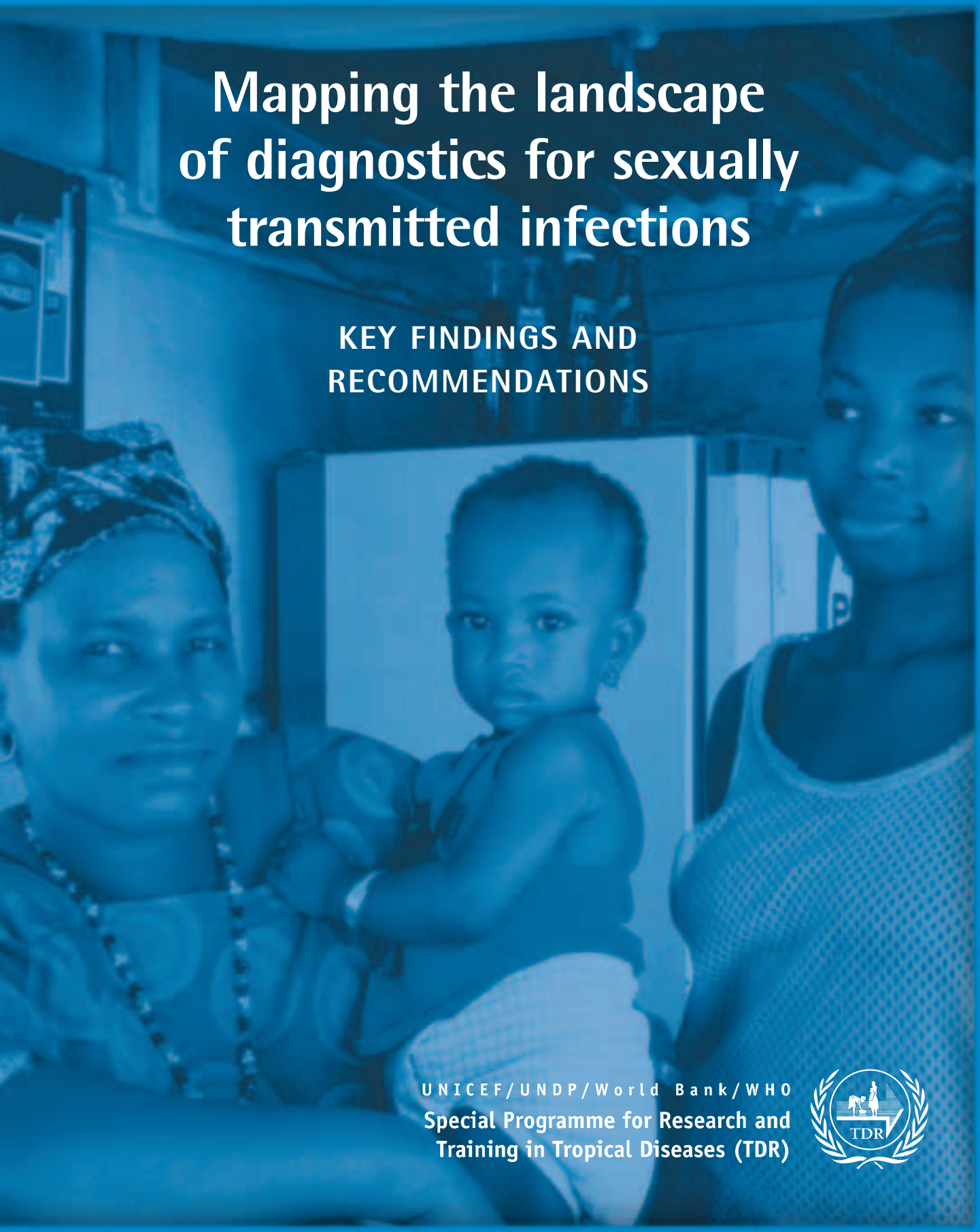
Mapping the landscape of diagnostics for sexually transmitted infections

KEY FINDINGS AND RECOMMENDATIONS



UNICEF/UNDP/World Bank/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

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Table of Contents

Preface

A meeting, jointly convened by the Sexually Transmitted Diseases Diagnostics Initiative (SDI) in WHO/TDR* and the Wellcome Trust and hosted by the Bill & Melinda Gates Foundation, was held in Seattle on July 18, 2002 to explore the possibility of building a global alliance to take on the task of coordinating the development and translation of improved diagnostics for sexually transmitted infections (STIs) into health care delivery in the developing world.

A consensus was reached early in the meeting that proceeding with an alliance focused on STIs rather than the broader field of diagnostics for infectious diseases was legitimate. It was also agreed that it would be important to map the landscape of existing private and public sector interest in this area, and develop clear and compelling descriptions of the needs and opportunities for the development of diagnostic tools before substantive discussions could take place with regard to the goals and the governance of a global alliance. A Planning Group drawn from the delegates at the Seattle meeting (Wellcome Trust, Bill & Melinda Gates Foundation, Rockefeller Foundation and USAID) contributed funds towards the mapping exercise. WHO/TDR, as convenor and secretariat for the Planning Group, was tasked with overseeing the project.

Three consultants with different areas of expertise were engaged to assist WHO/TDR in carrying out this work by mapping public and private sector interests in the area of STI diagnostics and making recommendations for the development of a STI diagnostics partnership. They are Dr Hannah Kettler and Ms Karen White from the Institute for Global Health in San Francisco, USA, and Dr Sarah Hawkes, from the London School of Hygiene and Tropical Medicine, UK. Dr Kettler is an industrial economist with experience and expertise in public private partnerships and Ms. White has worked in industry and provides an industry perspective on technical opportunities and activities in the development of diagnostics. Dr Hawkes is a specialist in STIs and reproductive health with experience of working in developing country programmes. This report contains their key findings and recommendations.

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* The SDI was founded in response to a widely-perceived need to improve care for patients with sexually transmitted infections (STIs) in resource-limited settings through improved diagnostics.
Since its inception, the SDI secretariat had been housed in various agencies and is currently in the World Health Organization (WHO) where it is managed out of the UNICEF/UNDP/World Bank/Special Programme for Research and Training in Tropical Diseases (TDR). The placement of SDI in the Product Research and Development group of WHO/TDR allows the initiative to benefit from the considerable expertise in product development, evaluation and implementation in the group and to exploit synergies in the development of diagnostics for other communicable diseases.

Executive Summary

After mapping the landscape of current donor/funder and private sector interest and activity, we have established that there is an urgent need to further develop new diagnostic tools for STIs that are designed explicitly to address the needs and conditions of populations in the developing world, where the disease burden is clearly greatest. The diagnostic tests currently available are either too expensive and require laboratory facilities or, if for point-of-care use in comparatively resource-poor settings, are not sufficiently effective.

We conclude that new point-of-care diagnostics are required that are **ASSURED**:

Affordable **S**ensitive[1] **S**pecific[2] **U**ser-friendly[3] **R**apid & robust **E**quipment-free **D**elivered[4]

The highest initial priorities for development of **ASSURED** diagnostics are the curable bacterial infections: syphilis, gonorrhoea (GC) and chlamydia (CT), based on a survey of key stakeholders and experts in STIs. From a public health perspective, rapid point-of-care diagnostics will achieve their greatest impact on disease prevalence (and, in time, incidence) if they are used in well-planned and coordinated screening programmes. On an individual case management basis, their use would improve quality of care (and reduce the risk of both under-diagnosis and over-diagnosis) for infected men and women, and reduce the likelihood of complications, including HIV transmission.

The environment and set of actions needed to optimally develop, evaluate, demonstrate use of, and distribute new effective **ASSURED** tests to developing countries are not present under the current constellation of organizations within the STI diagnostics field. In the commercial sector, private companies (where the majority of product development expertise sits) are predominantly working on STI diagnostics designed for profitable developed-country markets or niches. In the not-for-profit arena, a collection of programmes and organizations are working on STI diagnostics with developing countries as a focus but for strategic or resource reasons (or both), they are narrowly focused on specific activities. Many of the stages in the R&D-to-delivery spectrum are not being addressed at all and the programmes that do exist are not coordinated or linked in any coherent way to facilitate product advancement and uptake.

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[1] Sensitive - avoid false negative results.
[2] Specific - avoid false positive results.
[3] User-friendly - simple to perform, uses non-invasive specimens.
[4] Delivered - accessible to end-users.

In summary, the current barriers blocking development of suitable and effective STI diagnostic tools for the Developing World include:

- **A real (or in some cases perceived) lack of a commercial market**
- **Inadequate funding**
- **A poor understanding of tests needed**
- **Limited access to reference clinical materials**
- **Lack of access to strains and reagents**
- **Poor access to clinical trial sites**
- **A lack of transparency in the international regulatory processes**
- **Lack of access to protocols**
- **Lack of access to markets (regulatory and distribution)**
- **Limited public sector advocacy or coordination of R&D process.**

Explicit steps must be taken to address and remove these barriers, and move beyond the status quo. Resources – money, expertise – are necessary, but not the only answer, as the existing set of players also lack a common mandate to coordinate the process.

From analysis of the existing evidence, we conclude:

1. **The health and economic burden of STIs are significant and increasing globally**
2. **The STI burden is disproportionately concentrated in the Developing World**
3. **Serious complications can and are arising as a result of either mis-diagnosis or under-diagnosis**
4. **Affordable treatments do currently exist, but access is inequitable**
5. **Few diagnostic tools meet the product criteria needs of the Developing World.**

A focused, global STI diagnostics initiative with the explicit mandate and resources to lead, coordinate and, where appropriate, fill in the gaps in the pathway from research to patient, is urgently required. This initiative would pull together and help coordinate the activities of all public and private players in the existing fragmented space, and ensure that patients in resource-poor settings where disease burdens are high have proper and reliable access to new, appropriate STI diagnostic tools.

To be successful any new STI Diagnostics Initiative must incorporate:

- The ability to raise and disburse funds, manage and develop projects
- Clinical expertise in STIs
- Technical expertise in diagnostics
- The ability to manage and prioritize the medical and technical sides of the equation
- Ability to assess size and value of the markets for different diagnostics (that will vary depending on the targeted use)
- Clear articulation of the product specifications for new diagnostics
- A mechanism for developing Memoranda of Understanding, managing intellectual property rights, patents, and setting pricing
- Access to good clinical practice (GCP), good laboratory practice (GLP), and good manufacturing practice (GMP) capacities
- Links to policy and guideline drafters
- Links to users in developing country health systems
- Convening power
- A global view
- Developing World engagement

Introduction

Building on a recent increase in public-sector driven activity in the area of STI diagnostics (e.g. SDI, Wellcome Trust investments), the Wellcome Trust and WHO/TDR assembled a group of international stakeholders, leading researchers and funders in Seattle, Washington in July 2002. The meeting had five goals:

1. **Discuss technical mechanisms to address the need for improved diagnostic tools for STIs in the developing world**
2. **Identify areas of synergy with other diagnostics development activities**
3. **Estimate resource needs to make concrete progress in STI diagnostic development**
4. **Develop a shared vision among funding agencies and key stakeholders**
5. **Determine the feasibility of establishing a collaborative framework or multi-agency funding alliance for this purpose.**

A consensus was reached early in the meeting that proceeding with an alliance focused on STIs rather than the wider field of diagnostics for infectious diseases was legitimate. It was also agreed that it would be important to map the landscape of existing private and public sector activities and interests in this area, and develop clear and compelling descriptions of the needs and opportunities for STI diagnostics development before substantive discussions can take place on the goals and governance of a global partnership.

This report presents the key findings of the landscaping exercise plus recommendations for what steps might be taken to overcome the existing obstacles hindering acceleration of the process towards the development, delivery, and use of effective, affordable and appropriate diagnostics for STIs.

The results and conclusions presented here are drawn from analysis of information obtained from interviews with international experts (see Appendix 1), industry and organization websites, along with material and data from the SDI based at WHO/TDR in Geneva, and related literature on public-private partnerships. In addition, a questionnaire on the utility and impact of STIs point-of-care diagnostics was e-mailed to over 90 national STI programme managers in low- and middle-income countries around the world.

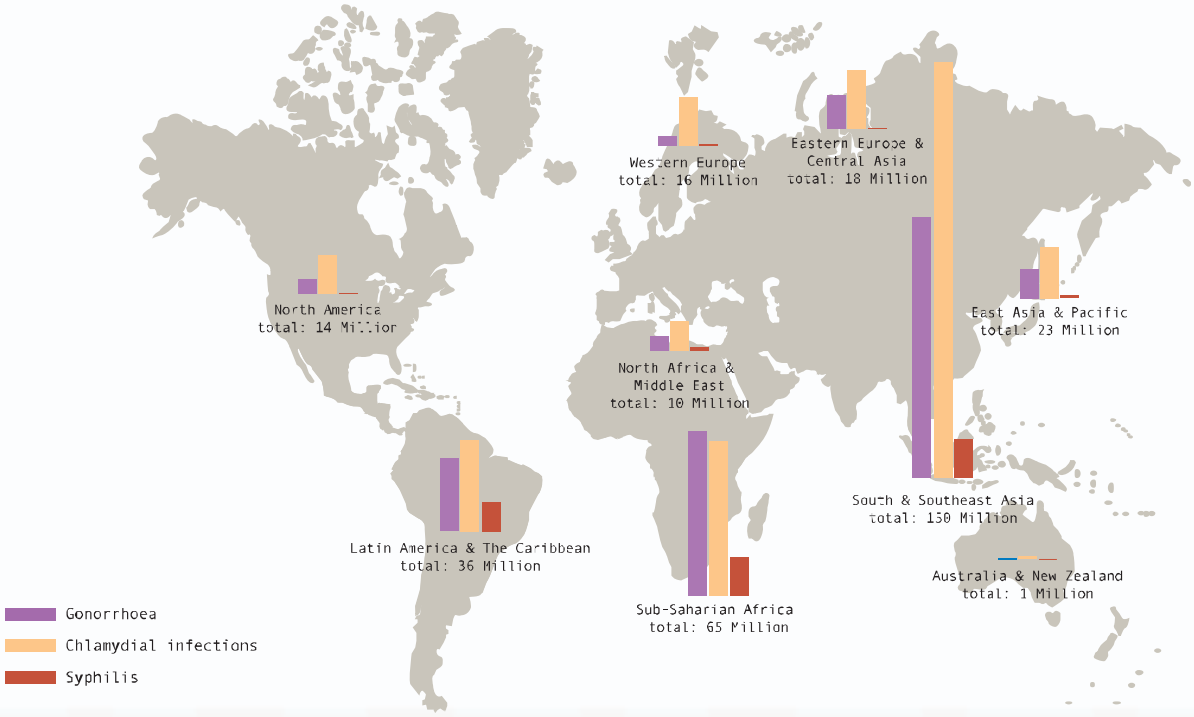
1. Urgency for developing diagnostic tools for STIs

There is an urgent and pressing need to develop either new or improved diagnostic tools for STIs. STIs should be a top public health priority throughout the Developing World, and the situation is worsening rather than improving. They impose a significant and major disease burden and are an expensive drain on already limited health budgets. Diagnostics for STIs do currently exist, but few are appropriate for use in developing countries, where 90% of STI cases occur.

Finding 1 Control of STIs should be a global health priority. The worldwide burden of disease associated with these preventable infections is enormous (see Fig. 1). Annually, over 340 million new cases of curable bacterial STIs are identified worldwide (along with millions of new cases of viral infections).

Figure 1.

Estimated new cases of curable STIs among adults (1999)



Source: Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections: World Health Organization, Geneva 2001, WHO/HIV_AIDS/2001.02

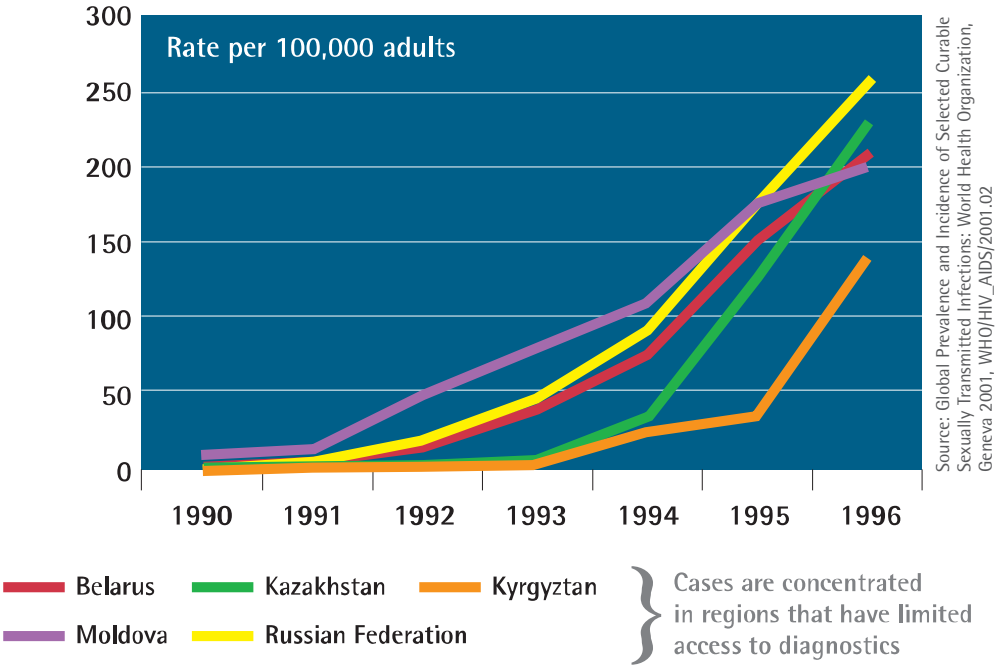
Finding 2 High concentrations of STI cases by locale tend to be strongly correlated with a number of economic and social conditions, including:

i. Economically resource-poor status;
ii. Inadequate and dysfunctional health systems;
iii. High rates of urbanisation, creating markets for sex work in cities;
iv. Demographic profile with high proportion of young people;
v. Gender inequalities which result in a lower status for girls and women;
vi. Cultural and economic barriers to diagnostics and treatment access.

In many developing countries, one or more of these conditions are on the increase resulting in ever more STI cases. For example, as shown in Fig. 2, the economic and social upheavals caused by the breakup of the Soviet Union have resulted in a significant increase in syphilis prevalence among adults in the new, independent republics.

Figure 2.

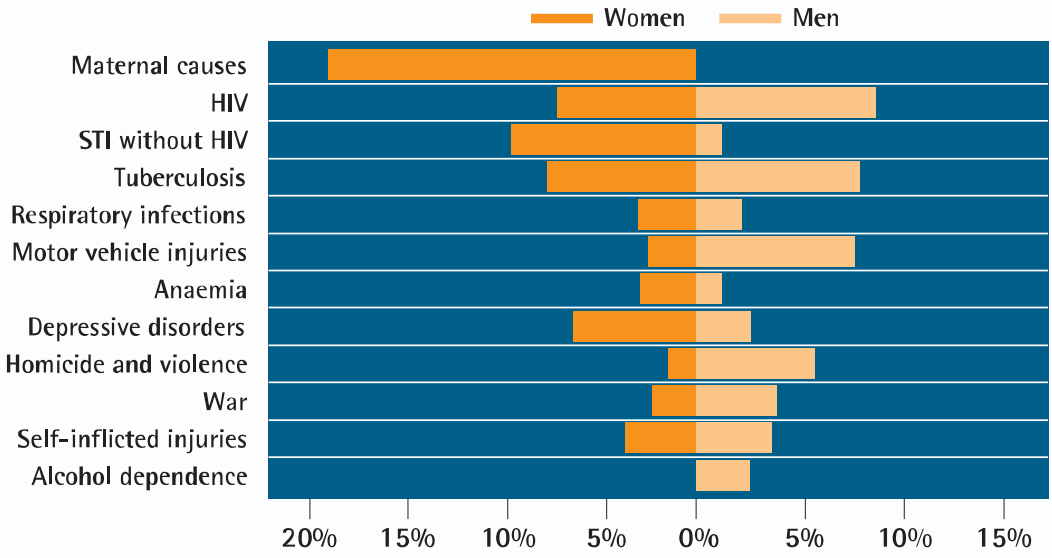
Rates of syphilis in former Soviet Union (1990–1996)



Finding 3 STIs are costly. According to the 1993 World Development Report published by the World Bank, STIs, excluding HIV, ranked second (above both HIV and tuberculosis) for adult women in developing countries, as explained in Figure 3.

Figure 3.

Burden of disease in adults 15–44 years old in the Developing World by sex (1990)



With such a high prevalence, especially among women, STI infections (and associated complications) are a significant drain on public and private sector health care resources. It is estimated that in many parts of the world, the vast majority of STI diagnosis and management is sought in the private sector. In these cases, treatment for STI symptoms can constitute a substantial share of an individual's or a household's health care expenditure. (See Box 1).

To add to the significant direct costs, these infections are associated with indirect costs brought about by complications from untreated infections, or poor-quality care and mis-diagnosis. There are also significant social costs associated with these infections and related complications (see Box 2), especially for women. STIs are often stigmatized conditions associated with

expressions of guilt, blame and shame. Infertility, for example, can be used as grounds for divorce and abandonment. In high STIs prevalence areas, such as some areas in sub-Saharan Africa, it is estimated that over half of all female infertility occurs as a result of undiagnosed and untreated STIs.

Box 1: Household spending on reproductive tract infections (RTIs) in western India

A survey of 1100 randomly selected households in and around the city of Udaipur, western India, investigated expenditure on reproductive and child health (RCH) care. Within this category of expenditure, services for RTIs* ranked the top expenditure for households. Furthermore, families surveyed spent more of their own money to treat symptoms of RTIs than they spent on child health care and all forms of safe motherhood combined (pre- and post-natal, obstetric and abortion services).

Source: Indian Institute for Health Management (2000). Financing Reproductive and Child Health Care in Rajasthan. USAID, New Delhi.

* RTIs include infections that are acquired sexually, iatrogenically (e.g. during inserting of IUDs or abortion) or endogenously (e.g. due to proliferation of organisms normally present in the body).

Box 2: Consequence of undiagnosed and mis-diagnosed STIs

- *An increased risk of HIV transmission*
- *Adverse outcomes in pregnancy* – ectopic pregnancy, stillbirths, prematurity
- *Ill health and death of neonates and infants* – blindness, pneumonia, congenital syphilis, herpes encephalitis
- *Chronic complications in infected sexually active men and women* – chronic pain, lifelong infection, infertility, neoplasias (genital cancers including cervical cancer).

Source: Sexually transmitted diseases, *Holmes, K.K., et al. (Eds) McGraw-Hill (2002).*

Finding 4 Most STIs do not cause any symptoms and when they do, the symptoms are either very mild or non-specific. Undetected infections can lead to serious consequences as described in Box 2, page 8.

The introduction and effective use of diagnostics can significantly improve health intervention efforts and plays an important role in controlling STIs. Current affordable treatments exist in most settings; the key challenge is to target infected populations. If cheap diagnostics were accessible, the patient or health system (in collaboration with international aid where necessary) could absorb the costs of both diagnosis and treatment. According to our research[1], national STI programme managers estimate that they could afford to spend somewhere between US$ 0.10 and US$ 2 per diagnostic test – with most STI programme managers estimating their programmes could afford point-of-care diagnostics if the price was less than US$ 0.50 per test.

Finding 5 Many of the drugs needed to treat common bacterial STIs successfully are included on the WHO List of Essential Medicines. Table 1 details the global median price of the medicines needed to treat three of the most prevalent bacterial STIs – infections which were judged to be a priority for the development of rapid test technology in the stakeholder surveys undertaken for this report.

Table 1.

Indicative drug costs for treating diagnosed STIs

Infection to be treated	Medicine to be used – from WHO Essential Medicines List	Drug regimen costs per adult treated (US$)
Gonorrhoea	Ciprofloxacin 500mg	0.56
Chlamydia	Doxycycline 100mg bd x 7 days	0.14
Early syphilis	Benzathine benzylpenicillin 2.4million IU	0.23

Note: Drug prices are the median drug costs (when obtained from international procurement agencies) taken from the International Drug Price Indicator Guide published by Management Sciences for Health and available at **www.erc.msh.org/mainpage.cfm** (accessed 06/06/03)

[1] These estimates of what kind of test they could afford do not reflect the possibility that the introduction of better tests might free up resources currently spent on medications and health care.

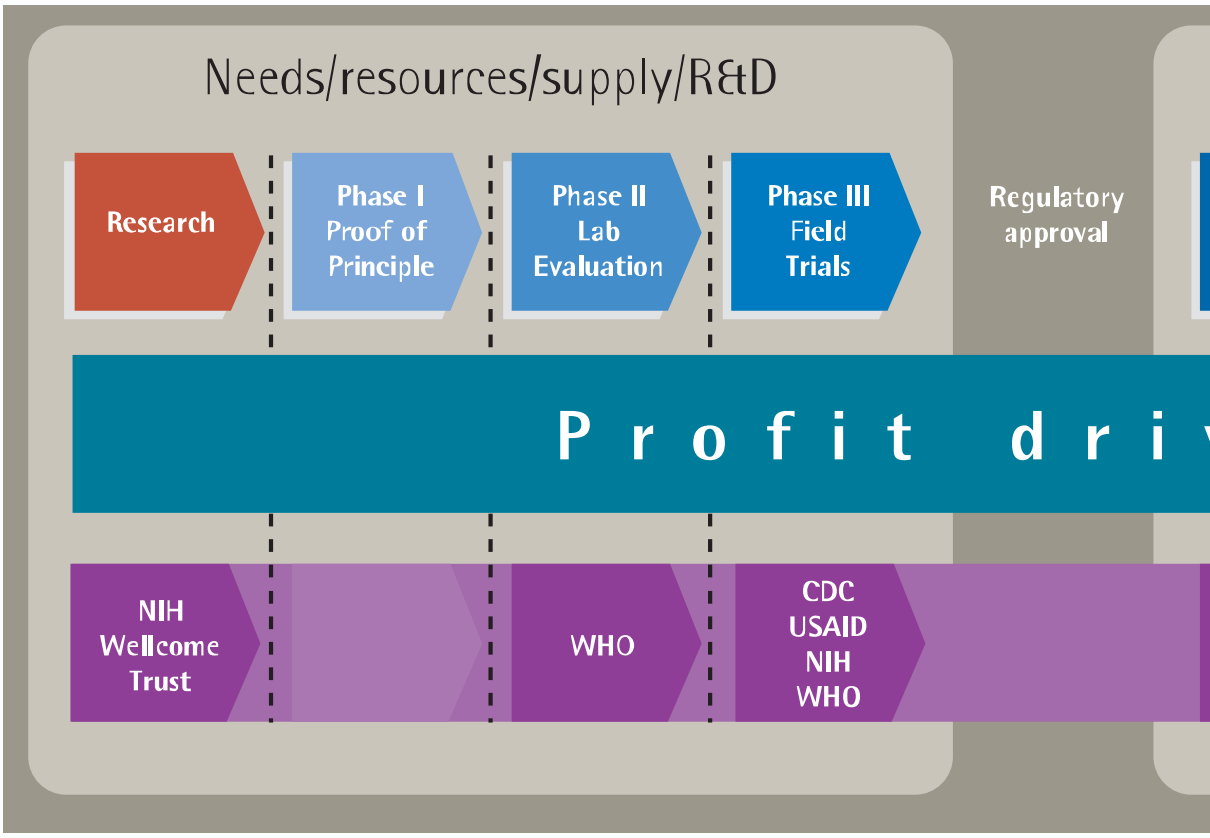
2. Why a diagnostic initiative now?

The time is right for a coordinated, focused initiative to address the urgent need for new STI diagnostic tools appropriate for the developing world. Unprecedented opportunities exist to utilize new technologies and to make a significant, measurable impact. There is currently no concerted effort for exploiting these opportunities to develop new diagnostic tools for STIs appropriate for the developing world.

2.1. Status quo is not working

Private pharmaceutical and biotechnology companies drive, direct and coordinate the development and introduction process for products geared at what are perceived as profitable diseases – heart disease and cancer, for example. They draw in partners as neces-

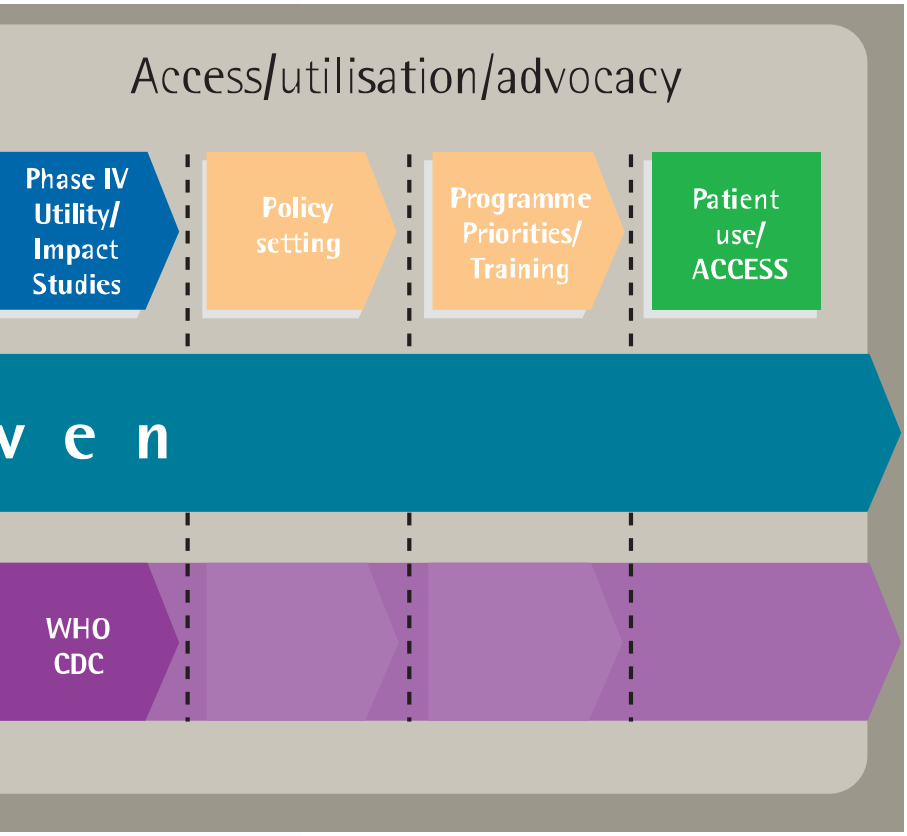
Figure 4.
STI Diagnostics: Current landscape



sary to achieve their goal of getting an effective product in to the hands of people who can afford to pay for it[5]. Put simply, overarching disease-wide leadership and direction are not required to stimulate progress in potentially profitable diseases such as cancer and heart disease. In the Developed World, effective molecular tests for bacterial STIs are widely available, however for the patients in countries where up to 90% of cases occur, use of these tests is not feasible.

These motivators, and the resulting "market driven" integrated process from research to patient do not exist for rapid point-of-care STI diagnostics. Private companies in the business of product development do not have an incentive to meet specifications for patients in developing countries. Companies that are actually investing in products that might be appropriate for patients in the developing world tend to be small and under-resourced (Appendices 2 and 3). These companies are not familiar with regulatory regimes, clinical trial sites, delivery networks, and R&D partner organizations and therefore are not likely to prioritize the developing country markets, especially as they do not expect to make any money there (see Figure 4).

[5] It is well known that the health systems in the developed world leave out many people who need the health tools but cannot afford them.



= *No perceived market no incentive for test development*

Phases of diagnostics development

Phase I:
Product Development – Optimization of process and kits

Phase II:
Laboratory –based evaluation Evaluation of test sensitivity, specificity and reproducibility using convenience or archived samples

Phase III:
Field Trials – Assessment of performance and operation characteristics of product in target populations

Phase IV:
Utility/Impact Studies – Assessment of impact of diagnostics on prevalence of infection, incidence of infection, and incidence of complications

Efforts to develop tests designed for developing countries are stalled by a number of factors. Unlike the development process for profitable diseases (such as diabetes and heart disease), activities focused on STI diagnostics for developing countries lack leadership and coordination across the stages. Furthermore, many stages lack sufficient investments and resources (see Box 3).

Box 3: Factors deterring public and private sector engagement in the development of STI diagnostics for the developing world

Public Sector

- Development by investigator, not directed at product development
- No coordination
- Lack of research for diagnostic development (e.g. on specimen)
- Lack of partners and methods of distribution sites
- Lack of funds to coordinate activities

Private Sector

- Low return on investment
- Unaware of needs (product specifications, market size)
- Unfamiliar with regulatory requirements
- Lack of developing country trial sites

Public research programmes tend to be investigator-driven with relatively little public grant money going explicitly into diagnostic product development. With a few exceptions, such as SDI, public organizations are not staffed with people who have the experience or incentives to conduct product development, and no group is tasked with the responsibility of coordinating the work that is funded and conducted over a disparate number of sites.

Duplication of effort and competition for scarce resources in some areas exist along with complete neglect of other stages, especially the downstream "access, utilization and advocacy" activities. USAID (US Agency for International Development), CDC (US Centers for Disease Control and Prevention), EU (European Union), DFID (UK Department for International Development), FHI (Family Health International) and the Population Council all provide some support to activities along the process but the resources are inadequate and there is little coordination across the donors as regard to priorities and filling gaps (see Figure 4).

There is a clear and urgent need in developing countries for new, appropriate diagnostic tools for STIs. There are opportunities to utilize current technologies to make an impact,

however, neither the public sector nor the private sector is in a position by itself to take a leadership role and drive ideas and products through the pipeline. To take the decisive steps towards remedying this situation, we present in the next chapter (see page 16) a detailed picture of the developing country demand for, and existing supply of diagnostics for STIs.

2.2. Opportunities

Advancements at a scientific and technical level on the one hand and evidence of health impacts from mathematical models and small pilot projects in the field on the other, together support the idea that real progress can be made towards addressing the urgent need for STI diagnostic tools in developing countries.

2.2.1. New knowledge

- **Genome knowledge** – With information from the genomes of organisms causing three STIs (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum*, the causative agent of syphilis), the mapping of the human genome, and the better ability to monitor human reaction to infection, there is optimism about opportunities to identify new targets which will lead to earlier detection of STIs and greater sensitivity of tests to detect STIs.

- **Development of new platforms** – The threat of bioterrorism and response to that threat (especially in the form of new monies) has created a demand for rapid detection of chemical and biological agents, a demand to which researchers and companies have responded with an expansion of work on new rapid test technologies.

- **Expansion of existing and the creation of new initiatives** – The SDI, housed at WHO/TDR and largely funded by USAID, has expanded its portfolio of activities over the past couple of years. New public-private partnerships with important potential synergies with STI diagnostics, especially the Foundation for Innovative New Diagnostics (FIND), and the International Partnership for Microbicides (IPM) now exist. Organizational lessons learned, as well as resources and products, can be leveraged to accelerate the process of addressing the development of tools for STIs.

2.2.2. Opportunities for impact

- **Creating value relatively quickly** - New diagnostic tools can be developed for a fraction of the cost and in much less time than either a drug or a vaccine. This suggests that focused funding and effort should be able to produce viable tools in a relatively short period of time. As an example, Corixa, a Seattle-based company, was able to develop the k39 test for the diagnosis of Leishmaniasis in less than a year with an investment of US$ 1 million for test development. TDR-coordinated field trials of this test are ongoing.

- **Rapid positive health impact** – Case study evidence suggests that when coupled with appropriate and sustainable infrastructure, training, and investments in the education of providers and at-risk populations, the introduction of STI diagnostic tests can have a significant and relatively rapid impact on health (see Box 4).

Box 4: Impact of a diagnostic test on congenital syphilis in Haiti

Non-treponemal tests, such as the Rapid Plasma Reagin test (RPR) for diagnosis of congenital syphilis have been around since the 1950s and are affordable (US$ 0.20), quick (8 minutes) and simple to use (i.e. involve few steps) but require electricity to run the rotator and to refrigerate the reagent. As a result, many local primary health care clinics in developing countries have to rely on a regional clinic, though shipping increases the time between test and result from minutes to weeks and carries the risk of lost or mixed-up results or that the patient never returns for the result or treatment.

In 1996, the Bill & Melinda Gates Foundation and USAID, invested in the installation of solar powered 6-volt batteries in 12 dispensaries in the Artibonite Valley of Haiti. The power generated was used to run a centrifuge to separate the blood and a rotator for processing the RPR. The RPR reagent was stored in a propane-powered refrigerator. The rate of congenital syphilis in that region decreased by 75% (from 552/100,000 live births in 1995 to 172/100,000 live births in 1998) as a result of screening and treatments.

Source: Fitzgerald D. et al., American Journal of Public Health, 2003, Vol. 93, No. 3: 444-446.

- **Impact on HIV** - Alarming increases in STIs are typically associated with collapse of public health systems and social upheavals. Political and economic reforms in the former Soviet States and China has led to rapid and uneven economic development. These countries are now on the brink of an exploding HIV epidemic fueled by huge migration of the rural population into urban centres to seek employment and proliferation of sex industries in these boom centres. With changing access to health services, these migrants and sex workers are stigmatized and marginalized from the health care system. Innovative programmes to provide point-of-care services using rapid STI tests have the potential to avert these burgeoning epidemics.

3. Demand Landscape

Current need for appropriate diagnostic products for key STIs is not being met. It is important to note that population needs cannot be adequately met through the development of new tools alone. A successful initiative must also insure that these new tools are properly utilized.

3.1. Current approaches to STI diagnosis are inadequate and/or inaccessible

Current approaches to STI diagnosis rely upon a number of different but often complementary approaches:

Aetiological diagnosis through the laboratory is the most accurate and, generally, the most costly approach to diagnosis. The depth and scale of laboratory testing can be adapted appropriately for use at different levels of a health care service but even the most basic laboratory-based testing and diagnostic procedures (such as Gram stain or wet mount) depend upon the availability of trained personnel, infrastructure such as microscopes and electricity, and reliable, on-going supply sources of reagents. The more sensitive and accurate gold standard procedures (e.g. nucleic acid based amplification assays) tend to be too expensive for routine use in resource-poor settings.

Syndromic diagnosis relies on health care professionals being able to identify and treat the clinical syndrome caused by STIs. Syndromic diagnosis aims to provide treatment for all the most common infections linked to a particular cluster of symptoms. So for example, instead of receiving treatment just for CT, a person would be treated for CT and GC because of their common symptoms. In the case of a woman with genital ulcers, a person would be treated for syphilis and chancroid, not just syphilis. Syndromic diagnosis is relatively simple to use, and can be incorporated into all levels of (public and private) health care systems.

However, there are problems with using this approach for the most common symptom in women – vaginal discharge. Women with vaginal discharge are often over-diagnosed and over-treated for STIs when they are in fact suffering from endogenous infections (due to proliferation of organisms normally present in the body), or no infection at all. Over-treatment carries not only financial implications, but is also associated with social implications – as discussed above, women diagnosed erroneously with an STIs may be at risk of gender-based partner violence if they have to inform their sexual partners about their diagnosis and need for partner treatment.

A second, and perhaps more serious limitation of the syndromic diagnosis approach for STIs, is the fact that it fails to diagnose the many women infected with *Neisseria gonorrhoeae*

and/or *Chlamydia trachomatis* but without symptoms. The low sensitivity of syndromic management algorithms for this population, results in infected women (and possibly to a lesser extent, infected men) not being treated.

Given the problems associated with the existing diagnostic strategies for STIs. there is an urgent need for new tools that meet the ideal product profile of " **ASSURED** point-of-care diagnostics". These are diagnostics which are:

Affordable **S**ensitive[1] **S**pecific[2] **U**ser-friendly[3] **R**apid & robust **E**quipment-free **D**elivered[4]

3.2. Which diseases should we target?

The highest initial priorities for development of point-of-care (POC) diagnostics are the curable bacterial infections: syphilis, GC, and CT. The non-sexually transmitted endogenous infections: candida species – i.e. yeast, and bacterial vaginosis are, in fact, the most prevalent infections in women and could be well served by new POC tests. However, these infections are relatively cheap to treat and the likelihood of cost-effectiveness of POC diagnostics remains an unresolved issue.

It is less clear what the likely impact of improved POC diagnostics for the viral infections (with the exception of HIV) might be. Developments of affordable treatments (in the case of herpes simplex viruses) and/or prevention interventions (e.g. access to an effective vaccine against human papilloma virus) are generally perceived to be higher priorities for effective public health control programmes against these infections.

3.3. Utilization and possible impact of diagnostics

From a public health perspective, rapid POC diagnostics will achieve their greatest impact on disease prevalence (and, in time, incidence) if they are used in screening programmes. On an individual case management basis, their use would improve quality of care (and reduce the risk of both under-diagnosis and over-diagnosis) for infected men and women, and reduce the likelihood of complications including HIV transmission (see Box 5 and Figure 5 on page 18).

In a limited number of developed country cases, STIs screening programmes have been introduced with an impact on prevalence and complication rates, but often at significant economic cost. There are currently no examples of widespread screening programmes

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[1] Sensitive - avoid false negative results.
[2] Specific - avoid false positive results.
[3] User-friendly - simple to perform, uses non-invasive specimens.
[4] Delivered - accessible to end-users.

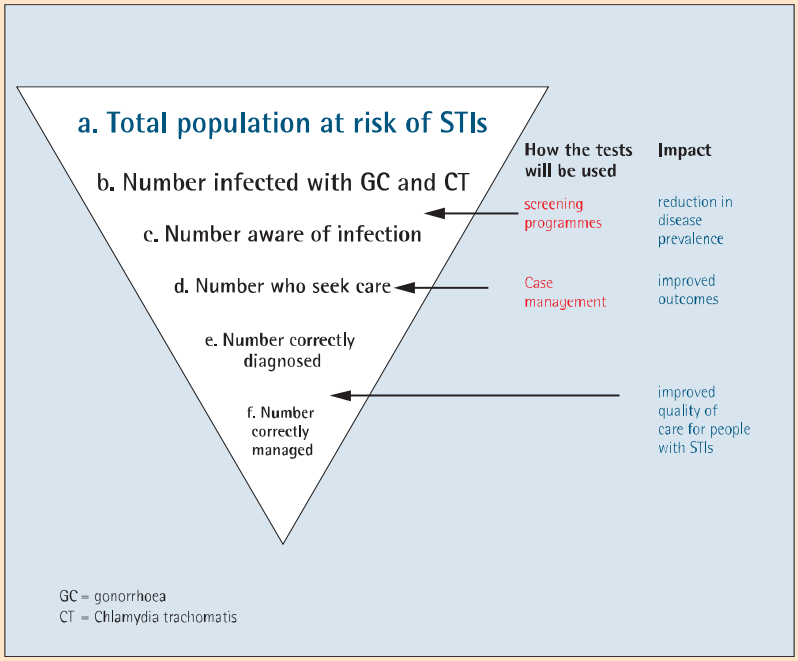
for chlamydia and gonorrhoea in developing countries. Countries have legislated policies for screening pregnant women for syphilis, but, in practice, few developing countries have implemented them nationally. A survey of 22 sub-Saharan Ministries of Health found that despite the existence of national screening policies in more than 75% of the countries, few antenatal clients are screened.[6]

Box 5: Utilization of STI diagnostics

The 'inverse pyramid' of STI prevention and care illustrates that the number of people who are infected with an STI is significantly greater than the number of people who receive effective diagnosis and management for their infection. The steps down the pyramid are as follows:

Figure 5.

Likely utility and impact of point-of-care diagnostics



a. Total population at risk of an STI.
b. Number of people infected with an STI (GC and/or CT in this case).
c. Number aware of infection. This tends to be smaller than the actual number infected as there is a high percentage of asymptomatic carriage.

[6] Gloyd S, Chai S. and Mercer MA. Antenatal syphilis in sub-Saharan Africa: missed opportunities for mortality reduction. Health Policy and Planning 2001;16 (1):29-34

d. Number who seek care. This is smaller then those infected because people, even those with symptoms, often do not seek care.[7]
e. Number correctly diagnosed. In the absence of available and effective diagnostic tools, people receive incorrect diagnoses.
f. Number correctly managed. Even if the correct diagnosis is made, the provider needs to prescribe the correct treatment; the patient needs to purchase the full course of drugs and take the full course; and the patient's sex partner(s) need treatment at the same time (not always true for syphilis, which is infectious only for a limited time – treatment of partner is important for health of partner, but not to interrupt transmission of disease).

Primary prevention programmes aim to reduce the prevalence and incidence of STIs in the population, and would be expected to decrease the size of the top of the inverted pyramid. Rapid point-of-care diagnostics are expected to change the inverse pyramid in a number of ways and lead to both a reduction in prevalence (decreasing the size of the pyramid's top) and a broadening of the base.

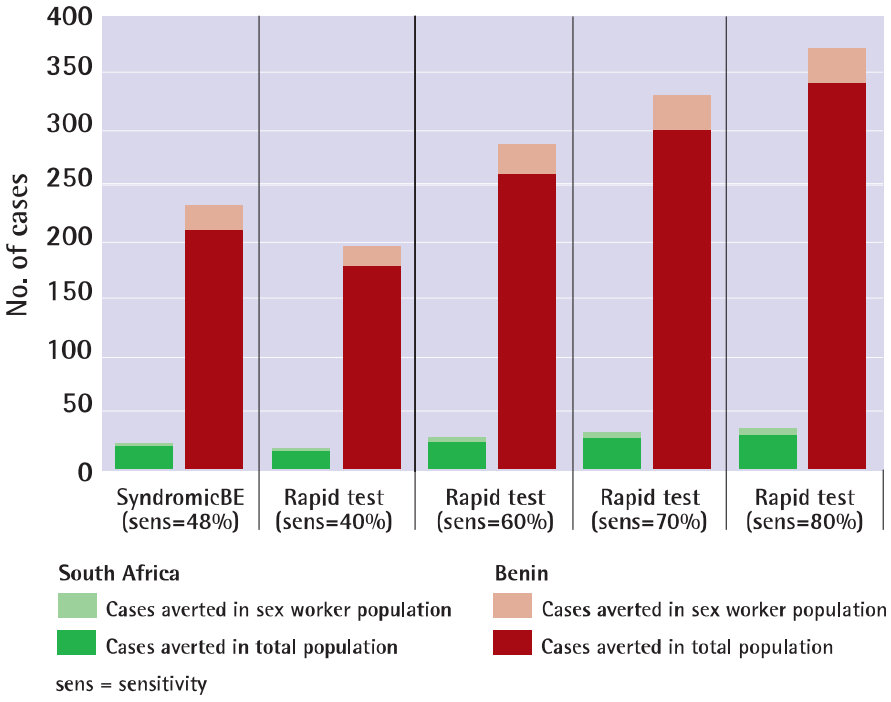
New, **ASSURED** tests for syphilis, GC, and CT are the top priority. Once in hand, we must determine how to apply these tests effectively and ensure that they are accessed by the populations who can best use them. While the implementation of screening programmes are expected to have a significant impact on disease prevalence, in practice there are pertinent questions of feasibility, acceptability, costs, cost-effectiveness, cost-recovery, sustainability and the associated policy implications that need to be addressed before the widespread use of STIs screening programmes in developing countries can be envisaged.

Figure 6 (on page 20) illustrate the potential impact from introducing POC rapid tests as screening tools for gonorrhoea and chlamydia in two different populations – sex workers in Benin, and antenatal clinic populations in South Africa. In Benin, HIV prevalence is 42% among sex workers, and 3% in the general population. Introduction of a rapid CT/GC test would have a significant impact in terms of HIV cases averted, when the HIV epidemic is not generalised. In South Africa, by contrast, where the epidemic is generalized across the population (HIV prevalence in women attending antentatal clinics is 28%), the impact of the rapid test introduction would be much lower (Vickerman, P. et al, unpublished).

[7] Reasons include but are not limited to out-of-pocket plus opportunity costs of seeking services; the stigma associated with the disease; accessibility of services; perceived quality of service provision.

Figure 6.

Impact of screening with POC STI diagnostics on HIV infections in Benin and South Africa



4. Supply landscape

Unlike other "diseases of poverty" where the majority of cases occur in the developing world, (e.g. malaria, leishmaniasis and chagas disease), there are public and private markets for STI diagnostics in both the developed and developing worlds. Industry has responded to the developed countries' demand with effective tests. However, as the previous section discussed, the product criteria for the developed country and the developing country markets can be quite different. While cost and simplicity are attractive features, in the end, governments, hospitals, clinics and individuals in the developed world are primarily looking for highest performance criteria possible. Laboratory facilities and a sensitive/specific test (now using nucleic acid technology (NAT)) have become the gold standard. There is evidence that the introduction of NAT-based laboratory tests that greatly outperform traditional tests has turned attention away from the pursuit of POC tests (Communication, Alan Herring).

4.1. Existing tools: Limitations and opportunities for improvement

For the priority diseases - syphilis, CT and GC - there are rapid immunoassay-based tests on the market (20, 15, and 9 respectively). Most are marketed by small companies and are based on slight modifications of a limited number of platforms. On the positive side, the products tend to be simple, low tech, and inexpensive. On the negative side, these tests lack sensitivity and specificity, tend to require invasive (blood) specimens, and in the case of the syphilis tests, do not distinguish between treated and untreated infection. On balance, therefore, few of these products meet the ideal **ASSURED** product profile and new research and investments are required to develop those that match the profile needed. As can be seen in Table 2, three different product development strategies can be considered to improve upon the currently available set of products; a combination of all three is likely to produce the best results:

Table 2.

Development of new diagnostics

Strategy	Process	Resources	Timeline
1. Improve existing tools	-Develop specifications -Fund, manage and coordinate private sector or universities	~US$ 2-3 million	2-3 years
2. Adapt available platforms	-Develop specifications -Fund, manage and coordinate private sector	~US$ 5 million	3-5 years
3. Develop new platforms	-Search for bright ideas	~US$ 10-12 million	≥10 years

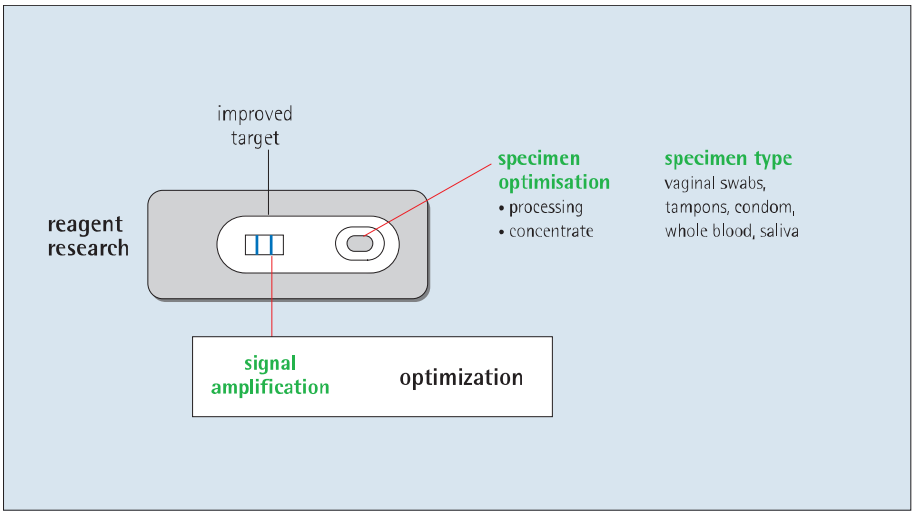
Strategy 1: Improve existing tools

There are significant, largely unexplored opportunities for working with industry, universities, and other research organizations to improve existing tests. Opportunities (see Figure 7) include:

- Conducting additional, focused reagent research;
- Improving detection methods, and signal amplification (e.g. using immuno-floures-cence tags);
- Optimizing specimen concentration and processing (e.g. using magnetic beads).
- Improving specimen type required (e.g. using oral fluid technologies)

Figure 7.

Opportunities for modification of existing STI diagnostic tools



One should not presume that "modifications" necessarily imply low risk, cheapness and/or short-term investments. Some changes might be relatively easy to try out and test in the field, such as specimen optimization, while others, such as modifying testing systems, may involve a lengthy process of re-optimizing, laboratory and field testing - not unlike the normal development process for a new diagnostic.

Box 6: Examples of opportunities to improve existing tests

CASE 1

Qualpro (India) and Standard (DPR Korea), two companies currently involved in TDR's SDI syphilis evaluation to compare the performance and operational characteristics of rapid treponemal tests, have expressed willingness to work with SDI to improve their current rapid tests thereby enabling them to distinguish between a past treated infection and a new active infection. This can be done by way of one of two approaches: research on new reagents and novel targets. or optimization of an existing test.

Required resources

Investment in test development by the private sector or novel target work by academia may take 3-5 years and cost US$ 2-3 million. Optimization of the existing test could take an investment of US$ 0.5-1 million but there is a risk that, in the end, it is not possible to distinguish between active and treated infection using an antigen-antibody test.

CASE 2

The Wellcome Trust has awarded approximately US$ 3 million (£1.7 million) over five years to Dr Helen Lee and colleagues at the University of Cambridge, to develop a simple and inexpensive antigen dipstick test for the detection of chlamydia. This test optimizes a detection system for an existing reagent, and will likely enhance the sensitivity and specificity and ease of use of the product. Since 1997, Dr Lee has successfully developed a prototype, which will soon be evaluated.

Strategy 2: Adapt available platforms

A second, complementary course towards developing new ASSURED tests is through investments in platform technologies that have, to date, not been applied towards STIs, are not currently developed as a POC test, or, are still in an early development stage. New platforms worth consideration going forward include, but are not limited to, amplified NAT test, proteomics/genomic sequencing, nanotechnology, and micro-fluidic technology (e.g. surface plasma resonance technology for a rapid test for CT). Laboratory-based NAT tools for STIs are already on the market in the developed world and a small number of biotechnology companies are working to create POC-based NAT tests. However, such tools are a long way from being easy to use and affordable enough for many resource-constrained settings. In general, companies, small or large, are not working

toward applying their new technologies to **ASSURED** specifications, partly because most do not know what these specifications are.

While in general, developing new tools through new technologies are likely to require long-term investments, there may be examples of cases where working to apply a new technology to a resource-constrained setting may realize results more quickly than attempts to modify a commercialized product.

Box 7:
Adapting technologies to meet ASSURED criteria

Several companies are working on a rapid NAAT (Nucleic Acid Amplified Test) for CT using microfluidics. It is estimated that it would take them US$ 1.2 million and perhaps 1-2 years to modify their test into a simple one that only requires a small heater. The technology can be adapted to include multiple diseases.

New platform technology and detection system

HandyLab (headquartered in Ann Arbour, Michigan) is developing a new diagnostic platform based on lab-on-a-chip technology for the detection of infectious diseases. The technology utilizes thermo-pneumatic pumps with on-chip pressure sources, on-chip micro-heaters and temperature sensors, miniaturized fluorescence detection, sample/analyte concentrators, thermal micro-valves and on-chip filtering. This allows the chip to automate sample preparation, reagent mixing, thermo cycling, detection and results. HandyLab has the platform, but could benefit from partnering to get access to the reagents, primers and probes for targeted infections. If they had access to the proper reagents and primers, HandyLab has stated that it would take about US$ 1.5-2 million and two years to develop a new product for STIs. The majority of the work would be on sample preparation for the new infection and, to the extent it is required, on multiplexing for multiple diseases in a single product.

Strategy 3: Develop new platforms

A third opportunity is to invest in the development of entirely new platforms. This is a much more expensive and longer-term strategy, which involves developing new technologies, or utilizing technologies from other sectors. One such example is the use of nanotechnology.

Resources to do the work

Having identified a multi-pronged approach towards developing new diagnostic tests for STIs, and specific, promising opportunities and approaches, the next critical question is what organizations are capable and interested in conducting the proposed work?

a) Private Industry (Developed World)

As is the case for drugs and vaccines, private companies are the primary drivers of translating research ideas, optimizing and testing diagnostics for market use. The in vitro diagnostics sector is characterized by a large number of companies but the market is highly concentrated with the top eight companies capturing at least 80% of global sales (Appendix 2). For STIs in particular, most large industry leaders focus almost exclusively on expensive laboratory-based technologies (Appendix 3). Only small biotechnology companies are seeking to combine existing and novel technology platforms with POC delivery, but they tend to have relatively few resources and limited expertise in global field trials, product manufacture, and distribution. Most look to license their products to other companies or partner with a larger company in order to complete the research to market process. Even companies developing point-of-care tests, are not designing their tests with the needs of the developing world in mind.

As the examples presented in Boxes 6 and 7 suggest, there are real. as vet. untapped opportunities to work with small companies in the pursuit of **ASSURED** products. However, a number of critical hurdles need to be eliminated to create a favourable environment for companies to participate. These hurdles include:

- A real (or in some cases perceived) lack of a commercial market
- Inadequate funding for R&D
- A poor understanding of tests needed
- Limited access to reference clinical materials
- Lack of access to strains and reagents
- Lack of access to clinical trial sites
- A lack of transparency and harmonization in the international regulatory processes
- Lack of standards for evaluation
- Lack of access to markets
- No public sector advocacy or coordination of R&D

These obstacles are not insurmountable and will need to be overcome to fully engage industry in the quest for new **ASSURED** products for STIs.

b) Emerging private resources (Developing World)

In terms of other, potentially available, private industry resources, there is already ISO-certified[8] large-scale manufacturing capacity in developing countries such as India, China and South Africa. Regulatory processes also exist in these countries, and are becoming more and more sophisticated. In China, Good Manufacturing Practice (GMP) manufacturing capacity will be required for all new diagnostics companies registering products after

[8] ISO certification involves meeting a series of standards, developed and published by the International Organization for Standardization (ISO) that define, establish, and maintain an effective quality system for manufacturing and service industries.

2004. In theory, at least, tests, once developed, could be manufactured in these sites for a low cost, provided technology transfer could be negotiated.

c) Resources/Programmes in the public (not-for-profit) sector

In the not-for-profit arena, public initiatives are focused on specific but isolated stages of the research-to-delivery pathway for rapid POC tests. Table 3 presents a non-exhaustive list of public programmes and donors.

Table 3.

Not-for-profit STIs diagnostics Research and Development programmes

	Research	Product development	Evaluation	Operations Research
DOERS	Universities	PATH Public Health Lab (UK) Helen Lee (Cambridge U) CDC	SDI (TDR/WHO) Universities	CDC Universities Horizons Programme FHI
FUNDERS	NIH Wellcome Trust MRC Rockefeller	Wellcome Trust DFID and DOH (UK) USAID	USAID CDC DFID	CDC DFID EU USAID

These programmes on their own cannot fill the many gaps in the STI diagnostic pathway. They tend to have narrow areas of focus, and funding delegated for specific tasks. Furthermore, due to limited mandates, funding, staff and communications systems, there is little coordination or hand-off of projects between programmes to move from one phase in the development process to another. University-based research projects, for example, are worked on in centres without product development teams or facilities and will often end without a plan or vehicle for translating the ideas into useable products (Communication, Milton Tam, PATH).

5. Summary of landscaping exercise

We have established an urgent need for new STI diagnostic tools that are designed explicitly to address the needs and conditions of populations in the Developing World. The tests currently available are either too expensive and require laboratory facilities or, if point-of-care, are not sufficiently effective (and may also be too expensive).

The set of actions needed to develop, evaluate, demonstrate use of, and distribute new effective tests to developing countries is not taking place under the current constellation of organizations. Private companies, where the majority of product development expertise sit, are working on STI diagnostics for profitable developed country markets or niches. For large companies this commonly means advancing the performance of laboratory-based tools; small companies are exploring point-of-care applications of new technologies but most of these products are still in an early research phase and/or are not designed to fit the limited infrastructure conditions (and purchasing power of) developing countries. In the not-for-profit arena, a collection of programmes and organizations are working on STI diagnostics with the developing countries as a focus but for strategic or resource reasons (or both) are narrowly focused on specific activities. Many of the stages in the R&D to delivery spectrum are not addressed at all. The programmes that do exist tend not to be coordinated or linked in any way to facilitate product and information advancement.

Explicit steps must be taken to move beyond the status quo. Resources – money, expertise – are constraining factors to conduct any one of the activities listed, but additional resources alone will not solve the problem, as the existing set of players lack a common mandate and a coordinating mechanism that keeps everyone focused on that mandate.

A focused initiative with the explicit mandate and resources to lead, coordinate and, where appropriate, fill in the gaps in the pathway from research to patient for STI diagnostics is required. This initiative would pull together the public and private players in the fragmented existing space and ensure that patients in resource-poor settings have access to new, appropriate STI diagnostic tools.

6. Going Forward

To initiate a discussion about how to structure an initiative that properly builds on existing activities and infrastructure to advance this mandate, we first identified the specific activities where work is required to fill gaps in the STI development process.

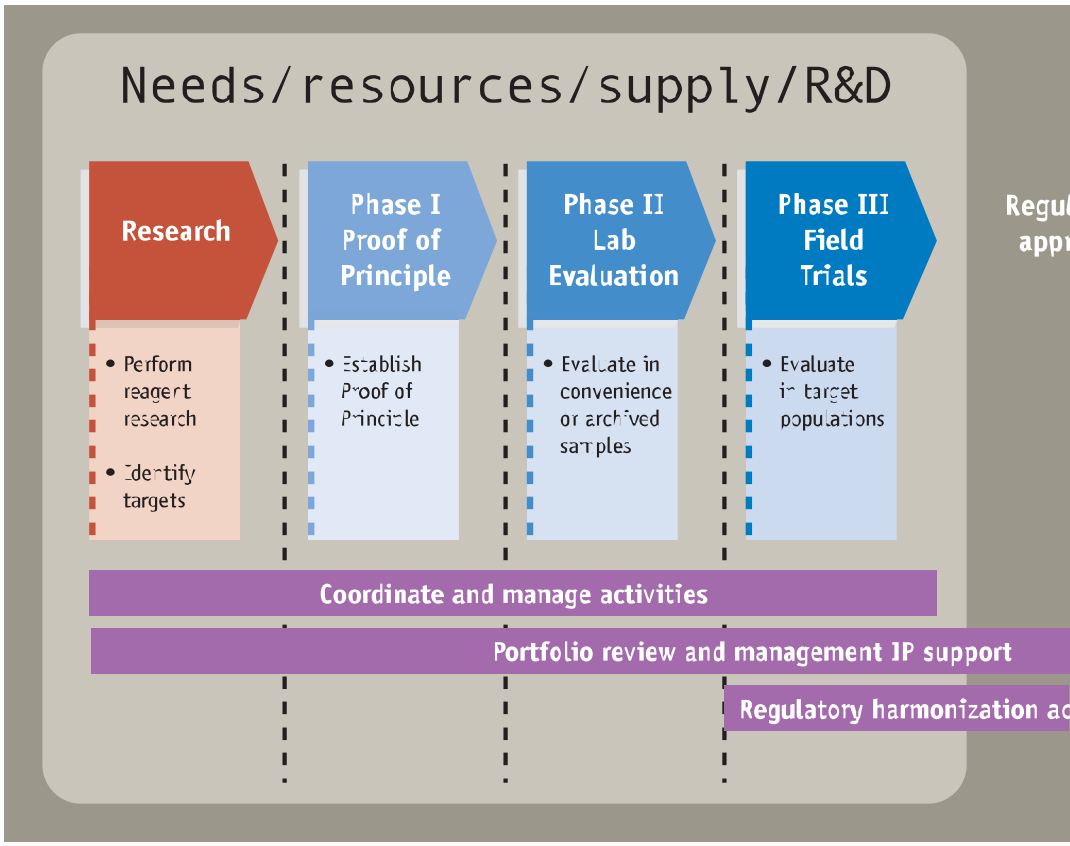
6.1. The scope of activities

The range of activities to be included in the initiative maps onto the research-to-patient spectrum discussed earlier. As illustrated in Figure 8; these include:

- focused research
- co-development
- clinical trials
- demonstration/operations research
- impact studies
- policy recommendations and guidelines.

Figure 8.

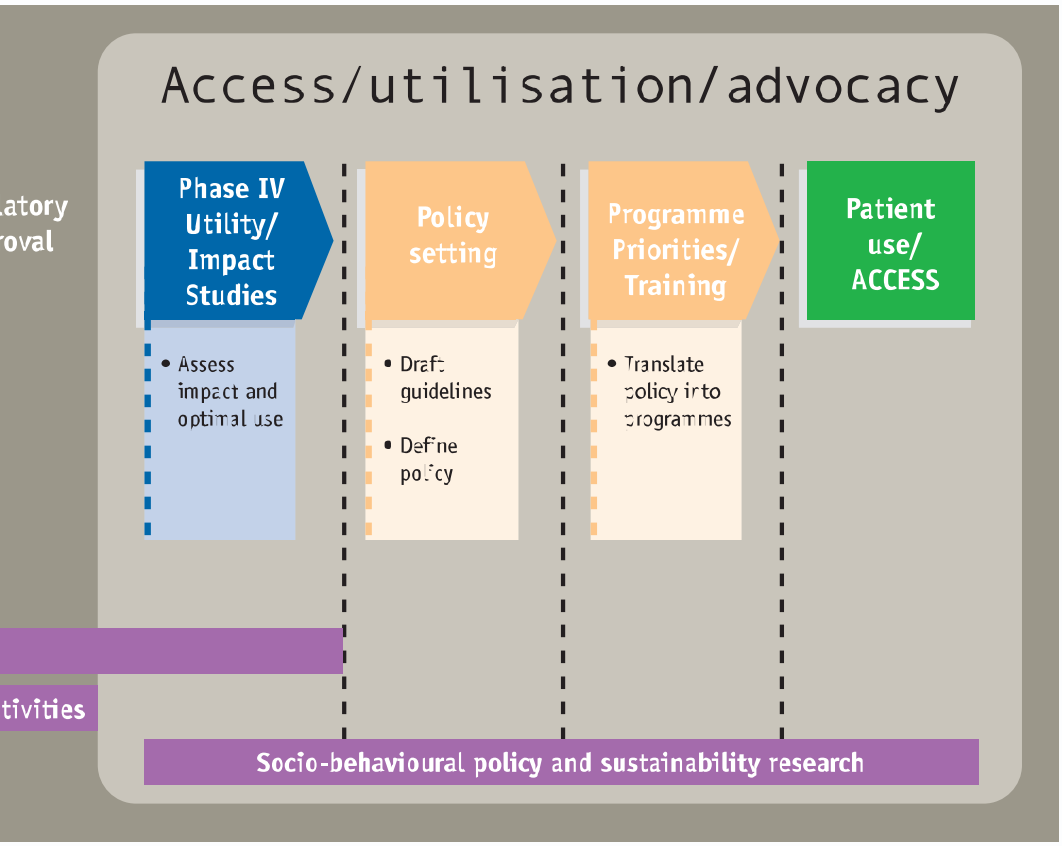
STI Diagnostics: Ideal landscape



In addition to specific sequential stages in the research-to-delivery process, there are also a set of horizontal activities that are needed to advance the diagnostic development process, including project review and coordination, intellectual property rights and portfolio management, and socio-behavioural and policy research.

For any given disease, a unique set of actions are required to deliver **ASSURED** tools, given differing current conditions, namely the availability of quality products on the market, the state of scientific knowledge, and the existing R&D pipeline. To tackle syphilis, for example, a two-pronged approach might be appropriate. Basic research is required to identify mechanisms to distinguish active from treated disease. At the same time, existing, marketed tests must be evaluated and the suitable candidates identified and promoted for use in the field. By contrast, CT requires product research to optimize the format and platform of existing tests, i.e. to improve their speed, sensitivity and user-friendliness.

Furthermore, the development of an **ASSURED** product is not enough, in and of itself, to ensure that it reaches the intended target audience. Diagnostics need to be simple enough that they can be used in a sustainable way despite limited or lack of health infrastructure. Further research-based steps are needed to facilitate the use of these tests, including field evaluations, utility and impact studies, socio-behavioural policy and research into sustainability of product usage.



Box 8 provides examples of activities for each phase.

Box 8: Phases of diagnostics evaluation

PHASE I STUDIES

Proof of Principle (Preclinical studies), including:

• The initiative could initiate requests for proposals (RFPs) to conduct focused reagent research. Specifically, an example of such research is to develop reagents for a syphilis test that could distinguish active from treated disease, to identify or alternative targets or biomarkets for priority STIs through genomics and proteomiccs. RFPs and funding innovative early stage research are necessary to ensure products entering into the pipeline for evaluation and possible application.

Estimated cost: US$ 1 million/year (US$ 500,000 each for each priority STI and syphilis).

Product Development

• In order to prime the development pipeline, RFPs could be issued for the optimization of process and kits for syphilis, CT and GN. There is an urgent need to optimize the format and platforms of existing (immunoassay) diagnostic tests for chlamydia and gonorrhea. This includes enhancements such as the ability to use non-invasive specimens such as saliva, improved sensitivity and specificity and improvements in ease of use.

Estimated cost: US$ 1 million/year.

• SDI's current work conducting evaluation trials on existing test would need to be expanded, to include additional tests and field sites. There should also be a concerted effort to get developing country evaluation sites involved in the development of new products. This effort will likely include the development of a specimen bank for syphilis, and the quantification of bacterial load in genital specimens from individuals infected with CT and NG.

PHASE II STUDIES

Laboratory-based evaluations of rapid test performance using convenience or archived samples for analytical sensitivity, specificity and reproducibility vs. gold standard.

Estimated cost: US$ 1 million/year (5 trials at US$ 100,000 each with multiple tests per trial).

PHASE III STUDIES

Field evaluation of test performance and ease of use in the population(s) for which the test is intended, including:

• Assessment of performance characteristics in target populations

Estimated cost: US$ 750,000/year (US$ 100-250,000 for each of 4 sites).

• Cost-benefit, cost-effectiveness, pricing.

Estimated cost: US$ 750,000/year (US$ 250,000 per site in 3 sites per year).

PHASE IV STUDIES

Utility and impact studies

Operations reseaarch to determine the impact, cost-effectiveness and cost-benefit of different strategies for test introduction and adoption.

Estimated cost: US$ 5 million (5 studies over 5 years at US$ 1 million per study).

Horizontal Support Activities

• *Policy Guidelines* –

The initiative will sponsor at least one meeting per year of 10-15 experts to work on the drafting of STI diagnostic policy guidelines – includes policy analysis to determine opportunities and possible barriers to use of rapid tests, regulatory harmonization activities.

Estimated cost: US$ 150,000 year.

• *Intellectual Property (IP) support* –

The initiative will provide support to companies seeking access to the necessary pieces of IP involved in the creation of new diagnostic tools. This support will include legal support in negotiating access to patents.

Estimated cost: US$ 150,000 year (US$ 30,000 per research/development project – assume 5 projects)

• *Review projects, coordinate and manage portfolio* –

As it builds up a portfolio of projects, the initiative will review and select projects for support, coordinate their progress, manage activities, making decisions at key decision points as to what to drop and what to advance.

Estimated cost: US$ 200,000 year.

• *Socio-behavioural, Policy and Sustainability Research* –

There is a need for social and behavioural research focused on acceptability of tests. For syphilis, the most pressing need is policy and programme analysis to identify barriers to implementing and utilizing existing diagnostics. For GC and CT, there is a need for research on the acceptability and accessibility of interventions to reduce disease burden (e.g. screening programmes). The research will also include market analysis of pricing policy and willingness to pay for test, and determination of steps required to scale up 'pilot projects'.

Estimated cost: US$ 250,000 year.

In the process of selecting specific projects for the portfolio, the initiative will seek an optimal balance between need and feasibility as well as expectations about short- and long-term returns, i.e. establish a balance between low-hanging fruit and attractive but more risky and long-term investments. For example, returns from investments in the modification of existing immunoassay tests are more immediate but with perhaps less health impact than those in uncertain, and more expensive, as yet untested, platform technologies. The initiative will also seek to leverage its resources by identifying and utilizing a range of partners to carry out its activities.

Specifically, within the status quo, there is limited focused private sector involvement due to the (real or perceived) lack of a commercial market for new tests which meet Developing Country needs. This is further exacerbated by the limited public and philanthropic sector funding to help push R&D activities. Within the industry, there is still a poor understanding of test requirements, limited access to strains and reagents, clinical trial sites, protocols and markets. The SDI at TDR has begun to promote public sector coordination of R&D and uptake activities but its limited resources have restricted its impact. In thinking through what alternative options might be feasible and more effective, we must gauge each idea against a short list of "requirements" for successfully filling the gaps in a meaningful and coordinated manner.

These requirements include:

- The ability to raise and disburse funds, manage and develop projects
- Clinical expertise in STIs
- Technical expertise in diagnostics
- The ability to manage and prioritize the medical and technical sides of the equation
- Ability to assess size and value of the markets for different diagnostics (that will vary depending on the targeted use)
- Clear articulation of the product specifications for new diagnostics
- A mechanism for developing Memoranda of Understanding, managing intellectual property rights, patents, and setting pricing
- Access to good clinical practice (GCP), good laboratory practice (GLP), and good manufacturing practice (GMP) capacities
- Links to policy and guideline drafters
- Links to users in developing country health systems
- Convening power
- A global view
- Developing World engagement

A global partnership with the characteristics above is crucial to the success of a STI diagnostics initiative. We should also consider what models for partnerships already exist and what lessons we can learn from their establishment processes as well as assessments of progress towards accomplishing their mandates. A partnership made up of players from both the public and private sectors with an interest in STI diagnostics needs to be developed. The partnership should have a shared vision of accelerating the R&D process and ultimate delivery of new and improved tools for the diagnosis of STIs in the Developing World.

APPENDIX 1

Key informants interviewed for mapping the demand landscape and managers surveyed

Telephone and face-to-face interviews were conducted with the following key stakeholders addressing issues of priorities, utility, impact, feasibility and sustainability of point-of-care tests within existing national STI/RTI control programmes.

We would like to thank all these people for their valuable contributions to this piece of work.

1. Dr Johannes van Dam
   Deputy Director HORIZONS programme
   Washington DC, USA

2. Professor David Mabey
   Professor of Communicable Diseases,
   London School of Hygiene & Tropical Medicine
   London, UK

3. Dr Gina Dallabetta
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   HIV/AIDS Prevention and Care Department
   Family Health International
   Arlington, Virginia, USA

4. Professor Michel Alary
   Groupe de recherche en épidémiologie
   University of Laval
   Quebec, Canada

5. Professor Myron Cohen
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6. Dr Caroline Ryan
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   National Centre for HIV, STD and TB Prevention
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7. Dr Ward Cates
   President/Chief Executive Officer
   Family Health International
   North Carolina, USA

8. Dr Graham Neilsen
   Senior technical officer on STIs,
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9. Professor Ron Ballard
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10. Professor Ned Hook
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    School of Medicine
    University of Alabama at Birmingham
    Birmingham, Alabama, USA

11. Dr Adrienne Germain
    President
    International Women's Health Coalition
    New York, New York, USA

12. Professor Judith Wasserheit
    Director, HIV Vaccine Trials Network
    Professor of Medicine, University of Washington
    Seattle, Washington, USA

13. Dr Jamie Uhrig
    Consultant on HIV/AIDS and STIs
    Ha Noi, Vietnam

14. Dr Nathalie Broutet
    Department of RTIs
    Reproductive Health Research
    WHO, Geneva, Switzerland

15. Professor Sir Leszek Borysiewicz
    Principal, Faculty of Medicine
    Imperial College
    London, UK

16. Dr Suellen Miller
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    University of California, San Francisco,
    OB/GYN and Reproductive Sciences
    San Francisco, California, USA

17. Dr Beverly Winikoff
    Gynuity Health Projects
    New York, New York, USA

18. Professor Richard Hayes
    Professor of Infectious Disease Epidemiology
    London School of Hygiene & Tropical Medicine
    London, UK

19. Dr XiangSheng Chen
    STI/HIV Programme
    WHO Office,
    Beijing, China

Country Programme Managers who responded to the e-mailed questionnaire

A short questionnaire on the perceived utility and impact of rapid point of care tests was e-mailed to over 90 national programme managers of STI programmes in low-and middle-income countries around the world. In addition to asking questions about the use of rapid point-of-care tests, the questionnaire also addressed issues of priority setting and the affordability of these tests. Issues of who funds programmatic activities were also covered in the questionnaire.

Responses were received from the national programme managers in the following countries:

- Angola
- Botswana
- Burkina Faso
- Czech Republic
- DR Congo
- India
- Indonesia
- Iran
- Lithuania
- Morocco
- PR China

We would like to thank the national programme managers from these countries for their valuable inputs. In addition, we received a great deal of help from the Regional Offices of WHO in order to identify the most appropriate people to complete the questionnaires. Our thanks go to all the WHO Regional Offices.

APPENDIX 2

Key companies in the in vitro diagnostics market

Major players

- Abbott Diagnostics, USA
- Bayer Diagnostics, USA/Global
- Beckman Coulter, USA
- Becton Dickinson, USA
- Johnson & Johnson, USA
- Dade Behring, USA/Germany
- BioMerieux Vitek, France
- Roche Diagnostics, Switzerland

Others

- Abaxis, USA
- ABX Diagnostics, UK
- Biosite Diagnostics, USA
- Bio-Rad Laboratories, USA
- Chiron, USA
- Cholestech, USA
- Cytyc, USA
- Diagnostic Products Corp., USA
- Digene, USA
- EM Diagnostics, UK
- Gen-Probe, USA
- Genzyme Diagnostics, USA
- Heska, USA
- Home Diagnostics, USA
- IDEXX, USA
- IGEN, USA
- Immucor, USA
- Inverness/Selfcare, USA
- i-Stat, USA
- Medtronic, USA
- Meridian Diagnostics, USA
- Menarini, Italy
- Myriad Genetics, USA
- Nova Biomedical, USA
- Olympus, Japan
- Organon Teknika, France
- Quidel, USA
- Radiometer America, Inc., USA
- Synbiotics/W3 Commerce, USA
- Tecan, Switzerland
- TriPath Imaging, USA
- Ventana Medical Systems, USA/France

APPENDIX 3

Key companies in STI diagnostics

Major players

- Abbott* Diagnostics, USA
- Becton Dickinson, USA
- Roche Diagnostics, Switzerland
- BioMerieux, France

Large players

- Chiron, USA
- Gen-Probe, USA

Others

- Acon*, USA
- Axiom*, USA/Germany
- Beacon* Diagnostics, USA
- Biokit*, Spain
- Biomax*, Croatia
- ChembioDiagnostics*, USA
- CTK Biotech*, USA
- Diesse* Diagnostics, Italy
- Digene, USA
- EY Labs*, USA
- Fujirebio Inc.*, Japan
- Golden Bridge*, USA
- IND Diagnostics*, Canada
- Innogenetics*, Belgium
- InTec Products*, USA
- International Immuno Diagnostics*, USA
- Kodak*, USA
- OraSure*, USA
- Omega Diagnostics*, UK
- Pacific Biotech*, Thailand
- PATH*, USA
- Princeton BioMeditech*, USA
- Qualpro Diagnostics*, UK
- Quidel Corp.*, USA
- Standard Diagnostics*, South Korea
- Thermoelectron*, USA
- Trinity Biotech*, Ireland
- Tyson Biomedical*, USA
- Unipath/Inverness*, UK
- University of Cambridge*, UK
- Wampole Labs*, USA

* Produces point-of-care or rapid tests.

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