infection from past, treated infections in areas of high disease prevalence.

2.3. The need for rapid diagnostics in syndromic management of STIs

The WHO has advocated syndromic management of STIs in settings where access to laboratory facilities for diagnostic testing is limited or not available (5). Syndromic management utilizes treatment algorithms depending on patient history and physical examination. This allows treatment of infected individuals in a single visit without depending on laboratory results. This approach has the advantage of low cost, simple and rapid treatment to decrease the risk of sequelae and further transmission. The major STI syndromes in adults include urethral discharge, vaginal discharge, lower abdominal pain (pelvic inflammatory disease), and genital ulcers. Since the

algorithms are not specific for the pathogens associated with each syndrome, syndromic management works with varying efficiency for different clinical syndromes in different populations. (6)

2.3.1. Urethral Discharge

The major STI pathogens associated with urethral discharge in men are *C. trachomatis* and *N. gonorrhoeae*. Treatment for gonorrhoea is expensive, and over treatment is therefore a waste of scarce resources in developing country settings. For men, the use of a Gram stained smear of urethral discharge to detect intracellular diplococci has a sensitivity of approximately 95% and a specificity of 98% for gonorrhea. The inclusion of Gram stain smear for the urethral discharge algorithm can reduce over treatment but microscopy facilities are not always available. An additional priority is a means of monitoring gonococcal antimicrobial resistance. However, neither of these applications is of the highest priority, since syndromic management of urethral discharge in men works reasonably well (7).

2.3.2. Genital Ulcers

Genital ulcers are commonly caused by *T. pallidum*, Herpes simplex virus type 2 (HSV-2), and *Haemophilis ducreyi*, the etiologic agent of chancroid. Syndromic treatment has worked well for genital ulcers although it is important to adapt the algorithm to local conditions and to monitor changing aetiology (8). A rapid point-of-care test could be helpful if effective treatment for HSV-2 were included in the algorithm. This is especially important given the growing evidence for the association of HSV-2 infection with HIV transmission (9). However, diagnostic development for genital ulcers cannot be considered a high priority since syndromic management works well for this condition in most settings.

2.3.3. Vaginal Discharge

The five common causes of vaginal discharge are *C. trachomatis, N. gonorrhoeae, Trichomonas vaginalis, Candida albicans* and bacterial vaginosis (BV).

The simplest flow chart, in which all women complaining of discharge are treated for all the five most likely causes, leads to over treatment. Risk assessment can reduce unnecessary treatment for *N. gonorrhoeae* and *C. trachomatis*, but it may be difficult to apply as risk factors vary markedly among populations (10). Risk assessment may also reduce the sensitivity of syndromic management for chlamydial and gonococcal infections. A combined sensitivity and specificity of 140% is the best that can be achieved for these infections (6). The use of clinical signs, such as mucopus from the endocervix, or various simple laboratory tests such as a pus cell count or a Gram stained smear of cervical discharge, or a leucocyte esterase dipstick (LED) test on urine have been tried. None of these was found to have a combined sensitivity and specificity approaching 140%.

There are simple tests for the management of vaginal discharge associated with *T. vaginalis* and BV. The whiff test and pH test can be useful in the diagnosis of BV. Microscopy using a wet mount of a vaginal smear is moderately sensitive and highly

specific for *T. vaginalis*. Both infections can be syndromically managed easily and cheaply so rapid diagnostics for these infections are not a priority.

Syndromic management for vaginal discharge is not cost effective in areas where the prevalence of chlamydial and gonococcal infections is low. In a Bangladeshi population with a combined chlamydial and gonococcal prevalence of 0.9%, the cost per case of gonorrhoea or chlamydia treated was $130 using the WHO syndromic management flow chart with risk assessment (11). It is, however, cost-effective if women are only treated for vaginal infections unless they have a positive test *for N. gonorrhoeae* or *C. trachomatis.* Rapid diagnostics for these two infections are therefore a priority in this setting.

2.3.4. Lower abdominal pain in women

The complaint of lower abdominal pain in women has a wide differential diagnosis. It is commonly caused by *C. trachomatis* and/or *N. gonorrhoeae* infection of the upper genital tract, and to a lesser extent, by the genital mycoplasmas and anaerobes. Clinical signs and symptoms are poor predictors of chlamydial and gonococcal infection. There is a need for a simple point-of-care test for *C. trachomatis* and *N. gonorrhoeae* for women with this syndrome.

2.3.5. Conclusions

- **The highest priority is for simple, cheap, point-of-care diagnostic tests for *N. gonorrhoea* and *C. trachomatis* both for screening of asymptomatic men and women at high to moderate risk of infection, and for reducing over treatment among women with vaginal discharge in both high and low prevalence settings.**

- **There is also an urgent need for a rapid point-of-care test to screen for syphilis in pregnant women that uses whole blood and can distinguish active syphilis from previous infection.**

Although the use of rapid diagnostics to screen for these three priority STIs would have the greatest impact in high risk and bridging populations, it is also important to evaluate their utility in the support of syndromic management. In particular, the use of rapid diagnostics in women presenting with vaginal discharge or lower abdominal pain in prenatal and family planning clinics at primary health care settings may improve the effectiveness of management of these two syndromes. The performance of these tests in special targeted interventions such as schools for screening adolescents, and pharmacies, where many people seek treatment for STD-related symptoms, should be considered.

3. Preparation for Field Trials of STI Diagnostics

A survey of commercial diagnostic activity by SDI showed that there are now over 40 rapid tests for the diagnosis of syphilis, chlamydia and gonorrhea marketed worldwide. Most are immunoassays for the detection of antigen or antibody in an immunochromatographic strip (ICS), or a lateral flow cassette format. These tests are being used in developing countries where there is neither regulatory review of company data on test performance nor independent evaluation of test performance and reliability. SDI has therefore shifted the focus of its activities from funding test development to test evaluations. The dissemination of information on test kit performance and appropriate deployment will serve to safeguard the public and to ensure the efficient use of scarce public health care resources.

3.1. Design of Diagnostics Trials

In the design of trials to evaluate diagnostics in field settings, it is important to consider the "who, where and how" associated with the use of these tests, i.e. on what populations and in what settings will these tests have the greatest impact on patient management and on disease control. To ensure that test performance data is valid and relevant, the evaluations should be carried out in populations for which they are intended and for indications identified as priorities for disease control and prevention.

A recent review of diagnostic trial literature showed that most trial designs are flawed (12, 13). The design flaws include inappropriate composition of both case and control groups; failure to analyze test performance in pertinent subgroups; bias in the selection of patients entering the diagnostic workup; bias in the test evaluation due to inadequate blinding; failure to demonstrate statistical power; failure to deal appropriately with indeterminate results and failure to demonstrate reproducibility of test results, especially when reader interpretation is required.

Trials should also be performed in accordance with WHO guidelines for Good Clinical Practice to ensure credible clinical trial data and the protection, rights, safety and well being of trial subjects (14). Trial data can then be widely disseminated through peer-reviewed journal publications.

It was proposed that rapid STI diagnostics be evaluated in 4 phases, the first 2 in the laboratory and the others in field settings:

Phase 1 - pre-clinical test evaluation (analytic sensitivity, cross-reactivity or specificity, reproducibility)

Phase 2 - proof of principle in easily accessible diseased and well subjects.

Phase 3 - demonstration of performance characteristics in the targeted populations

Phase 4 - delineation of the optimal cost-effective application and societal impact of new tests in comparison with existing tools

3.2. Design of field trials for priority STI rapid diagnostics

3.2.1. Laboratory-based evaluation of rapid diagnostics for *C. trachomatis* and *N. gonorrhoeae*

In view of the large number of rapid diagnostics for the detection of *C. trachomatis* and *N. gonorrhoeae*, and the high cost of field trials, it will be necessary to select a few of the most promising test using laboratory-based evaluations in reference laboratories using the following samples:

- A panel of samples prepared in the laboratory containing known numbers of target organisms (*N. gonorrhoeae* and *C. trachomatis*)

- A panel of well characterized clinical specimens. For syphilis, in particular, the clinical sample panel should be collected from populations similar to those in which the test is likely to be used, since endemic parasitic or bacterial infections may affect the specificity of the test.

- Stability of the test at high ambient temperature should also be estimated at this stage, to avoid conducting field trials on tests whose performance will not be maintained in the field

- The operational characteristics of the test will also be assessed e.g. ease of use, training time required, ease of visual readout, inter-observer variation and batch to batch variability.

Outcomes: test performance (sensitivity and specificity, against an agreed gold standard), shelf life and reproducibility of the test kit as well as ease of use.

3.2.2. Field trials of rapid diagnostics for *N. gonorrhoeae* and *C. trachomatis*

Objectives:

To evaluate the effectiveness of rapid diagnostics for gonococcal and chlamydial infection for:
1) Screening asymptomatic infections in high risk men and women
2) Reducing over treatment associated with syndromic management.

Ideally the test can be used to diagnose both infections in a single specimen.

Study populations:

1) Asymptomatic men and women presenting to primary health care facilities or STD clinics, who are at high or medium risk of infection. Outreach studies should be considered for high-risk populations such as commercial sex workers, and bridge populations such as clients of sex workers, migrant workers, and adolescents.

2) Women with symptoms or signs of lower or upper genital tract infection presenting to OB/GYN, antenatal, and family planning clinics

Methods and outcomes: Cross sectional observation study comparing rapid tests to agreed gold standard tests in moderate and high-risk populations

Specimens:

Specimen type: Since speculum exam is often not possible in primary health care facilities in developing countries, the following specimens should be used:
Women: vaginal swab, taken by the patient or the health care provider.
Men: first catch urine (20-30 ml)

Study design:
The rapid test should be compared with to the following gold standard tests:
C. trachomatis: a commercially available a nucleic acid amplification assay such as PCR or LCR;
N. gonorrhoeae: a nucleic acid amplification assay and culture.

Outcomes:

Screening:
- Sensitivity, specificity, positive and negative predictive value, proportion of infected women treated [NB. This will reflect the follow up rate as well as the sensitivity of the rapid test, since infected women who do not return would not be treated if only the gold standard test were available].
- Acceptability of the rapid test for patient and provider,
- Inter-observer agreement of test result

Symptomatic women:
- Sensitivity, specificity, positive and negative predictive value, compared to syndromic management as well as to the gold standard lab test; cost per infected woman treated.
- Acceptability of the rapid test for patients and provider
- Inter-observer agreement.

Assessment of Impact on targeted interventions:

In the longer term, the impact of screening with rapid tests on the prevalence of genital gonococcal and chlamydial infection could be measured by means of a community-randomised trial, or in a targeted population, the changes in disease prevalence could be monitored over time after the introduction of a screening programme.

3.2.3. Field trial of rapid syphilis diagnostics

Objective:

To evaluate rapid, simple point-of-care serological test for syphilis that can be used to screen antenatal clinic attenders in primary health care settings in developing countries to prevent congenital syphilis.

Ideally, the rapid test should use whole blood and can distinguish active disease from inactive/treated infection. However, this is not an absolute requirement for a test to be considered for field evaluations.

Study population:

Antenatal clinics attenders where the expected disease prevalence >1%

Methods and outcomes: Evaluation to be performed in 3 stages:

1. Laboratory-based evaluations of operational characteristics of rapid tests compared with an agreed gold standard in reference centres. The gold standard is RPR (including titre), confirmed by a treponemal specific test, such as TPHA or TPPA.

   Outcomes: Test performance (sensitivity and specificity), lot-to-lot variation and ease of interpretation including inter-observer variation

2. Feasibility of implementation and test performance in primary health care settings in developing countries

   Outcomes: Acceptability to patients and health care providers, inter-observer agreement, time taken to perform test. It will be important to compare the results obtained with an agreed gold standard in a sample of peripheral health facilities.

3. Impact on the incidence of congenital syphilis. Randomised trial: POC test vs current standard of care.

   Outcome: Proportion of women treated, serological outcome and prevention/detection of congenital syphilis, proportion of sexual partners treated, cost per adverse pregnancy outcome averted.

3.3. Criteria for laboratory and field site selection

The following should be used to guide laboratory site selection:

Laboratory site assets	**Criteria**
Staff	• Quality and qualifications • Proficiency
Facility	• Subscribes to external quality assurance • Equipment for gold standard testing • Storage space for specimens and data • Office space

	• Ability to transport specimens for external quality control • Communication with field site
Specific trial needs	• GLP standards of practice •Standard operating procedures •Data management capability • Trial site co-ordinator • Clerical support

Criteria to guide field trial site selection:

Field site assets	**Criteria**
Investigators	• Track record • Field trial experience • Commitment
Site	• Good standard of care • Mechanism of local ethical review • Government/community support • Treatment availability • Link to laboratory site with gold standard testing capacity
Patients	• Adequate number of infected patients
Staff	• Trained in GCP • Ongoing performance evaluation through external proficiency testing • Stable for duration of trial • Trained in data management • Clerical support
Facility	• Sufficient space for: -for patient confidentiality -for specimen and data storage • Easy access to and communication with laboratory site, esp. for specimen transport

3.4. Field site preparation

Preparation stages	**Details**
	• Protocol development with timelines, job descriptions • Site needs assessment
	• Identification/recruitment of staff • Training of field/clinic staff, lab staff and data entry/management staff, including workshops on the Principles and Practices of Good Clinical and

	Laboratory Practice • Local adaptation, translation and printing of questionnaires and consent forms
	• Procurement of supplies
	• Pilot (feasibility) study, site evaluation/monitoring

4. New opportunities for rapid test development

The challenge of developing an affordable rapid simple point-of-care test appropriate for use in resource-limited primary health care settings is enormous. The test has to be used in settings where there is possibly no electricity for test equipment or refrigeration for the storage of test kits or specimens, and the health worker has limited time and expertise to perform diagnostic tests. Ideally, the test should be used with non-invasive specimens as well.

As part of SDI 's role in facilitating test development, a session was devoted at this meeting to identifying gaps in knowledge, which stand as obstacles to test development. The research needed to fill these gaps will be explored in depth at a future SDI meeting.

4.1. Gaps in knowledge as obstacles to test development

There remain significant gaps in our knowledge of STI pathogens and the diseases they cause, which constitute major obstacles to development of rapid diagnostic tests. In particular, basic biomedical information related to the pathogens and technical information related to product development will likely result in an improved test which will meet the needs of health care providers in using it for patient management and disease control.

4.2. Biomedical Research needs

More information is needed on the natural history and pathogenesis of the SDI priority diseases for diagnostics. Since the genome sequence of *C. trachomatis* and Treponema pallidum are known and that of *N. gonorrhoeae* will soon be available, novel targets for diagnostics could be identified through genome searches and gene expression studies using microarray technology. Improved expression of gene products through new approaches to proteomics would also enable large-scale production of test targets.

The aetiology of approximately 30-50% of STI syndromes are no known. There is a need to search for yet unknown causative agents for these syndromes. The use of universal primers and other novel approaches to identify new microbial agents may be useful.

4.3. Product development research needs

The optimization of specimen collection and processing is important for improving the performance of rapid diagnostics.

Sample collection: More information is needed on the range of variability in specimen collection and on ways in which it can be overcome. Although studies have shown that self-administered swabs are superior to urine for nucleic acid based amplification tests for women with bacterial STIs, there is tremendous variability in vaginal swab collection, which may in turn affect test performance.

Sample content: More information is needed on the bacterial load in specimens from various anatomical sites, especially from non-invasive samples such as urine or saliva. The impact of hormonal changes, eg. in pregnancy, are not known. To define the lower limit of test performance needed for a test to be effective for each clinical indications and population, it would be important to understand the variability in the quantity and quality of pathogen or pathogen markers in specimens collected from different geographic areas, anatomical sites and from symptomatic versus asymptomatic individuals. The relationship between pathogen load and the risk of disease transmission or development of sequelae.

Assay and sample storage: The stability of test kits and of specimens at high ambient temperatures and humidity needs to be determined.

Sample preparation/processing: need to be developed which do not require heating or other complicated extraction procedures - sample processing techniques to maximize efficiency of detection

Standardization of reagents, quantitation protocols and a repository or specimen bank would facilitate test development and pre-clinical evaluation.

5. Operational Research Needs

Apart from the operational characteristics of the test, there are operational issues regarding the proper deployment, the acceptability and sustainability of rapid STI tests at primary health care settings

Validation of rapid STI diagnostics: rapid diagnostics need to be evaluated against gold standard diagnostic tests, in both symptomatic and asymptomatic individuals. It is essential that they should be evaluated in populations of intended use and that the study design should ensure adequate statistical power to determine sensitivity, specificity, and positive and negative predictive values with precision; and that the comparison should be performed in a blinded fashion.

Feasibility studies: The acceptability of rapid STI diagnostics to patients and health care providers should be determined in field settings in developing countries. The performance of rapid diagnostics under routine conditions, in terms of sensitivity and specificity as well as inter-observer agreement should also be determined.

Cost effectiveness: The cost effectiveness of rapid STI diagnostics should be determined in different settings: eg. high and low disease prevalence; and for different indications, eg. screening vs. management of symptomatic patients.

Public Health Impact: The public health impact of the use of RDTs should be determined in different settings, in terms of infections (STI and HIV) cured and prevented; sequelae prevented; and the development of antimicrobial resistance. Large community-randomised trials would be required to accurately measure public health impact, but this may not be the most appropriate use of limited funds; observational studies and modelling could also be informative.

Modelling: Useful information could be obtained by mathematical modelling of the deployment of tests with various levels of sensitivity and specificity in different settings and for different indications. Modelling could also be used to determine the minimum test performance required to make an impact. For example, a less sensitive point-of-care test will be more effective than a "gold standard" test, in which patients are asked to return for their results, when follow up rates are low (5).

Policy implications: Based on the results of the above studies, it will be important to develop guidance tools for programme managers at national and regional levels on the appropriate populations and settings under which rapid STI diagnostics should be used.

6. Conclusions

Principles

- A two-pronged approach is needed: continue to "prime the pump" with new diagnostic discovery while moving as soon as possible to field trials of existing tests.

- Don't let "perfect" be the enemy of "good": a rapid point of care test could have a major impact even if its sensitivity is below 80% compared to the gold standard.

- To stimulate industry efforts in rapid STI diagnostics development, SDI should leverage the buying power of industrialized countries whenever possible - availability of robust trial data will facilitate regulatory agency approval in industrialised countries and create markets for test developers.

- SDI must be a global effort to have the best chance of success - a collaborative framework of private-public sector partnerships in developing and industrialised countries and functional links to other WHO STI activities will be important.

- Consider related activities to assist work e.g. modelling

Priorities for rapid STI diagnostics

Disease	Indication	Study location	Specimen
C. trachomatis ***N. gonorrhoeae***	• **Screening of high risk populations** • **support syndromic management in high and low prevalence settings**	• **STD clinics; non-traditional settings, pharmacies, schools** • **primary health care clinics, including family planning**	**women-vaginal swab; men-urine**
Syphilis	• **Screening - need to distinguish active from past infection**	• **prenatal clinic**	**Whole blood**

Field Trials and Operational Research

- Review available data for each candidate test to prioritize for initial trials
  -Consultation to review evidence
  -Share information with interested parties e.g. SDI web site

- Pre-clinical evaluation: laboratory network
  -Standardized reagents
  -Specimen banks/repository

- Field trials of promising candidates in 3 stages:

  1) Assess test performance characteristics and cost-effectiveness in field settings in populations of intended use

  2) Assess patient and health care worker satisfaction, acceptability, affordability and sustainability in primary health care settings

  3) Impact on disease sequelae and transmission including HIV transmission

- Policy implications
  - Partner notification and partner services
  - Development of guidance tools for programme managers on the use of rapid STI diagnostics

Basic research to develop new diagnostic tools:

- Identification of new markers for disease
- Quantification of pathogen heterogeneity by geography, setting and symptomatic status, definition of relationship between organism load and transmission/sequelae
- Sampling technologies/materials, handling
- Identification of new etiologic agents for STI syndromes

SDI - information co-ordination/clearing house

-Ongoing monitoring of new candidates and pre-clinical data through an established network of laboratory and field sites trained in diagnostic evaluation, data management and analyses

-Dissemination of trial results

Appendix 1: References

1.

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Appendix 2: Public Sector STI Diagnostics Initiatives

1.1. The Sexually Transmitted Disease Diagnostics Initiative (SDI)

The SDI was formed in 1990 by a group of public health specialists and laboratory scientists with the aim of facilitating effective STD control programmes to reduce the burden of sexually transmitted infection in all populations, particularly in women and children, who suffer most from the sequelae of infection. It strives to achieve its mission by promoting:

- The development, evaluation and application of STD diagnostic tests for use at first level health care facilities in developing countries

- The establishment of mechanisms to ensure availability of these tests worldwide

The commercial situation in the early 1990s was that 5-10 large diagnostic companies were doing research and development for high-tech tools such as nucleic acid amplification assay. There is widespread marketing of new diagnostics in developing countries. The package inserts often report remarkable test performance but there is no regulatory control in most countries. The amount, source, and impact of increased spending on diagnostics are unknown.

The SDI expert working group published a set of technical specifications for a simple rapid test for chlamydia and gonorrhea, designed to be used at the point of care with no equipment (ref: Global Access). The lower limit of detection is 10^2 to 10^3 organisms/sample for *Neisseria gonorrhoeae*, and 10^4 to 10^5 organisms/sample for *Chlamydia trachomatis*. The test result should be available in 15 minutes or less, and easy to read with clear endpoint, preferably using non-invasive specimens. Stability of the test at ambient temperatures for transport and storage is also important. There should preferably be an internal quality control, but an external control is acceptable. As part of its advocacy role, SDI performed a market analysis for STI tests in an attempt generate sustained interest and commitment from industry to develop such a tool.

SDI also funded investigator-driven research projects to facilitate test development (Global Access). These include the development of DNA based dipstick tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae,* monoclonal antibodies and polyclonal antibodies against *Haemophilus ducreyi* proteins to use as capture antibodies for the diagnosis of chancroid, and immunochromatographic strips to detect antibodies specific for *Treponema pallidum* for the diagnosis of syphilis. In addition, funds were used to establish a specimen bank to help researchers from both private and public sector in their test development. The specimen bank consists of laboratory grown STD organisms as well as clinical material and a specificity panel for checking cross reactivity to normal flora of the genital tract.

In 1999, SDI became a part of The UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) (ref:Global Access). TDR has traditionally focussed its activities on African

trypanosomiasis, Chagas disease, leishmaniasis, leprosy, lymphatic filariasis, malaria, onchocerciasis, schistosomiasis, dengue and tuberculosis. Like other TDR diseases, STIs suffer from a lack of industry activity, as they are diseases of the poor and where activity does exist, more direction is needed to determine the role for new tests and integrate them into control strategies to ensure proper use. There is also a need for ensuring public safety and protection from poor quality diagnostics leading to improper disease management.

A recent survey showed that there are now over 40 rapid tests for the diagnosis of STIs under development or marketed in different countries. Most are immunoassays in a dipstick (immunochromatographic strip, ICS) or card format or in lateral flow cassettes. These tests are being used in developing countries but their quality is unknown and independent evaluation data are unavailable. As a result, SDI has now shifted its focus from funding test development to:

1) **Funding and organizing test evaluations and field trials**

2) **Funding biomedical research to facilitate test development**

3) **Funding operational research to ensure appropriate deployment of RDT for STIs**

4) **Developing a framework for public and private partnerships**

1.2. The Wellcome Trust

The Wellcome Trust has given £ 4 million in support of research on STI diagnostics in recnt years, ranging from the development of rapid dipstick tests for the detection of *Chlamydia trachomatis* to the development of a multiplex PCR diagnostic test for organisms causing discharge-type sexually transmitted infections. The Trust also supported trials in STI management in urban communities.

The Wellcome Trust funds people, places and collaborations for science-led projects through its international competitive peer review process. It also funds capacity strengthening and direct research costs with no overheads. It makes direct awards to overseas institutions.

The WT/WHO collaborative framework will build upon the Trust's investment in this area and stimulate further high quality research on STI diagnostics.

1.3. The U.S. Centers for Disease Control and Prevention

The CDC currently fund the following projects on STI test development and test evaluation:

<u>STD test development</u>

1. Point of care, CLIA "waiverable" rapid tests for syphilis (latex agglutination and strip test, using modified cardiolipin or *arp* antigen) to be compared to compare to RPR or FTA-ABS.

2. Quantitative PCR for *Chlamydia*

3. Sub-typing for *Chlamydia* and syphilis

STD test evaluation

1. Multi-site comparison of PATH ICS assay for syphilis with RPR and TPPA in STD clinic patients

2. Evaluation of rapid tests for Ct, BV and TV in sexually active 12-19 year olds (Biostar for Ct, FemExam for BV, Affirm VP for BV, TV)in adolescent girls. The gold standard reference tests are Ct: EIA, LCR, PCR, TMA, culture; BV: Amsel and Gram stain; TV: culture and PCR.

3. Comparison of STD testing strategies in incarcerated women by determining the treatment rates for on site tests (Biostar OIA for Ct, Gram stain for gonorroea) with urine LCR.

1.4. USAID

USAID is interested in the development of low cost, simple, and accurate STD diagnostic tools for its programs in HIV/AIDS, maternal/child health and reproductive health/family planning. USAID has been a strong supporter of SDI activities in the past. It has also directly supported PATH in developing diagnostic tools for developing countries such as HIV and syphilis dipstick tests as well as development of dipstick tests for gonorrhoea and chlamydia.

In addition to test development, USAID also supports improvements in STI management and operations research aimed at improving current methods of controlling STIs and in presumptive therapy and pre-packaged therapy. It is experienced in providing assistance with management of information systems, commodity management systems and with policy/advocacy in adopting new products and procedures.

USAID has strong collaborative relationships with the NIH and the CDC, especially where there is joint programming in country such as the LIFE or GAP countries. It also has collaborative relationships with investigators both U.S. based and in developing countries. It has experience in operations research, access to at-risk communities, and in providing training that complement the scientific capacities of other partners. USAID's strengths lie in its existing capability to conduct operations research in reproductive health in partnerships with government and local NGOs.

USAID is a likely "early adopter" of new diagnostic tools and can contribute to clinical trials in:

- **Site selection, assuring that the settings are representative of intended end users.**
- **Community preparation and involvement.**
- **Developing training materials for end users of STI diagnostic tools.**

1.5. National Institute of Allergy and Infectious Diseases, National Institutes of Health

The STD Diagnostic Research and Development Program at the NIH has been funding RDT development for its diseases of interest: gonorrhea, chlamydial infection, syphilis, chancroid, genital herpes, HPV, trichomoniasis, non-gonococcal urethritis, vaginitis, candidiasis and bacterial vaginosis. The ideal RDT should be rapid (20 mins), uses non-invasive sample such as saliva or urine, inexpensive ($1.00 US) and easy to use. The format would be a CLIA waived/feasible as POC test or "Home-test" used as a preliminary screening test leading to health care seeking for confirmatory diagnosis and treatments.

NIH funds academic based investigations through contracts and grants as well as cooperative agreements and interagency Agreements e.g. with CDC/NIH/USAID. It also funds industry-based investigations through its Small Business Innovative Research Grants. Its resource commitment for 1992 – 2001 is estimated at $17.3 million US. Projects are funded with the following research objectives:

- Target for specific disease identification
- Test development which includes research and development and manufacturing development
- Test evaluation: evaluation of prototypes, reagent panels, comparison of commercially available tests
- Appropriate non-invasive samples
- Sample collection/processing
- Test utilization

Some of the funded projects to facilitate test development include: 1) identifying new biochemical markers for gonorrhea, non-gonococcal urethritis, syphilis, trichomonas, candidiasis and bacterial vaginosis; 2) improving specificity of tests for syphilis serology and chancroid; 3) test format development such as dipstick format, hybrid

capture; 4) non-invasive sampling projects such as improving urine collection to enhance antigen capture assays; saliva as an alternative to blood for syphilis.

The NIH has funded the establishment of a specimen bank of laboratory grown reagents, clinical samples and specificity panels to evaluate commercially available tests. It has also supported test utilization projects such as collection of biomedical samples during behavioral surveys. Its investment in genome Sequencing and post-genomics STD GEN relational database may yield novel diagnostic targets.

From this summary of the current activities and commitment for the development and evaluation of new STI diagnostics by WHO/TDR, the Wellcome Trust, CDC, USAID and NIH, it is clear that there are considerable areas of synergism and opportunities for collaboration. It is hoped that this meeting may serve as a starting point for a framework for future collaboration.

The Wellcome Trust Meeting, 1999

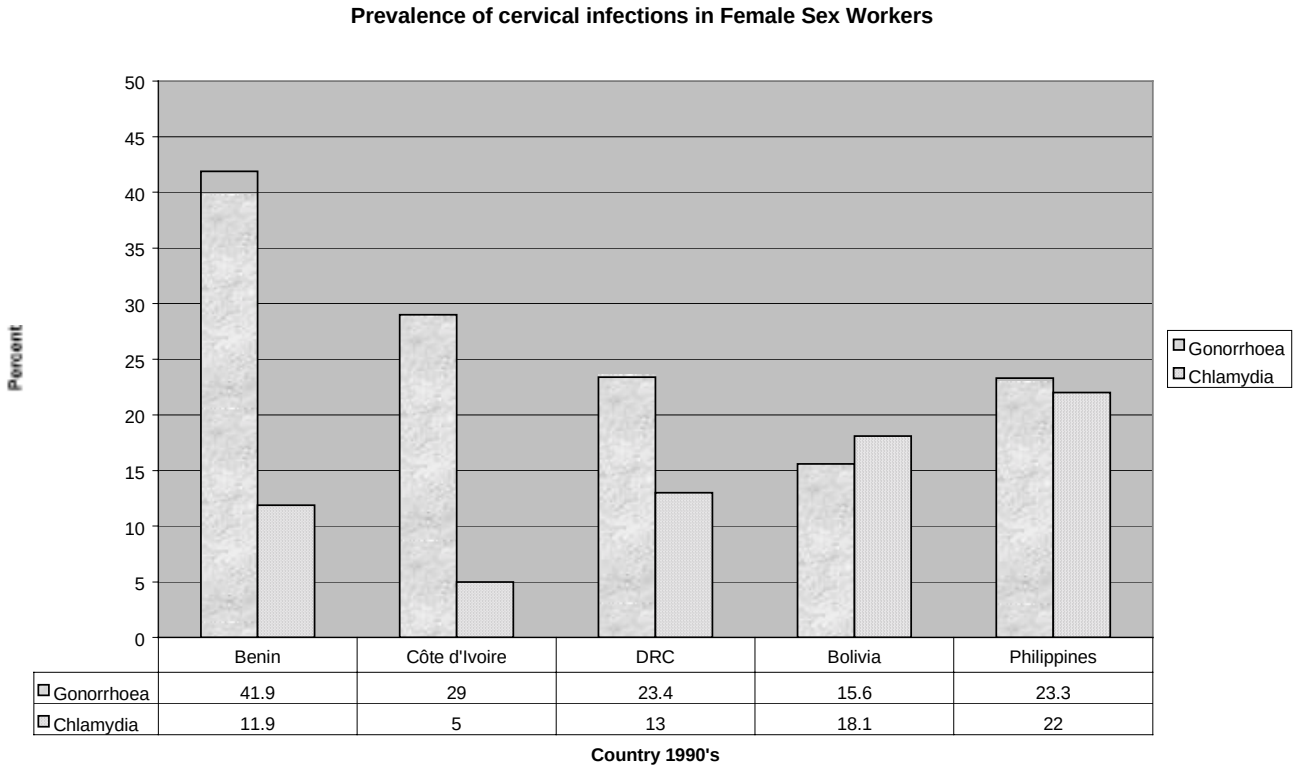
In 1999, the Wellcome Trust sponsored a meeting in Durban, South Africa, on STI Diagnostics in the Developing World. State-of-the-art diagnostics for the most common STIs were described, followed by the identification of STI diagnostics needs for developing world settings, especially point of care rapid diagnostic tests (RDTs) which allow non-invasive sampling**.** As a follow-up to the Durban meeting, WHO/TDR and the WellcomeTrust decided to sponsor a joint consultation to define a path for the translation of existing STI RDTs into primary health care settings in the developing world in January, 2001. This will also serve as a conduit for promising STI tests presently under development to be evaluated and operationalised in a field setting.

STI syndromic management supplement

Small PM, Perkins MD. More rigour needed in trials of new diagnostic agents for tuberculosis. Lancet, 2000, 356:1048-1049.

Gift TL, Mitchell SP, Hook EW III, Kassler WJ. The rapid test paradox: when fewer cases detected lead to more cases treated. Sex Transm Dis 1999; 26: 232-240.

Appendix 3: List of Participants



	Benin	Côte d'Ivoire	DRC	Bolivia	Philippines
Gonorrhoea	41.9	29	23.4	15.6	23.3
Chlamydia	11.9	5	13	18.1	22