



AN ASSESSMENT OF THE SOUTH AFRICAN MARKET FOR A POINT-OF-CARE TEST FOR GONORRHOEA AND CHLAMYDIA

FIND, November 2020

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ABBREVIATIONS

| | | | |
|----------------|--|--------------|---|
| ABS | antibiotic stewardship | SAASP | South African Antimicrobial Stewardship Programme |
| AMR | antimicrobial resistance | SANAC | South African National Aids Council |
| ANC | antenatal care | STI | sexually transmitted infection |
| ART | antiretroviral therapy | TPP | target product profile |
| ARVs | antiretrovirals | TV | <i>Trichomonas vaginalis</i> |
| BV | bacterial vaginosis | VDS | vaginal discharge syndrome |
| CAPRISA | Center for the AIDS Programme of Research in South Africa | WHO | World Health Organization |
| CIDER | Centre for Infectious Disease Epidemiology and Research | | |
| DHS | Demographic and Health Survey | | |
| FSW | female sex workers | | |
| GPs | general practitioners | | |
| GTI | genital tract infection | | |
| HIV | human immunodeficiency virus | | |
| HPV | human papillomavirus | | |
| MAC | Ministerial Advisory Committee | | |
| MSM | men who have sex with men | | |
| MUS | male urethritis syndrome | | |
| NDoH | National Department of Health | | |
| NG/CT | <i>Neisseria gonorrhoeae</i> / <i>Chlamydia trachomatis</i> | | |
| NHI | National Health Insurance | | |
| NHLS | National Health Laboratory Services | | |
| NICD | National Institute for Communicable Diseases | | |
| NSP | National Strategic Plan | | |
| PEPFAR | the United States President's Emergency Plan for AIDS Relief | | |
| PHC | primary healthcare | | |
| POC | point of care | | |
| PQ | prequalification | | |
| PrEP | pre-exposure prophylaxis | | |
| RDT | rapid diagnostic test | | |

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EXECUTIVE SUMMARY

All indications suggest that South Africa's sexually transmitted infection (STI) burden is among the highest in the world. However, nationally representative data are incomplete or based on limited sampling; therefore, estimates rely on assumptions and expert opinion, as opposed to a strong body of evidence. South Africa also has a high burden of communicable and non-communicable diseases, including the highest HIV burden and the most extensive HIV treatment programme in the world. Increasingly, adolescent girls and young women are the focus of the country's national HIV programme. Researchers are also documenting the substantial asymptomatic burden of STIs in South Africa, especially in younger populations.

When ill, 71% of South Africans seek care in the public sector, although private general practitioners are commonly attended by both the insured and non-insured. STI care is integrated into primary healthcare and thus highly decentralized. South Africa has a large and highly centralized laboratory network serving the public sector, the National Health Laboratory Services (NHLS). An Essential Laboratory List guides test availability, and a handful of rapid diagnostic tests (RDTs) are performed on-site at the primary healthcare level (e.g. HIV, haemoglobin, and malaria RDTs, with demand for other tests met by central laboratories. The National Institute for Communicable Diseases (NICD) is a public health laboratory that performs regular *Neisseria gonorrhoeae* (NG) drug resistance surveillance and etiological studies to validate South Africa's STI syndromic management guidelines.

South Africa's STI response is guided by the National Strategic Plan for HIV, TB and STIs 2017–2022. Although the strategy aligns with WHO's global strategy for the same diseases, it is largely unfunded due to insufficient resources for healthcare and STIs in particular.

South Africa has an active antimicrobial resistance (AMR) response, anchored in the Essential Medicines Department of the National Department of Health

(NDoH) and advised by a multisectoral Ministerial Advisory Committee (MAC). To date, the MAC's efforts related to human health have focused on antibiotic stewardship at the hospital level.

With respect to STIs, household surveys indicate that 60 to 70% of patients seek care when experiencing symptoms; however, expert estimates are lower, suggesting 60% of men and 40% of women seek care for STI symptoms. While the public sector is overwhelmingly the first point of contact for most illnesses, there is reason to assume that, given privacy concerns, some proportion of individuals with a symptomatic STI might turn to the private sector; however, no recent data on private-sector care-seeking for STIs are currently available.

South Africa uses the syndromic approach to STI management and reviews the guidelines regularly. Although these guidelines recommend routinely asking STI screening questions and performing speculum examinations, healthcare worker workloads, space constraints, lack of equipment, and cultural restraints may prevent consistent implementation.

Surveillance activities include case reporting from clinics (reportedly incomplete and not accessed for this report), sentinel site reporting, and periodic microbiological studies validating syndromic management. The last of these activities has raised concerns about the limitations of syndromic management of women with vaginal discharge. A 2017 NICD study of 315 men presenting with male urethritis syndrome (MUS) did not identify any resistance to extended-spectrum cephalosporins, supporting the currently recommended treatments. The study did recommend enhanced surveillance, particularly among men who have sex with men (MSM) populations.

While there is a strong imperative for change in STI management, the path forward is unclear. Data on high rates of untreated, asymptomatic STIs continue to emerge and, in ethical terms, a response

focusing on the asymptomatic burden is likely. The case is perhaps stronger in South Africa than in other countries, given the HIV burden and the desire to prevent further HIV infections by reducing any potential transmission risk caused by STI-related inflammation. While South African experts acknowledge the many limitations of syndromic management, especially in women, it is not clear whether a shift to full etiological testing can be made in the near term, given limited resources and other priorities. Typically, South Africa looks to WHO guidance, cost-effectiveness modelling, and local pilot programmes to inform these decisions.

Interview and survey results suggest that South Africans prefer an optimal test, capable of detecting asymptomatic infection, although the target prices for the minimal test are more acceptable. At scale, however, even the minimal test price (US\$ 3) exceeds what is affordable without external funding or emergence of resistance to the current first-line treatment.

There is no consensus around replacing syndromic management, and its major limitation in the eyes of many is not overtreatment but missing cases. The investment case for testing in lieu of syndromic management is difficult to make with today's treatment prices, with first-line treatments being less expensive than the proposed TPP1 Minimal test price. There may be scope for testing in women only, given the etiological data on the diverse causes of vaginal discharge syndrome (VDS), especially if there is the potential to detect more infections.

The picture will certainly change if resistance to first-line treatments begins to emerge in NG, as the NDoH is quite engaged in antimicrobial resistance, and the first-line treatment for NG, ceftriaxone, is an important medicine commonly used for pre-referral and in-hospital treatments. However, even if resistance did begin to emerge, budget constraints mean that testing might initially be reserved for individuals who return with persistent symptoms or will only be adopted when NDoH is forced to switch to a more expensive first-line treatment (when these become available).

FIND is supporting the development of a *Neisseria gonorrhoea/Chlamydia trachomatis* (NG/CT) point-of-care (POC) test and carried out interviews with

relevant stakeholders. Interviewees suggested many potential use cases for the optimal NG/CT POC test (TPP1 Optimal), including screening sex workers, MSM, adolescents and young women, pregnant women, pre-exposure prophylaxis (PrEP) enrollees, and those attending HIV testing sites. Currently, NDoH and partners are working to mobilize funding to pilot STI testing in PrEP sites.

Perhaps uniquely to South Africa, any new POC test would need to compete with central laboratory testing, as well as near-patient platforms such as GeneXpert. The adoption of any new NG/CT POC test will heavily depend on how NDoH weighs the risk of loss to follow-up and the impact of having an immediate result on the epidemic, i.e. through expedited partner therapy, which researchers are currently trialing.

Although the market presents several challenges (e.g. low priority of replacing syndromic management with etiological management, and competition from central laboratory and near-patient tests), given the high burden of STIs in South Africa, the public health impact of testing could be quite compelling, and is therefore worth further engagement in this market. There is also a strong interest from leading clinicians and NDoH in implementing STI diagnostic testing in the country. The challenge is to mobilize sufficient resources and prioritize various target populations and indications for use. Additional evidence will be necessary to address key questions about the most effective interventions and policies.

OBJECTIVES AND METHODS

In 2016, there were an estimated 87 million new cases of gonorrhoea globally. *Neisseria gonorrhoeae* (NG) has developed resistance to most available antibiotics, and in 2018 the first case of extensively drug-resistant (XDR) NG was reported. In low resource settings, providers generally use the WHO syndromic approach for managing symptomatic patients, which leads to both under- and overtreatment. To enable etiological case management, the Foundation for Innovative New Diagnostics (FIND) is supporting the development of a *Neisseria gonorrhoeae/Chlamydia trachomatis* (NG/CT) point-of-care (POC) test.

In early 2019, FIND completed a high-level market assessment to size and understand the potential market for such tests. Despite the considerable need for testing (i.e. a high number of people eligible for NG testing), there was significant uncertainty around the level of actual demand for a new test, as well as concerns around many potential barriers to access. As a result, FIND has undertaken a more in-depth market assessment in selected countries.

This report summarizes the results from market research in South Africa, specifically considering the areas listed in Table 1.

Table 1: Market research areas of focus

| Market | |
|--|--|
| Key use scenarios for the TPP | For the given TPP, what are the use scenarios and market segments that are likely to exhibit the highest demand or be prioritized most by MoH in terms of public health? |
| Financing, elasticity of demand and WTP | <ul style="list-style-type: none"> ▶ What is the financing strategy for key market segments/use scenarios? <ul style="list-style-type: none"> + For the public sector, given the TPP test price, what are the likely volumes for each use scenario and how could these be funded? How can the investment case be made? + What is the WTP for the public sector self-paying and the private sector? |
| Policy and advocacy | <ul style="list-style-type: none"> + Local stakeholder landscape. Identify the key actors in the country related to these priority segments/ use scenarios (STI and AMR sectors, researchers, donors, NGOs, other partners, private associations, private clinics and laboratory networks. + For each of the major stakeholders, what is the value proposition? How does a test add value? + Given this, what evidence, validation and evaluation processes are needed to support adoption? |
| Testing practices | <ul style="list-style-type: none"> + Understand existing testing practices, use cases, care-seeking behaviour, access to testing. + Provider adherence to current guidelines. + Current practice vs. future practice with a new test – map out what may need to change with the introduction of a new test. |
| Launch tactics | |
| Regulatory considerations | <ul style="list-style-type: none"> + Will the new test require WHO PQ, does the test fit the WHO testing and PQ process? + Is the test compatible with international guidelines? + Will the new test require changes in national guidelines? + Are national market authorization processes complex? |
| Test selection and procurement | <ul style="list-style-type: none"> + Public: how is test selection and procurement likely to be done? Is there a need for a local distributor/ agent presence and if so, what role will they play? + Private: how is test selection done? |
| Distribution | <ul style="list-style-type: none"> + Public: how does the distribution function? + Private: what options exist for product distribution (for manufacturing without local presence)? Who are the key diagnostics distributors? |
| Training and communication | <ul style="list-style-type: none"> + What training is required for healthcare workers to support the introduction and uptake of a new test? + What past training has been conducted for healthcare workers around STIs or AMR? + What community sensitization is being performed to increase care-seeking behaviour for STIs? + What community sensitization is being performed to increase awareness of AMR? + What is needed to support the introduction of new tests? |

TPP, target product profile; MoH, Ministry of Health; WTP, willingness to pay; STI, sexually transmitted infection; AMR, antimicrobial resistance; NGO, non-governmental organization; WHO-PQ, World Health Organization prequalification



Ultimately, the insights provided by this market research will inform product development, support the shift from syndromic management to etiological testing and overall assist the launch strategy of new diagnostic tests in LMICs.

The methods included:

- ▶ An extensive desk review of reports, including strategic sexually transmitted infection (STI) and antimicrobial resistance (AMR) documents and selected literature on STIs, HIV and AMR in South Africa.
- ▶ A review and analysis of relevant data, including STI incidence estimates, etiological and resistance survey data, and recent household survey data.
- ▶ A May 2019 site visit to an urban primary care clinic and participation in a workshop on the positioning of new antibiotics for NG.

- ▶ Fourteen interviews with experts, conducted between March and September 2019, both in person and over the phone. Interviewees included South Africans involved in providing care, conducting research (into STIs, HIV and/or AMR), surveillance, or modelling, and working for National Department of Health (NDoH).
- ▶ Responses from South African stakeholders who participated in a global online survey about access to NG testing were analysed. Six of the ten respondents were among the experts interviewed. The other four survey respondents included representatives from the WHO local office, the national lab, and academia.

The work for this report was completed during the second half of 2019, except for the online survey which was conducted during the first quarter of 2020.

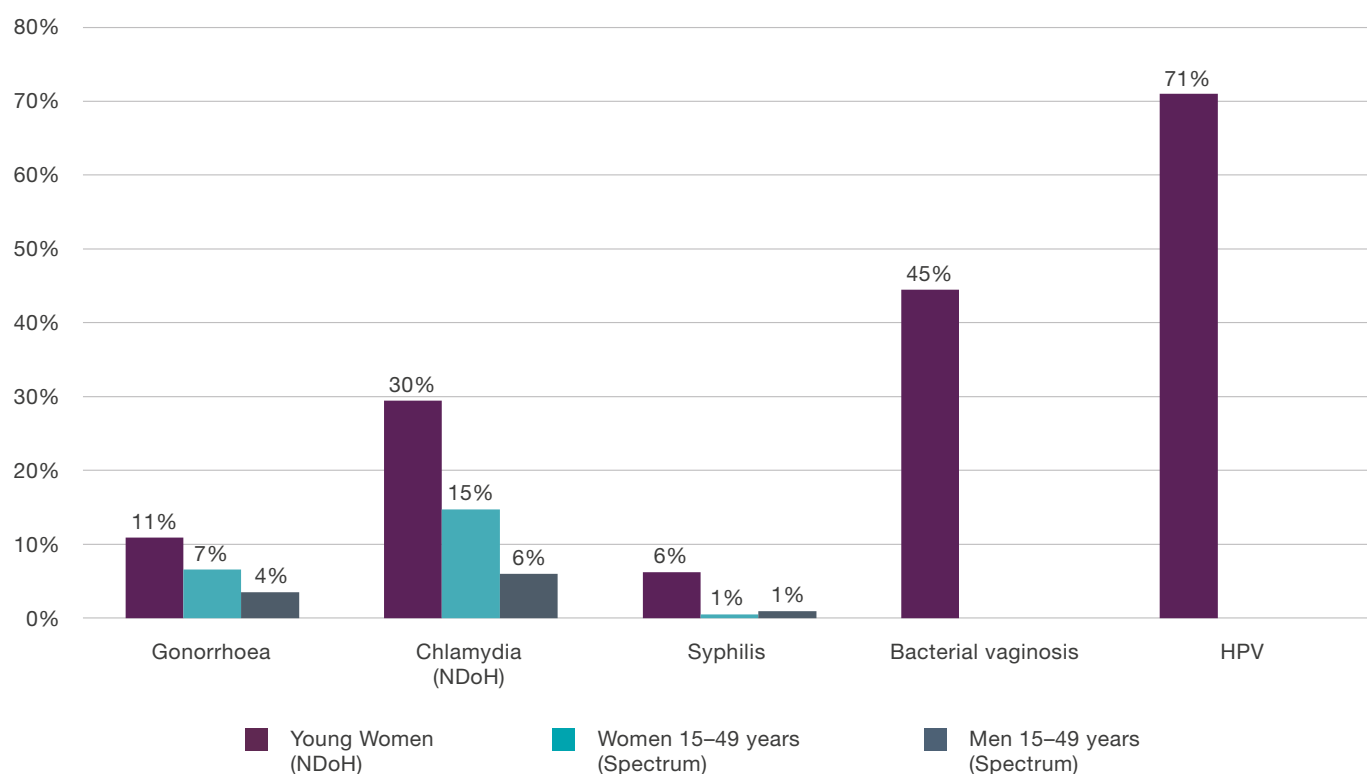


Source: FIND/Ashraf Hendricks

BURDEN AND EPIDEMIOLOGY OF GONORRHOEA AND OTHER STIs

By all estimates, the prevalence of STIs in South Africa is among the highest in the world. That said, there are limited nationally representative epidemiological data on STIs, and the various estimates are not aligned (Figure 1). In 2018, NG, CT and syphilis incidence estimates were developed using the Spectrum model¹; these estimates suggested there are more than 10 million episodes per year of NG and CT in South Africa.

Figure 1: South Africa STI prevalence



Sources: SANAC.² Kularatne et al³

Table 2: Estimated incident case numbers (2017, ages 15–49)

| STI | Women | Men | Total |
|-------------------|-------------|--------------|-------------|
| Gonorrhoea | 2.3 million | 2.21 million | 4.5 million |
| Chlamydia | 1.9 million | 3.87 million | 5.8 million |

Source: Kularatne et al.

These incidence numbers should be interpreted with caution: there is an enormous discrepancy in the Spectrum model estimates of cases treated and reported by the NDoH.

For example:

- ▶ Spectrum estimates that 2.1 million NG and CT cases are treated each year in South Africa. The NDoH indicates that 1.4 million new STIs (including NG/CT and other STIs) were treated in populations older than 15 years, in 2015/2016⁴. The difference between the two estimates suggests substantial underreporting by public sector facilities as well as high care-seeking rates in the private sector; these rates do not align with the household survey data (described below).
- ▶ In men, Spectrum estimates that 1.1 to 3.2 million cases of male urethritis syndrome (MUS) present for care annually; however, during 2017 there were only 310 000 MUS cases reported by clinics.

The Spectrum study authors suggest that the missing cases either i) present for care but are not treated, ii) are treated in the public sector but not reported, or iii) are treated in the private/informal sector but not reported. While it is likely that case reporting could be strengthened, there is also scope for improving the model inputs, e.g. gathering more representative data and improving the assumptions made where there are no data.

Despite these limitations, the available data suggest an extremely high STI burden, with many asymptomatic and untreated infections, and little change in NG/CT prevalence despite investments in HIV/STI prevention and treatment⁵. During the interviews with experts, many experiences and data points from recent studies (often unpublished) were shared, confirming South Africa's "alarmingly high" STI burden⁶. The experts also emphasized the burden of asymptomatic STIs, especially in women.

Broader epidemiological context

Epidemiologically, South Africa has high burdens of HIV and tuberculosis, high maternal, neonatal and child morbidity and mortality, an increasing growing burden of non-communicable disease, and high levels of violence and trauma. Of relevance to NG testing is sexually transmitted HIV. South Africa has both the greatest HIV burden and the largest antiretroviral treatment programme in the world. In 2018, 7.7 million people in South Africa were living with HIV, approximately 19.1% of the adult population (ages 15–49), with 4.4 million people receiving treatment.

Many of the factors contributing to the high burden of HIV are equally relevant to STIs. Early sexual debut, engaging in risky sexual behaviour, concurrent sexual partnerships, cyclical intergenerational sex, and inadequate condom use drive ongoing sexual transmission of HIV⁷.

The South African National Aids Council (SANAC) has outlined the following key and vulnerable populations for HIV and STIs⁸:

- ▶ Sex workers. In 2016, the government launched its first national approach for reaching sex workers.
- ▶ Men who have sex with men (MSM). In 2017, the government released the first lesbian, gay, bisexual and transgender HIV strategy, which also included the transgender population.
- ▶ People who inject drugs are identified as an at-risk population, but little else is known about them.
- ▶ Children and orphans are a vulnerable group. Prevention of maternal HIV transmission has decreased infections in children, but more than 2 million orphans remain vulnerable to HIV and STIs.
- ▶ Currently, adolescent girls and young women represent a disproportionate number of new HIV infections each year, and the NDoH has prioritized this group. Contributing factors include gender-based violence, poverty, and the low status of women. Partner age differences are common and help drive the infection, i.e. very young women become infected by male partners who are several years their senior.

South Africa is rolling out pre-exposure prophylaxis (PrEP) and has around 45,000 PrEP users. Nine projects have been completed, while there are six ongoing and two planned PrEP demonstration and implementation projects¹⁰. The NDoH has plans for approximately 200 sites in the next five years, and rollout priorities were informed by cost-effectiveness analysis and advocacy. Most PrEP studies have focused on adolescent girls and young women, followed by a few studies investigating MSM, sex workers and adolescent men. Generally, interviewees report slow uptake and retention challenges.

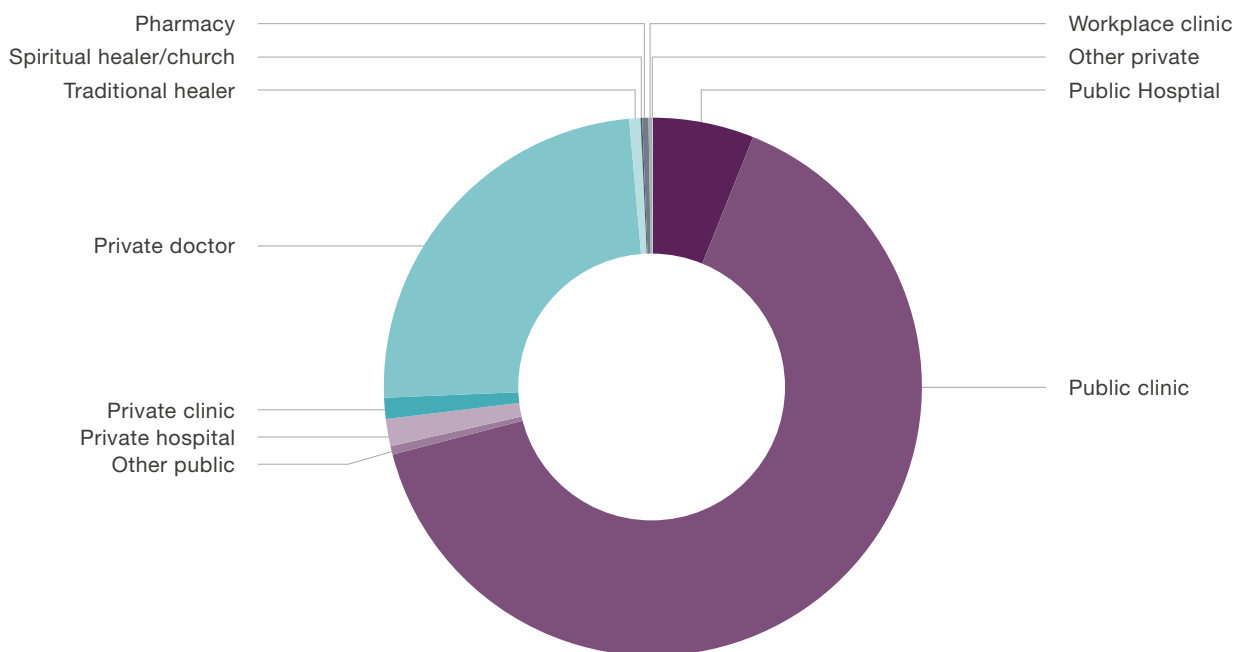
STRUCTURE OF HEALTHCARE

The unequal distribution of funding, access, infrastructure, and human resources characterizes South Africa's health sector. Healthcare is highly concentrated in urban areas, despite a sizable rural population. While only 16% to 17% of the population is insured, the private sector consumes about half of the country's health spending¹¹.

A variety of outlets provide healthcare; however,

public health clinics (65%), followed by private general practitioners (24%), are the most common first points of contact for illness or injury (Figure 2)¹². Those with insurance tend to seek care in the private sector,¹³ and comparing the percentage covered by insurance (16–17%) with the overall rates of care-seeking in the private sector (29%) suggests that approximately 12% of the population pay out of pocket for private care.

Figure 2: Households' usual place of consultation for illness or injury, 2018



Source: *General household survey, 2018*

Public sector

Overall, 71% of households first seek care in the public sector, mainly at clinics. Since 1994, South Africa's health system has been very primary care focused, supported by policies such as the 2010 national re-engineering strategy for primary care and the 2013 Ideal Clinic initiative, which have comprehensively improved the quality of primary care through a focus on staffing, infrastructure and resources. Ongoing work on a National Health Insurance Scheme also includes a heavy emphasis on strengthening primary healthcare.

Nurses form the backbone of public sector primary care, as South Africa has relatively few doctors compared with other upper middle-income countries. Care is provided in an integrated, "one-stop-shop" manner. Although a few specialty clinics serve key populations, STI care is generally integrated into primary care and thus highly decentralized. During the last two decades, HIV care and treatment have been a high priority, and South Africa has decentralized antiretroviral therapy (ART) to the primary care level through nurse-initiated management¹⁴.

The NDoH is responsible for developing national health policies and setting standards, as well as monitoring the performance of health services across different provinces. Within the NDoH, there is an STI programme manager (post currently vacant) and an AMR focal point; these roles are further described in the next section.

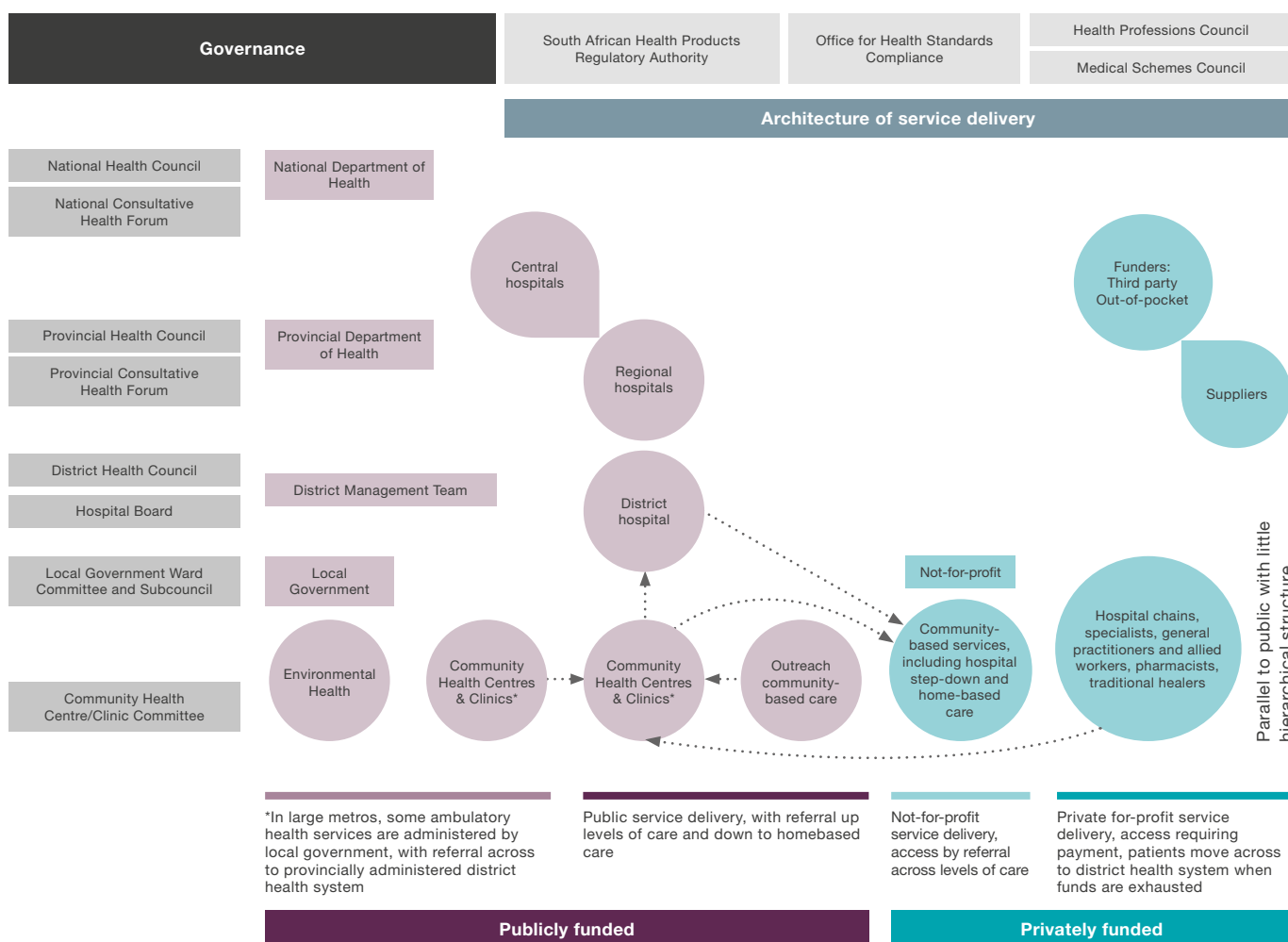
Nine provincial departments of health are responsible for healthcare delivery, including the management of provincial health budgets. Provinces decide how much of their budget to allocate to healthcare. They develop local policy aligned with national policy, run health facilities and employ healthcare workers. They are also responsible for rolling out new initiatives. Provinces oversee the three tiers of hospitals (tertiary, regional, and district) as well as the country's 3500 primary health clinics and mobile clinics.

Primary health clinics are usually the first point of contact for patients and are mostly staffed by

nurses and a growing number of lay workers, largely supporting HIV programmes, with doctors playing a supportive role. In 2015, there were 120 million visits to primary healthcare (PHC) facilities (2.2 per capita)¹⁵. In some of the larger cities, the municipal government runs clinics, which refer patients to the provincial hospitals.

Going forward, the South African government seeks to address the inequities in the health system in the private and public health sectors through a major health reform, i.e. the implementation of National Health Insurance (NHI). The NHI development process has been ongoing for several years and proposes a central insurance scheme, with contributions based on income¹⁶. All South Africans would have access to a package of services delivered by the public and private facilities. The plan would be implemented over several years, although there are concerns about costs, services included in the basic packages of services, and quality of care.

Figure 3: Governance and architecture of South Africa's health system



National STI response

At a high level, South Africa's STI response is guided by the fourth National Strategic Plan (NSP) for HIV, TB and STIs (2017-2022), developed by SANAC¹⁷. Previous NSPs focused on HIV and TB; however, the current plan includes STIs in light of their "seriousness as a public health problem and a risk factor for HIV."¹⁸ The NSP contains several targets for STIs, although these are less detailed and actionable than the targets for HIV and TB.

While the NSP envisions broad access to HIV, TB and STI care, it also recommends a data-driven approach to intensifying services in high-burden districts,¹⁹ as well as a sharper focus on adolescent girls and young women and key and vulnerable populations. Additionally, PrEP is directed to those who are most likely to benefit, including adolescents, sex workers, MSM, and people who inject drugs.

A review of the STI strategy (2017-2022)²⁰ suggested several critical national-level priorities for STIs. However, because this strategy is not fully funded, the priorities described below are included here as an indication of the vision for STIs and the initiatives the NDoH would like to pursue, rather than as a set of activities that are being fully implemented²¹.

The STI strategy includes the following:

Asymptomatic infections. The strategy emphasizes the challenge posed by a high burden of asymptomatic infections, and the proposed response involves the development and implementation of a sexual history screening tool, followed by either targeted etiological testing or presumptive treatment. Specifically, the strategy says:

Detect and manage asymptomatic STIs. *This is vital as so many STIs are asymptomatic. The starting point is to take a concise STI (sexual) history to screen if the client is at risk of an asymptomatic STI, and if so, do etiological testing. If this is not yet available at a particular clinic, presumptive treatment should be given. This service should be integrated with existing systems, such as MSM-friendly clinics, ART and ANC*

clinics, FSW programmes, contraceptive services, sexual assault services and through pre-exposure prophylaxis programmes and post-exposure prophylaxis (PEP) services. The screening history tool will also be used at community level through peer outreach or ward-based outreach teams, who will then refer at-risk clients for further assessment or presumptive treatment.

Increase laboratory support and use of POC testing methods for common STIs. *The ability to shift over time from presumptive treatment based on concise sexual histories to more accurate targeted screening for asymptomatic STI infections requires increased laboratory capacity, building on the current platforms for molecular testing. In addition, rapid POC kits, such as the dual gonococcus and chlamydia kit, will need to be introduced to improve screening as the evidence of their validity and viability emerges²².*

Increasing coverage of STIs through integration. The national STI strategy includes a target of increasing the number of STIs identified and treated by 40% in patients attending medical male circumcision, ART, HIV testing, and reproductive health services clinics. This will be done through training healthcare workers to recognize symptoms and perform clinical examinations of genital and extragenital sites.

Saturation coverage for high transmitters. Inadequate healthcare coverage of sex workers and MSM is a challenge, as well as a need to focus on "high transmitters" (despite the lack of surveillance data to identify them). The concept of "saturation coverage" of services in these populations is proposed, with an expectation of reduced transmission in the general population.

Strengthen management of persistent or complicated STIs. Although there are few data on the number of patients who do not respond to the current syndromic approach, it is a concern, and there are plans to strengthen care

for patients who return to clinic, including the need for etiological testing and for referral. At the secondary level, there are plans for testing and improved care.

Surveillance for NG resistance. Resistant gonorrhoea is identified as “an emergency,” and ongoing surveillance will be pursued.

Overall, and in line with WHO global strategy, South Africa’s STI targets include a 70% reduction in priority STIs, including gonorrhoea and syphilis; elimination of congenital syphilis; and 90% human

papillomavirus (HPV) vaccination coverage. Notably, the STI strategy outlines several diagnostic test targets, including: i) validating and introducing two POC tests for key STIs²³, ii) increasing by 40% the number of NHLS laboratories testing for STIs, and iii) increasing by 40% the number of pregnant women and key populations screened for asymptomatic infections. The strategy mentions POC tests for syphilis/HIV and NG/CT but provides no specific details. The STI strategy includes many ambitious targets and activities; however, the programme is not fully funded and few of these activities are being carried out.

National AMR response

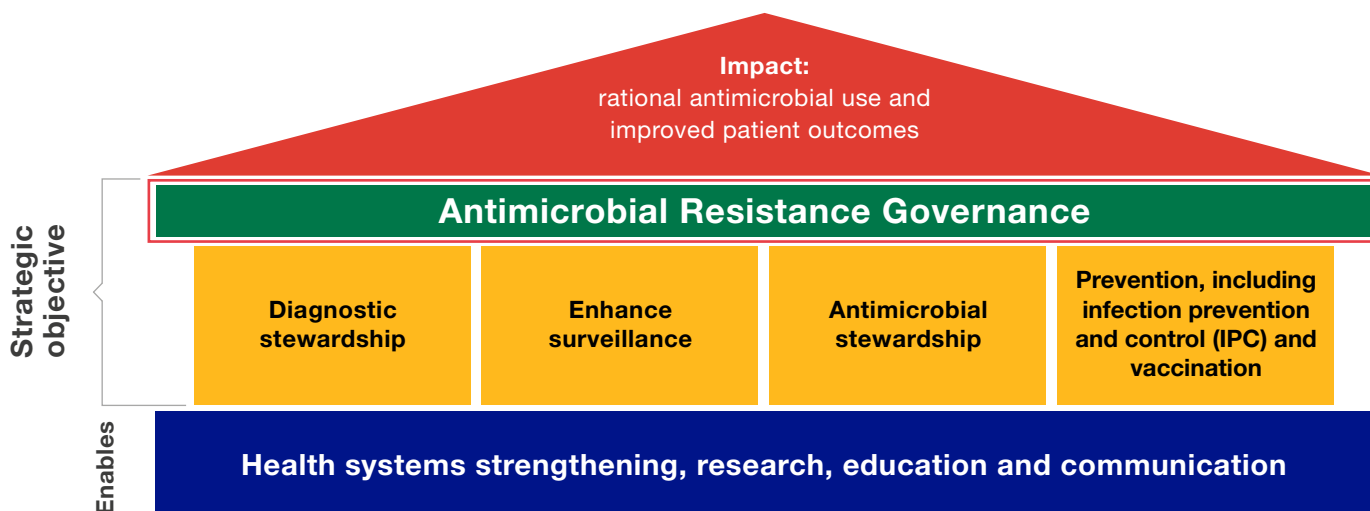
The level of use of antimicrobials in South Africa is high, similar to that of other major emerging economies, where access to antibiotics has increased through improvements in health systems²⁴. In recognition of the increasing threat posed by AMR, South Africa has developed an AMR strategy and its implementation is underway.

In 2011, and initially supported by the Center for Disease Dynamics and Economic Policy, a comprehensive AMR Situation Analysis was published in a local medical journal. This led to the creation of the South African Antimicrobial Stewardship Programme (SAASP), a working group of the regional infectious disease society²⁵. SAASP plays a role in antibiotic stewardship (ABS), training and awareness-raising (e.g. advocating for mandatory continuing professional

development on ABS); harmonizing and developing guidelines; liaising with the NDoH; and developing recommendations for interventions. It has developed a free online course and pocket guidelines for prescribers, and its 2018 annual meeting focused on the pivotal role that nurses play in ABS²⁶.

In 2014, the NDoH launched the National AMR Strategy Framework, a high-level outline for a “One Health” approach, encompassing multiple sectors. Notably, a diagnostic stewardship pillar, led by the NHLS, was added to the framework in 2015 to “ensure appropriate use of microbial diagnostics to identify pathogens and to guide therapeutic decision.” (Figure 4). In 2017, a plan was developed, followed by guidelines, for implementing the AMR strategy.

Figure 4: National AMR strategy framework



Within the NDoH, the pharmacy section has championed antibiotic stewardship. The Affordable Medicines Directorate, specifically the Essential Drugs Programme, is the focal point responsible for the implementation of the AMR strategy and serves as the secretarial and coordination point for the work of the Ministerial Advisory Committee (MAC) on AMR (Figure 5).

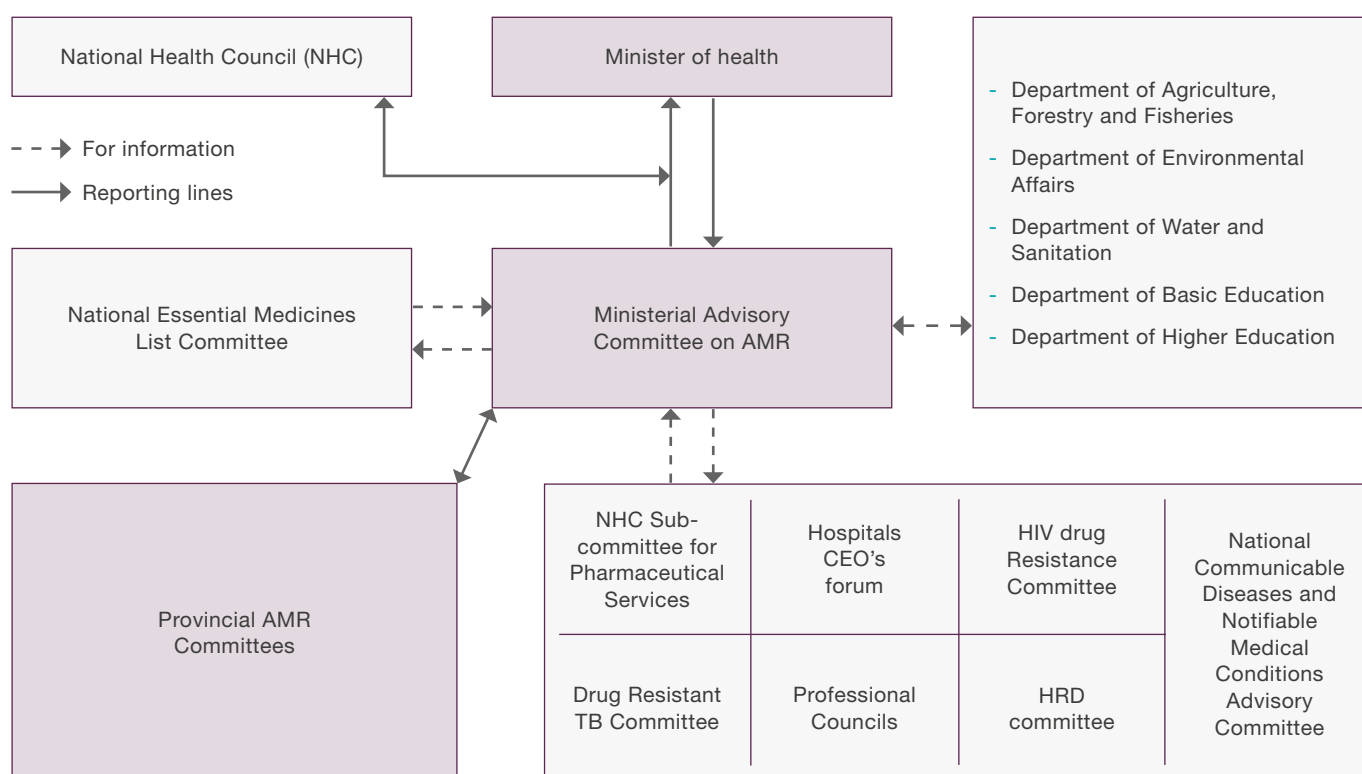
The MAC comprises 20 to 25 multidisciplinary, intersectoral members, reporting to the Minister of Health. The remit of the MAC is broad and includes advising on stewardship at all levels of the health system; advising on surveillance and reporting systems for antibiotic resistance and use; providing recommendations to the Essential Medicines List Committee; ensuring access to appropriate diagnostic tests and national guidance on their use; reviewing progress on AMR initiatives; developing national ABS guidelines, treatment algorithms, communications and advocacy campaigns; developing core curricula for health professionals and providing oversight of national and regional training course delivery; and advising on research.

To date, the MAC has primarily focused on establishing ABS programmes at the hospital

level. Work at the primary care level will likely first focus on conditions that drive antibiotic use, such as respiratory and urinary tract infections. Replacing syndromic management of STIs with etiological testing, even for NG, was not necessarily “on the MAC’s radar,” due to relatively low perceived levels of antibiotic use to treat STIs. However, if the NDoH were considering a new antibiotic, or if drug resistance to first-line treatment were to emerge, the MAC would likely advise the essential drugs group at NDoH, bringing in STI experts as well.

Within the NDoH, the pharmacy section coordinates regular reviews and publishes the Primary Health Care Standard Treatment Guidelines and Essential Medicines List²⁷. Most provinces adopt the “Adult Primary Care” algorithms or the Practical Approach to Care Kit guide, which are a set of flow charts based on the national guidelines and Essential Medicines List for providers at the primary level²⁸. One expert who is working with the guidelines and medicines committees indicated that antibiotic stewardship at PHC level is “front of mind” at the NDoH pharmacy division, citing an ongoing debate over the need to make pre-referred antibiotic treatments available for certain conditions.

Figure 5: Communication channels for the ministerial advisory committee on AMR



Source: *Guidelines on the Implementation of Antimicrobial Stewardship in South Africa: One Health Approach and Governance*

National health laboratory services

The National Health Laboratory Services (NHLS) provides laboratory services for the public sector, through a network of 268 laboratories based at hospitals²⁹ and linked through a single laboratory information system. The NHLS is designed to be a self-funding body, raising funds from provincial health departments for the tests performed. The HIV and TB epidemics require unprecedented volumes of testing and are a central mandate of the NHLS. Testing for these infections is managed by the National Priority Programmes of the NHLS. HIV testing is highly centralized in 16 laboratories, which perform viral load and early infant diagnosis, and 52 laboratories that perform CD4 testing. TB testing is more decentralized, with 207 laboratories equipped with GeneXpert, conducting approximately 2.5 million tests/year³⁰.

An essential laboratory list, the Primary Health Care Essential Laboratory List³¹, defines testing carried

out at PHCs. Only five tests are performed at these health facilities (haemoglobin, HIV, glucose, malaria RDT, and Rhesus factor). For most tests, samples are collected at PHCs and sent to NHLS laboratories by courier, with estimated turnaround times of 24 hours for most tests. Syphilis serology is among the tests that are sent out to NHLS laboratories. Most test results are returned in a printed format by the courier, although SMS printing is possible for HIV/TB results, as is online or telephonic access. For the rapid tests used at primary level, interviewees explained that the role of the NHLS is limited to initial validation and assessment.

The National Institute for Communicable Diseases (NICD) is a division of the NHLS. It is a public health-oriented entity, rather than a clinical diagnostic entity. For STIs, the NICD conducts regular etiological studies and NG resistance surveillance, described below.

Private sector

A largely insurance-based private sector serves high earners in South Africa. In 2018, 16% of the population (9.4 million) were covered by medical insurance, with higher concentrations among whites and people living in the largest metro areas³². The insurance market is highly fragmented, with >80 medical schemes. Private sector care is mostly concentrated in urban and wealthy areas.

Of the five private sector delivery channels (Figure 6), most comprise independent, private practice. There were approximately 8000 general practitioners (GPs) in private practice in 2014³³; these GPs are regulated by the Health Professions Council of South Africa. Most are paid using a fee for service model. There is no readily available information about GPs, the quality of their services, or their fees.

No information was available as to the extent of POC testing in GP offices, although one interviewee

suggested this would be a potential market for POC STI tests, while another indicated that the medical aid schemes do not reimburse POC tests. The three largest private pathology practices in South Africa are Ampath, PathCare and Lancet, collectively comprising about 90% of the market; they provide diagnostic services to private providers³⁴.

Traditional healers also play a role in South Africa, although estimates of the number of practitioners (200,000–300,000) and care-seeking rates vary³⁵. In the 2018 general health survey, only 1% of respondents reported first seeking care from traditional healers; however, many people likely consult traditional healers before or in parallel with conventional medicine and may withhold this information. No data were found on the role traditional healers might play in treating STIs. However, given linkages to sexual health and fertility, this role may be greater than what is reported.

Figure 6: Private sector delivery channels

| | Description | Key Organizations |
|--|--|---|
| Commercial facilities | <ul style="list-style-type: none"> ▶ Private for-profit facilities including clinics and private hospitals ▶ While the majority of commercial facilities are small and independent, private hospitals are largely part of three hospital groups that account for ~75% of the market | <ul style="list-style-type: none"> ▶ Hospitals Association of South Africa ▶ Three largest hospital groups: Netcare, Life Healthcare, Mediclinic |
| NGO clinics / social franchises | <ul style="list-style-type: none"> ▶ Private not-for-profit facilities owned / funded by local organizations or international donors, including clinics owned by NGOs and social franchises ▶ Several major social franchise networks dedicated to SRH (PSI, Marie Stopes and Society for Family Health) | <ul style="list-style-type: none"> ▶ PSI ▶ Society for Family Health ▶ Marie Stopes ▶ Broadreach healthcare ▶ Unjani Clinics |
| Private doctors | <ul style="list-style-type: none"> ▶ For-profit doctors who manage independent practices, or practice in either public or private hospitals ▶ While 70% of doctors practice in the private sector, they are mostly self-employed and clinics and hospitals have little oversight over them | <ul style="list-style-type: none"> ▶ South African Medical Association ▶ South African Private Practitioners Forum ▶ Southern African HIV Clinicians Society ▶ Pulse Health Solutions |
| Pharmacies | <ul style="list-style-type: none"> ▶ Private facilities in which individuals can purchase medicine, which may or may not be managed by a trained healthcare worker ▶ Approximately 20% of pharmacies have on-site clinics in which healthcare workers can administer care | <ul style="list-style-type: none"> ▶ SA Pharmacy Council ▶ SA Pharmaceutical Association ▶ Dis-chem |
| Higher education institutions | <ul style="list-style-type: none"> ▶ Health facilities and services at universities and TVET colleges managed by non-governmental or non-healthcare institutions ▶ National strategic plan for HIV recognizes schools and universities as critical environments to reach AGYW | <ul style="list-style-type: none"> ▶ HEAIDs ▶ SheConquers Campaign ▶ APPETD |

Source: Options analysis, 2017.

CURRENT STI MANAGEMENT

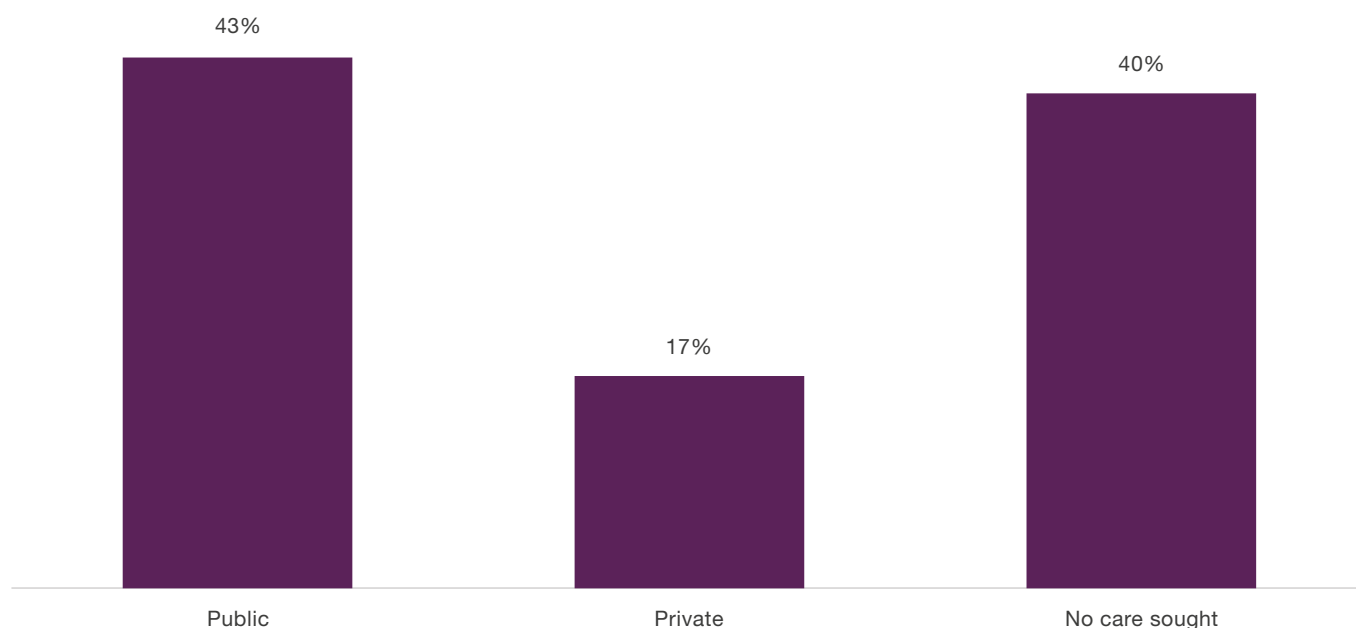
STI care-seeking and access to care

A National Health Facility Audit in 2011/12 assessed nearly 3500 public PHC facilities and found a high (94%) availability of STI services. However, access to services also depends on care-seeking behaviour. The 2018 General Household Survey³⁶ inquired about care-seeking behaviour among people who were ill (with any condition) during one month. Overall, 60% of those who had been ill had sought care (Figure 7). The 2016 Demographic and Health Survey (DHS)³⁷ asked men and women ($n = 183$ and 855 , respectively) who reported having an STI or symptoms of an STI in the past year if they sought care. Overall, 70% of women and 64% of men with self-reported STIs did seek advice or treatment (Figure 8).

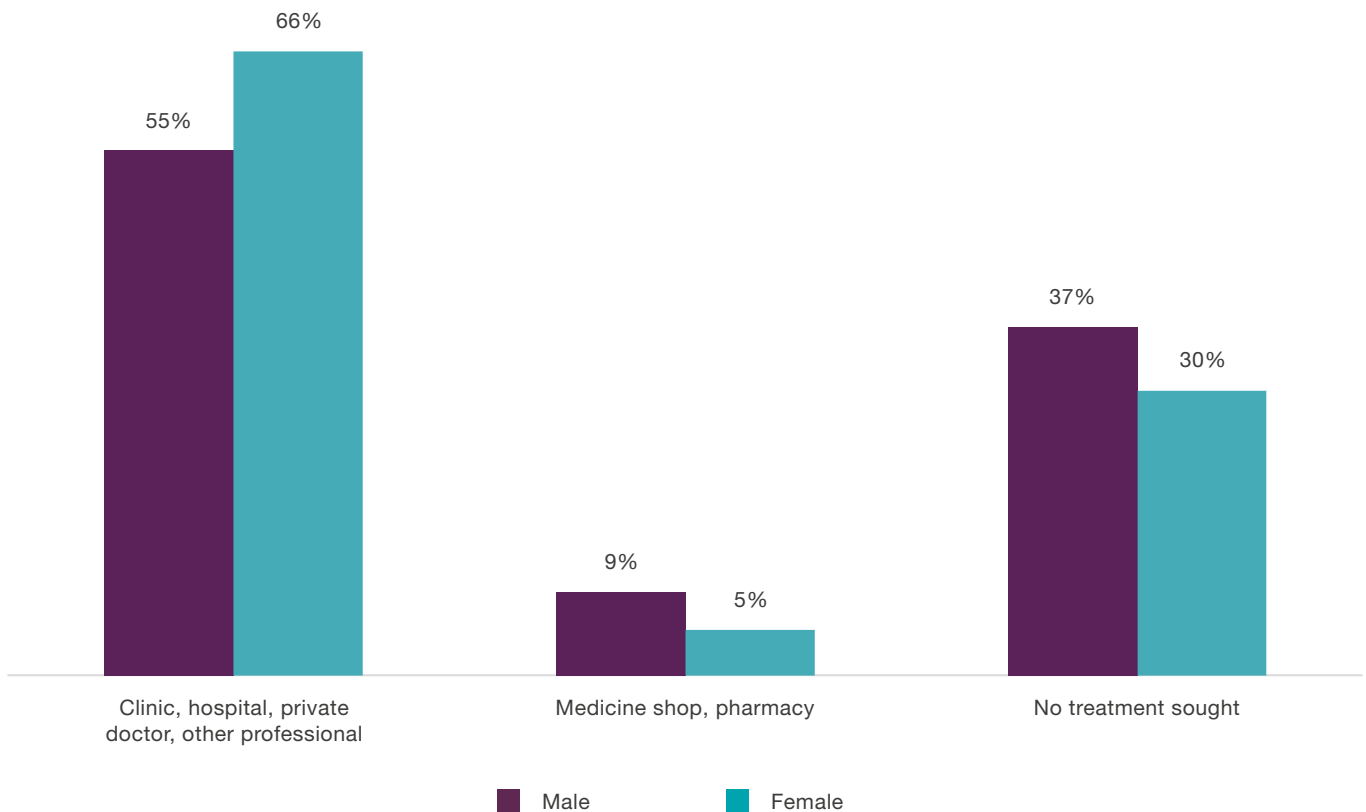
Notably, the DHS data on self-reported STIs show higher care-seeking rates, especially for women, than reported in the past or by other publications. For example, the current STI strategy cites a study performed in a rural South African district 20 years ago, which suggested that 98% of women

with STI symptoms did not seek care³⁸. Experts tend to consider that awareness of symptoms and care-seeking rates have improved in recent years; however, not everyone agrees with the DHS data. For example, for the 2018 STI Spectrum modelling exercise, local experts suggested the following assumptions: 60% treatment rates among symptomatic men in South Africa, and 40% treatment rates among symptomatic women³⁹. While these rates are higher than assumptions made for other African countries, they are not as high as the local DHS data for women. A recent study from a rural area found that one third of women had STI symptoms, but were not seeking care⁴⁰. Reasons for not seeking care among women included limited awareness of symptoms, embarrassment and fear of the reaction of clinic staff, and disappointment with previous treatment (i.e. recurrent or persistent symptoms). Among men, reasons for not seeking care included a lack of male staff and dissatisfaction with previous experience.

Figure 7: Percentage of people who were ill during one month and who sought care, by sector



Source: *General Household Survey data, 2018*

Figure 8: Percentage of men and women with an sti or symptoms

Source: DHS Survey 2016

There is reason to believe that, due to stigma, the role of the private sector in STI care may be more significant than that of the public sector, especially among those who can afford to pay, and among men, who generally have less reason for contact with public health services than women. As previously described, household surveys have shown that when they seek care for illness, 29% of South Africans turn to the private sector. Those with insurance prefer the private sector and a non-trivial number of uninsured individuals pay out of pocket for private sector care. An STI is an acute condition that can often be easily treated in a single visit; therefore, it would not be surprising if care-seeking in the private sector might be higher for STIs than for other common illnesses. Unfortunately, there are no recent statistics on private sector care-seeking behaviour for STIs, only studies from the 1990s indicating that half of STI care was sought in the private sector⁴¹. The 2016 DHS data on care-seeking behaviour for STIs does not distinguish between private and public professional care, other than to indicate that a small proportion of people seeks care in shops and pharmacies⁴².

Guidelines and management practices

Since the late 1990s, South African health workers have treated STIs using a syndromic management approach. This approach has the advantage of same-day treatment and can be easily implemented by nursing staff at primary care clinics. For women presenting with VDS, the 2015 guidelines include an age-based stratification. The new 2018 guidelines (not yet widely disseminated) have an algorithm for non-sexually active women, which first treats for candidiasis and bacterial vaginosis, and a second algorithm for sexually active women that treats discharge with ceftriaxone, azithromycin, and metronidazole. The new guidelines include a note recommending that all women with VDS have a speculum exam, whereas the 2015 guidelines instructed the provider to confirm the presence of discharge (The 2018 flowcharts are included as Annex 1).

Literature and interviews suggest that STI management, in practice, is highly clinician dependent.

A study evaluating the quality of STI service delivery found that syndromic management adhering to the guidelines was provided 61% of the time⁴³.

The guidelines recommend that health workers routinely integrate STI screening questions into all health visits⁴⁴ and that the consultation stationery includes HIV, TB and STI screening prompts. In practice, South African providers are not in the habit of asking screening questions, apart from about HIV and TB due to the heavy emphasis on these infections. Interviewees said that providers generally assume that a patient will bring it up if it is an issue. Providers also reported that it is easier to ask women these questions and that patients may be reluctant to answer questions about sexuality, especially in areas where the provider is a prominent member of the community. Workloads are another factor in not implementing STI screening: nursing sisters at PHC level are expected to provide HIV, TB, STI and chronic noncommunicable disease screening, and lack the time to go through all of these during every consultation.

The assessment of patients is also clinician dependent, often influenced by a clinician's training,⁴⁵ workload, and conditions at the facility. Although the recommendation is 35 patients per day, a nursing sister may see 60 patients per day, and consultation times are therefore quite short. For example, while a speculum exam may be recommended, frequently it is not implemented due to workload, lack of privacy in the clinic, or a lack of light, beds, and speculums. Providers suggested that, pragmatically, for VDS it is common practice is to ask the patient if their vagina itches. If the answer is yes, treatment for vaginosis and yeast infection is provided; if the answer is no, treatment for NG/CT is provided. Similarly, nurses do not frequently examine the genitals of male patients; instead, they treat them based on the symptoms reported.

Providers also reported that it is not unusual for patients who have been seen by different providers to repeatedly seek care for persistent symptoms. For example, commonly, a patient would first seek care from a private GP, but if their symptoms persist, they turn to a PHC. Alternatively, a patient at a PHC might first see a nurse in the family planning sub-section of the PHC. If their symptoms do not resolve, they switch providers by queuing in the

general acute illness section. One interviewee said it would not be surprising for a patient to report having had 5 to 6 courses of antibiotics. Uncertainty around returning patients appears to be a particular “pain point” for providers, and the latest treatment guidelines seem to reflect this challenge by including guidance for improved work-up of patients with persistent symptoms. For higher levels of care, new guidelines on how to manage cases, use tests and perform swabs have been developed. While the treatment would initially be a higher dose of empiric treatment, the patient would be asked to return once their laboratory results are available.

Communication with patients about an STI diagnosis is not uniform and is often ambiguous. Providers interviewed reported telling patients that they have an STI without referring to a specific disease; some tell the patient precisely what they are being treated for; while others are deliberately vague, telling patients they have a “urogenital infection” and that their partner also needs treatment. Some providers have concerns about telling patients that they definitively have an STI because of the stigma and implications; others feel the patient needs to know if they have an STI. Partner notification, while recommended by the guidelines, is irregularly implemented. Some researchers are exploring different methods of partner notification, including whether diagnostic testing/etiological confirmation improves partner notification rates, the acceptability of provider-led notification to partners, and expedited partner therapy. To date, the results seem mixed⁴⁶.

A 2014 study by the NDoH echoes the interviewees' comments about the quality of care for STIs.⁴⁷ This study used 195 standardized patient (SPs) to evaluate STI service delivery in 50 sentinel clinics. The findings showed improvement over an evaluation conducted in 2008, but pointed to several deficiencies:

- ▶ Only half of the SPs were offered a physical genital examination
- ▶ 64.8% were offered the correct treatment regimen
- ▶ 70.8% received a partner notification slip or counselling about discussing STIs with their sexual partners

- ▶ 62.0% of patients were counselled about practising safer sex
- ▶ Men were significantly more likely than women to be offered an HIV test (76.5% compared with 58.5%, $p = 0.039$) and to receive partner notification counselling (79.3% compared with 62.4%, $p = 0.020$)

A 2016 study that investigated antibiotic prescribing practice at the primary care level in Cape Town found that antibiotic prescribing for STIs was more appropriate than for other conditions; however, there was scope for improvement as 35% of the medicines given were incorrect, mainly due to dose-related errors or missing antibiotics.⁴⁸

There is little information about the quality of STI care in the private sector. Research conducted in the late 1990s showed that GPs did not adhere to national guidelines and had poor knowledge of them and that many did not prescribe the correct drug treatment, instead they provided prescriptions that were not effective. A patient's ability to pay also influenced prescribing, with uninsured patients often offered treatments that were less likely to work.⁴⁹ There are few recent data; however, one researcher reported looking into this area.⁵⁰ Experts sense that many GPs are following old guidelines (e.g. ciprofloxacin for VDS) with minimal/no testing. The current STI strategy includes goals around engaging and training the private sector; this likely reflects ongoing concern about shortcomings in this sector.

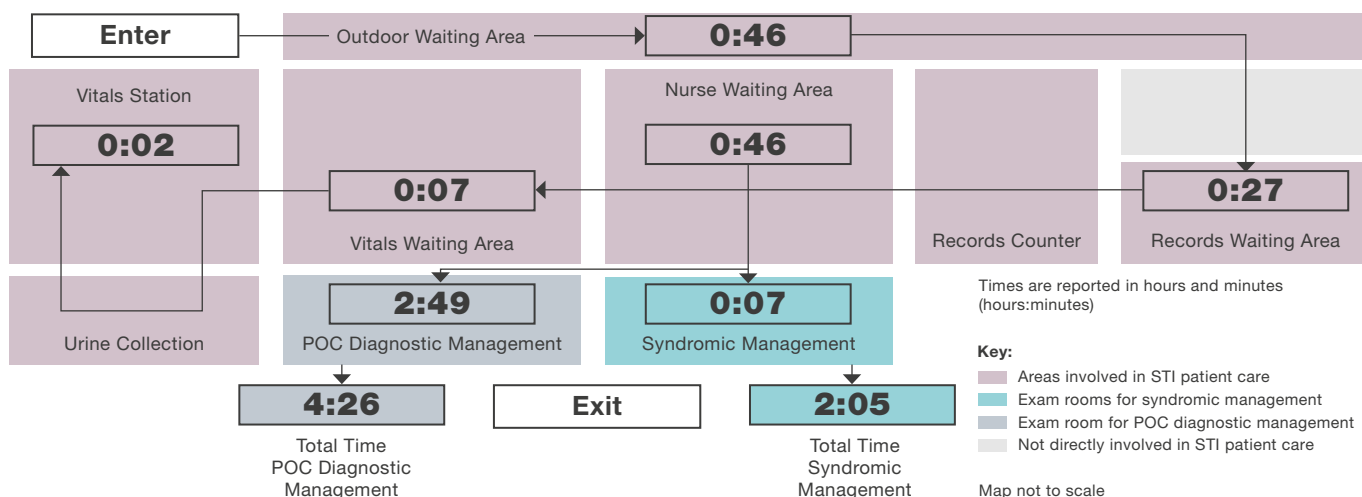
Clinic operations and diagnostic testing

Clinic operations are critical to appreciating how a POC STI test would fit into existing workflows and where it could add to waiting times, workloads, and cramped space. In general, studies show that patient visits for STIs (as well as other conditions) in the public sector are characterized by long waiting times and multiple queues. Similarly, depending on the clinic, provider workloads are often substantial. Additionally, there have been a few studies of POC test implementation, and the challenges related to obtaining same-day results. These studies are outlined below.

A recent study shed some light on syndromic versus POC testing for STIs, as well as the impact of testing for HIV and TB.⁵¹ The study took place at the largest public HIV, TB and STI outpatient treatment facility in Durban, where three doctors and fourteen professional nurses⁵² see, on average, 500 patients per day. The mean total visit duration for STI patients managed according to the syndromic guidelines was 2 hours, with just 6% of this time spent receiving care because patients waited in queues for multiple steps (Figure 9). A handful of patients with STI syndromes participated in a research study that included STI diagnostic testing (GeneXpert) and management based on these results. For these patients, the average visit time was almost 5 hours.⁵³ The study concluded that “as new POC tests become available for STI, HIV, and TB diagnosis and monitoring, they may result in even longer visits if implementation challenges are not addressed.”

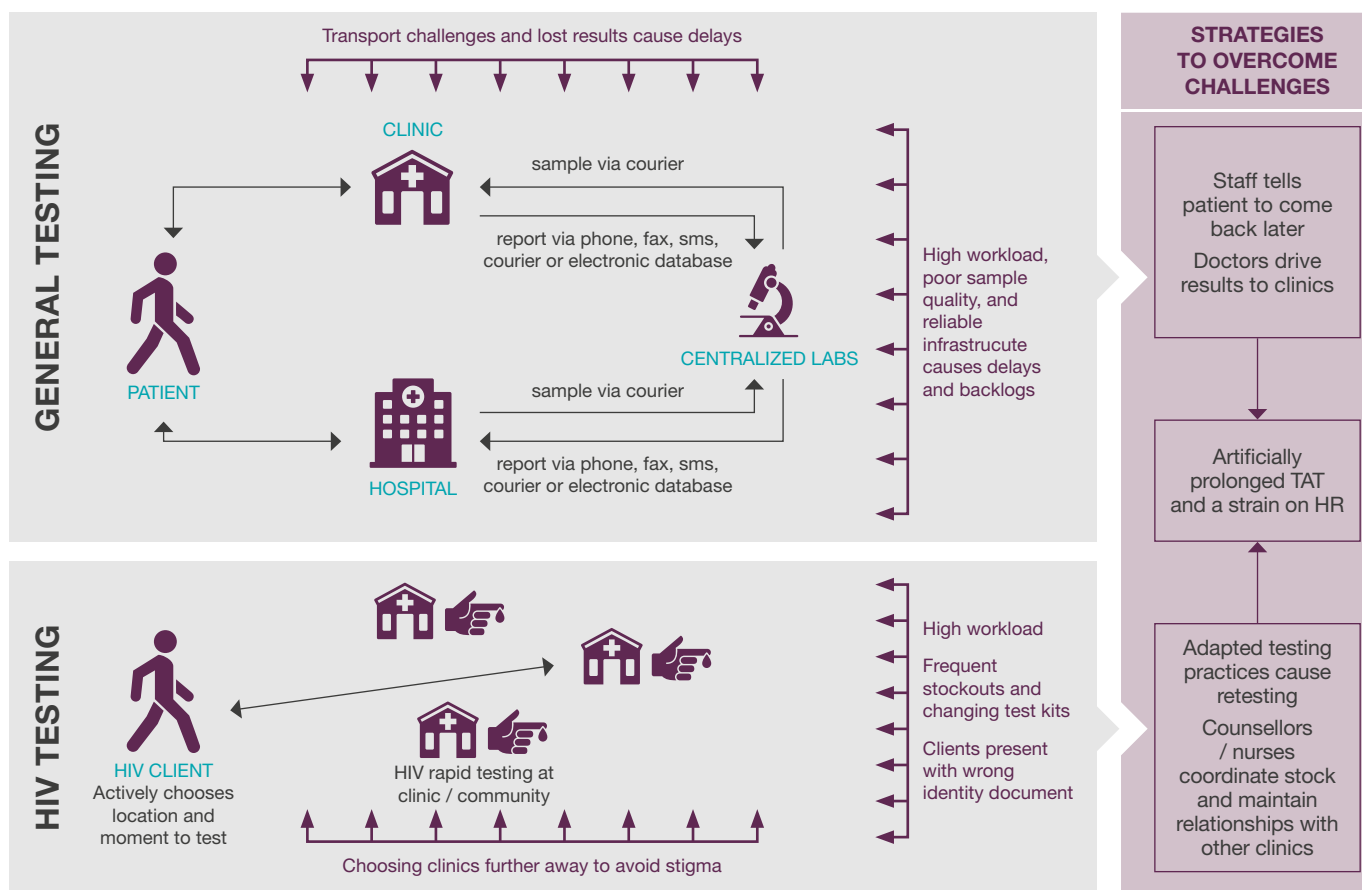
Another qualitative study of POC testing in South Africa found similar results: while some providers recommended more POC testing, others preferred central laboratory testing⁵⁴. The study highlighted the disadvantages of both the central laboratory testing system and HIV rapid testing. The main challenges around POC HIV testing related to supply stock-outs, workloads, and quality of testing. (Figure 10).

Figure 9: STI patient flow map for a large clinic in Durban, showing syndromic versus diagnostic (Genexpert) patient management



Source: *Stime et al. 2018*

Figure 10: Diagnostic pathways and barriers to POC testing in South Africa



TAT, turnaround time; HR, Human Resources

Source: *Engel et al. (2018)*

In 2014, the NDoH conducted a study that included similar clinic flow mapping for syndromic STI services. Visit times were similar or slightly longer, especially in rural clinics (Table 3). The study also revealed a number of challenges related to staffing

(need for task shifting), infrastructure (lack of beds and light in consultation rooms), and layout and other opportunities to improve the efficiency of clinic flow, mostly related to task shifting and stronger linkages to HIV care⁵⁵.

Table 3: Selection of clinic flow and wait times for STI services

| Management | Site | Process | Total time (hours: minutes) |
|-----------------------------------|--|---|-----------------------------|
| Syndromic | Urban clinic, seeing 500 patients/day (TB, HIV and STIs). Providers: 3 doctors and 14 professional nurses. | Wait to register, wait for vitals, wait for provider consultation, meet with provider for syndromic diagnosis and treatment. | 2:05 |
| Test and treat (GeneXpert) | Urban clinic, seeing 500 patients/day (TB, HIV and STIs). Providers: 3 doctors and 14 professional nurses. | Wait to register, wait for vitals, wait for a consultation with the research nurse, sample collection and testing with GeneXpert, wait for results, management based on results. | 4:56 |
| Syndromic | Urban clinic, seeing 650–700 patients/day Providers: 1 part-time physician and 20 professional nurses. | Wait to register in the general waiting area, register and proceed to the acute patient waiting area where vitals are sometimes taken. In the acute line, a triage nurse either treats immediately (simple cases, men) or refers the patient to wait for a consultation (typically women), see a nurse or doctor for diagnosis and treatment, and then HIV testing. | Ranged from 2:40 to 2:55 |
| Syndromic | Rural clinic, seeing 100–200 patients/day. Providers: 1 part-time physician, 8 professional nurses. | Wait for registration and vitals, (wait for HIV testing and counselling), wait for consultation, consultation with nurse for diagnosis and treatment. | Ranged from 3:30 to 3:55 |
| Syndromic | Rural clinic, seeing 100–200 patients/day. Providers: 1 part-time physician and 9 professional nurses. | Wait for registration, wait for consultation, consultation with nurse for diagnosis and treatment. | Ranged from 3:25 to 3:50 |

Interview results and these studies suggest variations in current practice would affect POC test implementation. One interview at a clinic involved an extensive discussion about incorporating a POC STI test into the clinic flow. A nurse and counsellor team pointed out that the workflow would depend on the sample type. For example, if it were a blood-based lateral flow test, it could easily be performed by the counsellor doing HIV testing or a health worker drawing blood for monitoring, both of which are routine practices. If a test required a provider to collect a vaginal or urethral swab, this would add time for swabbing and then obtaining the results and providing treatment. If it was a self-collected sample, this would also add time and require a private area. At one clinic implementing an STI study, women self-collected swabs in an extra consultation room.

Another interviewee felt that, while it might be difficult to incorporate STI testing generally at primary care clinics, a test could easily be incorporated into some of the sexual health-related sub-services of primary care clinics, where these exist, for example, family planning, Pap smears, HPV, and STI and PrEP services⁵⁶.

Surveillance, treatment and guideline updates

South Africa has three forms of STI surveillance:

1. Facilities report new cases of STIs and MUS through the District Health Information System was first implemented in the 2000s and is locally referred to as the National Indicators Data Set⁵⁷. It is not clear how complete these

data are, and they were not available for this report, other than a few citations of annual figures from other reports.

2. The National Clinical Sentinel Surveillance collects more detailed data on syndromes from approximately 270 clinics across the country. The aggregate numbers of MUS, Genital Ulcer Syndrome (GUS) and VDS cases are published.
3. Routine microbiological surveillance is conducted by the NICD and comprises surveys of syndrome etiology and NG drug resistance monitoring. The NICD publishes these reports and recommendations through its newsletters and website.

There is no surveillance covering the private sector, although drug-resistant NG is a notifiable disease, and private laboratories must report it.

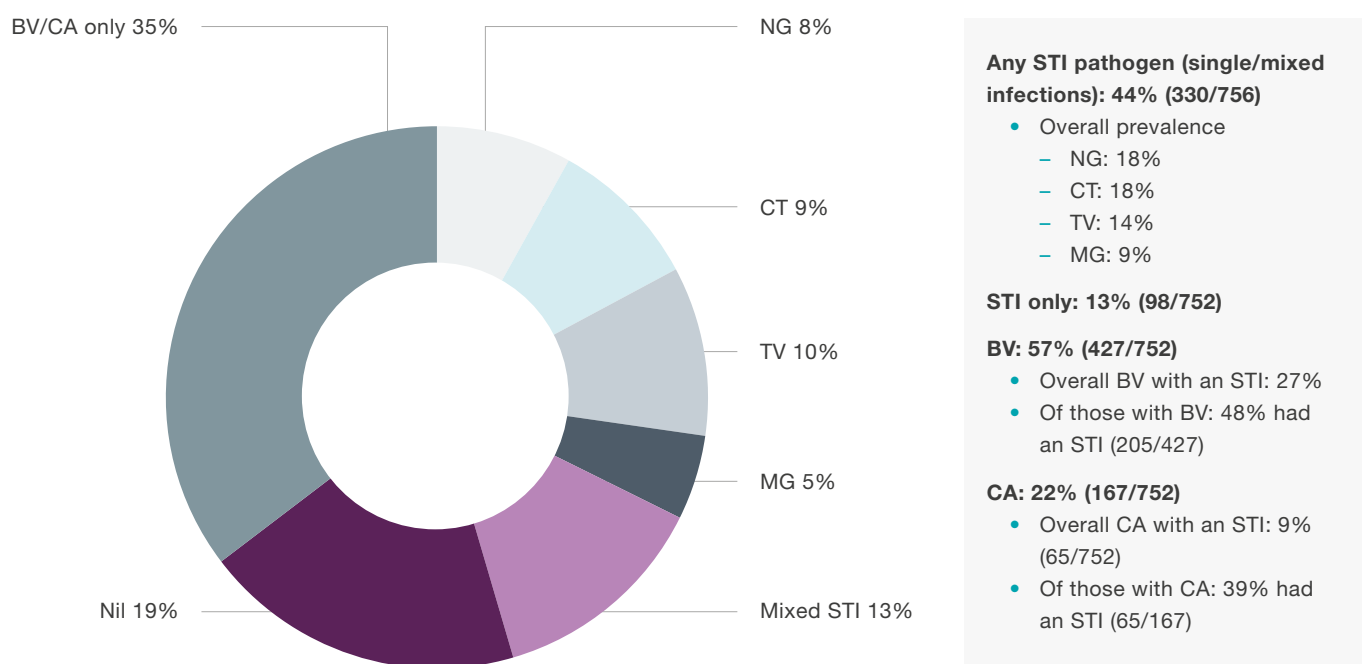
Unlike many LMICs, the NICD's STI section regularly validates syndromic guidelines by conducting etiological studies of the major STIs. Clinical surveillance has shown that together, MUS, VDS and GUS comprise 80% of all STI syndromes seen⁵⁸.

For syndromes related to NG, the latest etiological study found:

- ▶ MUS cases: 82% had NG, 22% had CT, 4% had *Trichomonas vaginalis* (TV), and 4% had *Mycoplasma genitalium* (MG) infection.
- ▶ VDS cases: only 44% had an STI, of which 18% had NG; 18% had CT, 14% had TV, and 9% had MG infection. Overall, 57% had bacterial vaginosis (BV) and 22% had candidiasis (CA); some cases with BV or CA also had an STI.

The most recent etiological study recommended no changes to the current MUS guidelines. For women, a change in the algorithm was recommended: removal of the age cut-offs for VDS and the addition of sexual risk characteristics for VDS. This change was based on BV being the leading cause of VDS and being associated with risk factors for traditional STI infections, as well as a lack of significant age differences among women infected with an STI or those with BV or CA. As noted above, these changes have been incorporated into the latest guidelines (2018). The NICD study also noted that “the syndromic management of VDS remains complex.” (Figure 11)

Figure 11: Relative prevalence of VDS etiologies, National STI surveillance, South Africa, 2014–2017, ($n = 752$)



Key:

Neisseria gonorrhoeae (NG); *Chlamydia trachomatis* (CT); *Trichomonas vaginalis* (TV); *Mycoplasma genitalium* (MG); bacterial vaginosis (BV); vulvovaginal candidiasis (CA)

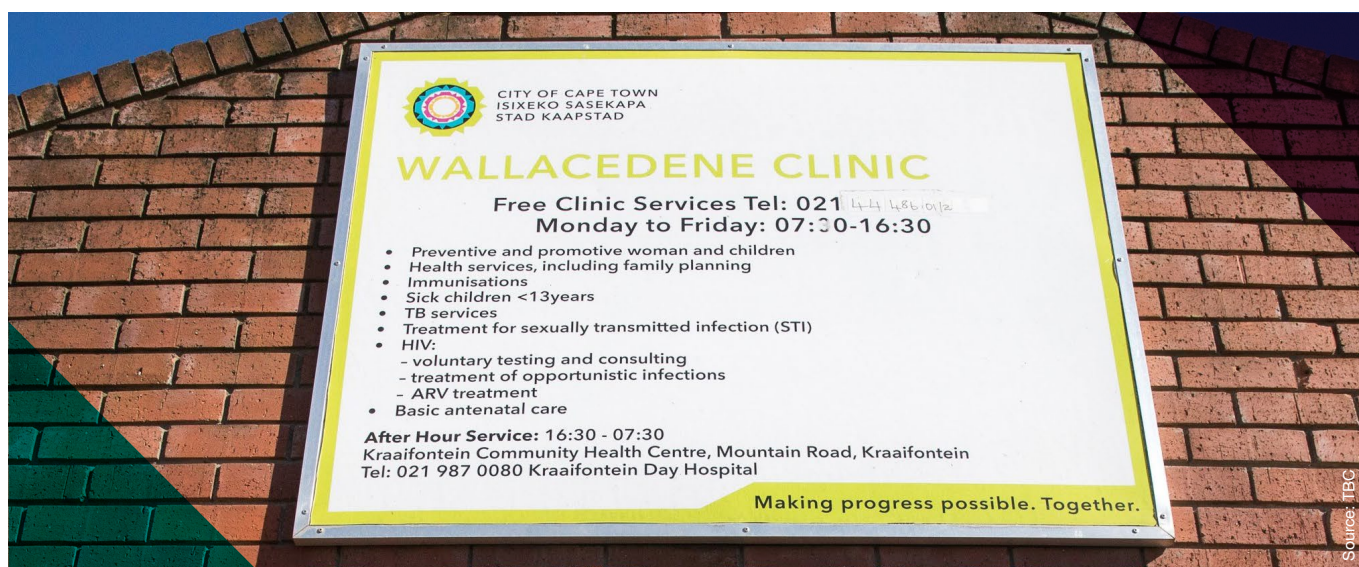
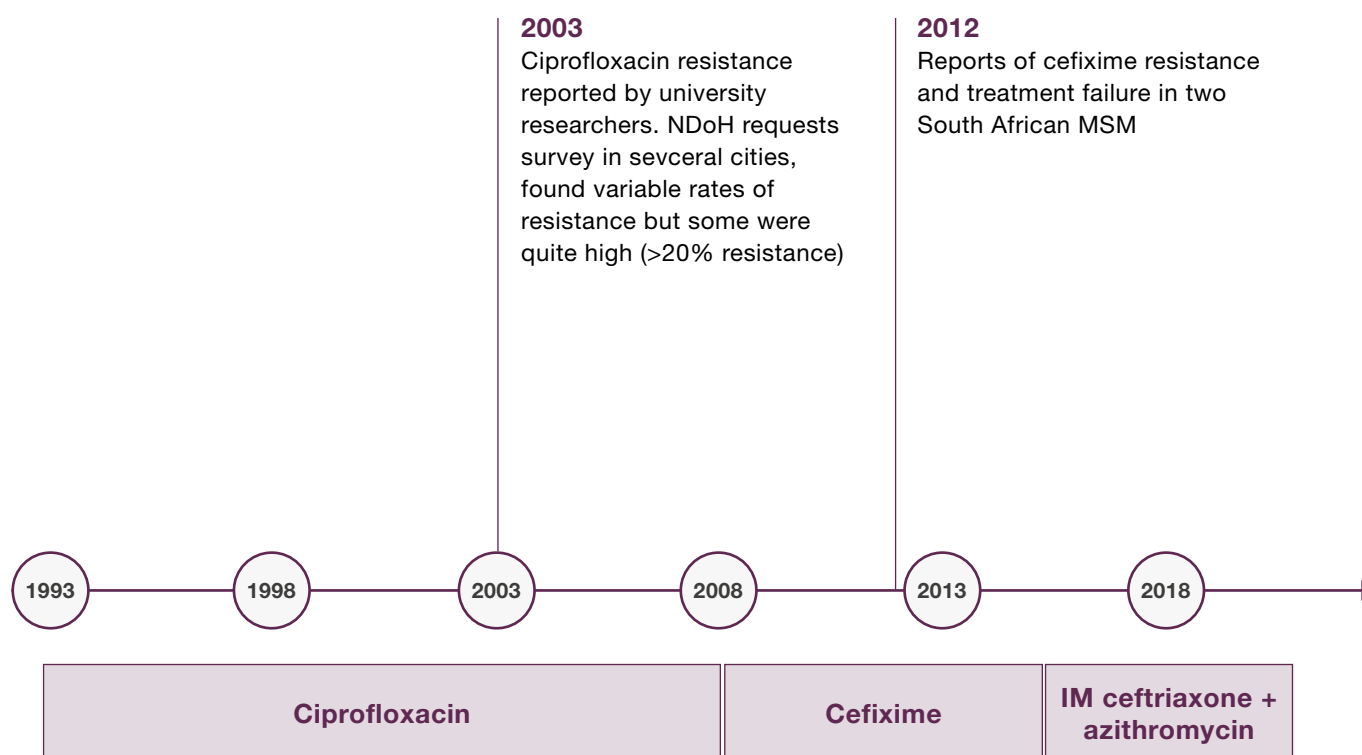
Source: Kularatne et al. (2017)

The NICD also conducts surveillance for antimicrobial resistant NG. Previously, it took several years from when fluoroquinolone resistance was first noted to the introduction of new treatment (Figure 12). In 2015, the guidelines were updated following the emergence of extended-spectrum cephalosporin resistance in two cases of cefixime treatment failure in 2012/2013; South Africa's guidelines are currently aligned with WHO guidelines. A 2017 NICD study of 315 men presenting with MUS did not identify any

resistance to extended-spectrum cephalosporins, supporting the currently recommended treatments. The study did recommend enhanced surveillance, particularly in MSM populations.

While interviewees valued the etiologic and resistance surveillance data collected by the NICD, they also noted that these data were underpowered and lacking in key populations where new trends might first appear.

Figure 12: Timeline of treatment changes for NG



KEY USE SCENARIOS FOR AN NG/CT POC TEST

The interviews explored potential use scenarios for two different versions of a POC NG/CT test, TPP1 Minimal and TPP1 Optimal (Figure 13) and how interviewees prioritized these use cases and test types. Overall, opinions diverged on preferences for a minimal versus an optimal test. Generally, clinicians and academics working on STIs and

HIV prefer screening tests to detect asymptomatic infections and consider syndromic management to be adequate. Experts with an AMR background could see the value in an inexpensive stewardship test (i.e. TPP minimal), but ultimately felt that cost considerations would drive adoption. Specific use scenarios and strategies are described below.

Figure 13: NG/CT POC test descriptions used for interviews

| | |
|---------------------|--|
| TPP1 Minimal | <ul style="list-style-type: none"> ▶ Diagnosis of gonorrhoea alone, or both gonorrhoea and chlamydia. ▶ Use in symptomatic patients at primary healthcare level, to improve syndromic management and facilitate appropriate antibiotic use. ▶ Sample type: in females, a self-collected or provider-collected vaginal swab; in males, a urethral swab (or possibly a urine sample). ▶ 10–30 minutes. ▶ Price: <US\$ 3 for a simple test e.g. lateral flow format. ▶ Performance is better than syndromic management, but sensitivity is insufficient for asymptomatic cases. <ul style="list-style-type: none"> + Lateral flow: sensitivity >80%, specificity >90% + Molecular: sensitivity >95%, specificity >95% |
| TPP Optimal | <ul style="list-style-type: none"> ▶ Diagnosis of gonorrhoea alone, or both gonorrhoea and chlamydia. ▶ For symptomatic patients at primary healthcare level, as above, as well as to support screening to identify previously undetected infections and asymptomatic screening. ▶ Sample: urine preferred; also, as above, vaginal swabs, (females) and urine (males); also rectal and pharyngeal swabs. ▶ 10–30 minutes. ▶ Disposable molecular format most likely; sensitivity >90–95%, specificity >98% ▶ Price: <US\$ 12 for a disposable, single-use molecular test. |

TPP minimal use cases

Most interviewees assumed that a diagnostic test for NG/CT would be used in all patients presenting with symptoms, and they were not focused on the specific performance characteristics but rather the pragmatic aspects of the test, such as sample type, time to results, and cost. A few providers suggested a more limited role for a test in routine management: they recommended initial syndromic management of patients and then, if the

patient had persistent symptoms, a test would be performed. These interviewees felt that providers need another approach to patients with persistent/recurrent symptoms and that they would welcome a diagnostic test that at this point in the “loop” to guide their next steps. In this scenario, these providers recommended working up the patient for resistance (likely by referral to a higher level of care) only if a patient returned for a third time.

Given the cost, one expert suggested that syndromic management might be replaced with a POC test in high volume sites and STI clinics, with the eventual rollout of testing to all PHCs.

A few interviewees suggested that uptake would be higher if a test could diagnose all STIs currently covered by a given syndrome; however, most appreciated the focus on NG/CT, given the desire to arrest NG resistance and frequent co-infection. They expected that a “second generation” POC test would include other STIs and at that point, clinicians “would see more value in this test.”

TPP optimal use cases

Interviewees envisioned many potential use scenarios for the optimal version of the test, although they suggested that cost, modelling, and advocacy would likely inform actual use of the tests. Potential populations for NG/CT screening included:

- ▶ Pregnant women attending ANCs, as “the stakes are higher here because of the potential cost to the baby.” However, researchers piloting ANC STI screening report challenges around the optimal timing of screening and risk of reinfection during a pregnancy.
- ▶ Patients seeking reproductive health services, e.g. family planning, or termination of pregnancy services.
- ▶ Women attending for cervical cancer screening (Pap smears are recommended once every ten years).
- ▶ Incorporation into HIV testing services, e.g. screening individuals who are being tested for HIV or only screening people who test HIV positive.
- ▶ ART patients: STI testing could be incorporated into monitoring tests, such as viral load or TB screening.
- ▶ PrEP enrollees: STI testing was “standard” for PrEP enrollees, who already underwent several tests.
- ▶ Adolescent girls and young women, as well as young populations more generally.
- ▶ MSM and sex workers attending, albeit few, specialized clinics.

- ▶ Peer delivery of testing, like HIV self-testing.

None of the experts mentioned STI screening in male circumcision clinics, although this group is included in the STI strategy.

Experts agreed that cost would be a primary driver in the adoption of any new test and the implementation of targeted screening. They recommended studies to better appreciate the yield of testing and cost-effectiveness of screening, as well as new approaches to stratify patients (e.g. ever had STI symptoms, sex without a condom within the past three months, a new partner in the past six months). Along these lines, the CIDER group at University of Cape Town recently completed a modelling exercise looking at the impact of screening at an overall population level, i.e. on reductions in prevalence. They considered only CT/NG screening, assumed equivalent performance to the GeneXpert test, and looked at screening in the youth, pregnant women, sex workers, and people receiving HIV care. The highest yield was in sex workers, while the greatest population impact occurred when screening the youth and people receiving HIV care⁵⁹. Other experts did not recommend adolescent screening and suggested a focus on populations where screening was most “justified” by 1) adverse pregnancy outcomes and 2) potential reductions in HIV transmission, especially in key populations. Overall, while interest in screening was high, there was no consensus around the optimal target population.

Prioritization of use scenarios

Two distinct approaches to testing emerged during the interviews, although there was considerably more enthusiasm for the optimal test and for use scenarios that involved screening and detection of asymptomatic infections. While this was the majority view, it also reflects the interviewees’ backgrounds: interviewees included many STI researchers, leading HIV clinicians, and providers of HIV care, PrEP and sexual health services.

Several of the leading HIV researchers have been conducting demonstration and implementation studies for PrEP. As part of these studies, routine STI testing has revealed “alarmingly high rates of STIs”, especially in young women. These results, many

not yet published, are creating a sense of urgency around STIs. Additionally, another group surveying the youth found “a silent genital tract infection epidemic in youth”, finding at least one genital tract infection (GTI) in 70% of adolescent females and 10% of young men, the vast majority of whom were not symptomatic⁶⁰. Anecdotally, several providers commented on high rates of infertility and pelvic inflammatory disease and suspect untreated STIs are the cause. Taken together, these interviewees feel that South Africa is “sitting on a time bomb” of untreated STIs and that “ethically” the emerging data on the “incredibly high burden of STIs” will require a response. At the same time, the implementation of STI testing during PrEP and other studies has revealed a surprisingly high acceptance of testing among both providers and patients, the latter made up of mostly adolescents and young women.

While they did not wholly dismiss replacing syndromic NG/CT management with a test, there was ambivalence about whether this would be the best use of limited funding, and most experts,

including epidemiologists, prioritized screening asymptomatic patients over replacing syndromic management for greater public health impact.

AMR experts pointed out that there are two different issues at stake in the use scenario discussion: on the one hand, there is an inexpensive test for stewardship; on the other, a screening test for asymptomatic cases.

Input from the NDoH was limited, as the STI programme manager position is currently vacant. However, the STI strategy emphasizes screening and treating STIs, mainly in asymptomatic populations, including screening several at-risk populations, e.g. adolescent girls and young women, sex workers and MSM.

An online survey conducted during the first quarter of 2020 asked global respondents to rank various use cases; ten respondents from South Africa participated and prioritized both screening use scenarios as well as testing symptomatic women. (Figures 14 and 15)

Figure 14: Ranking of eight different use scenarios for a POC NG/CT test

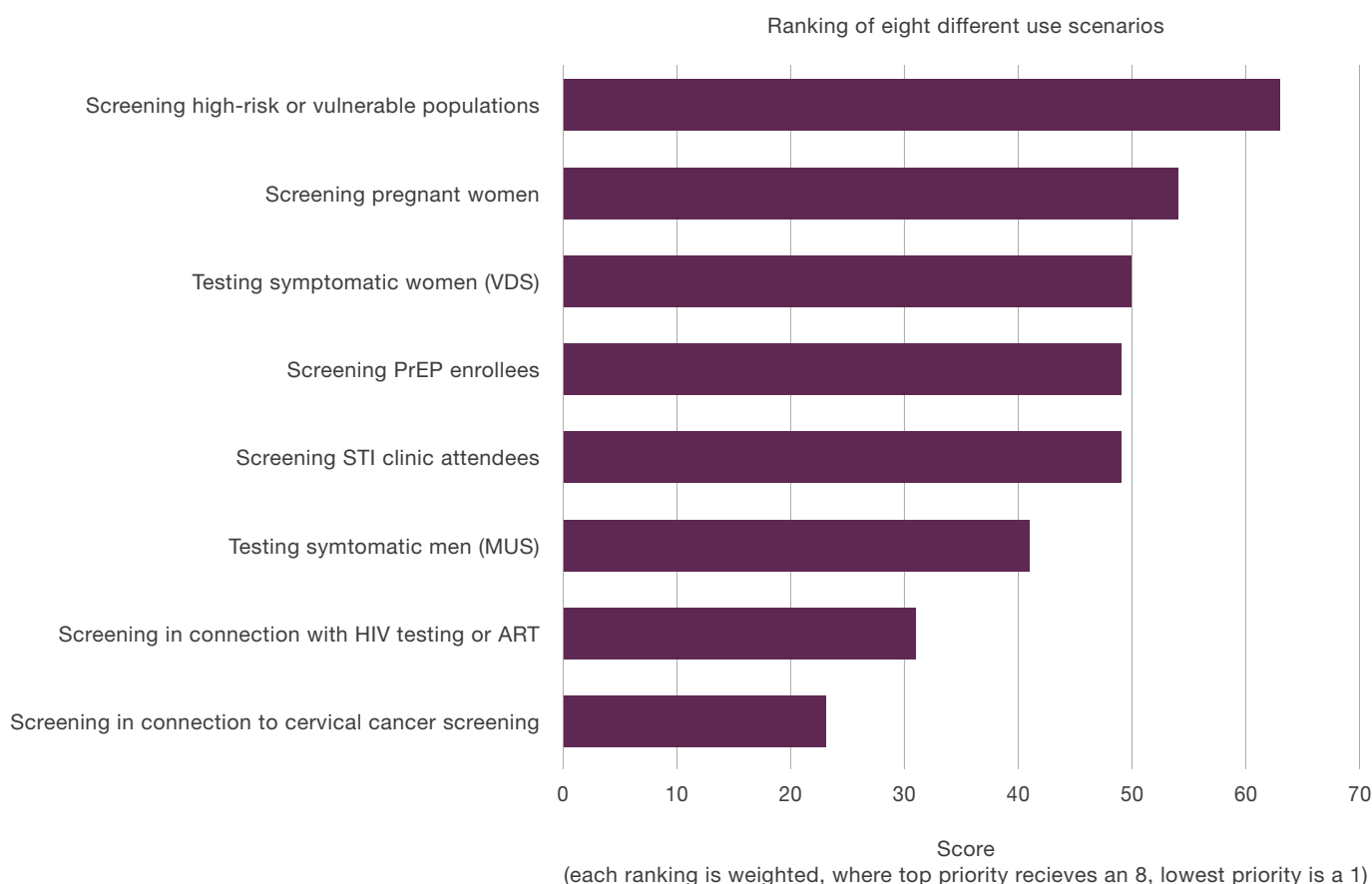
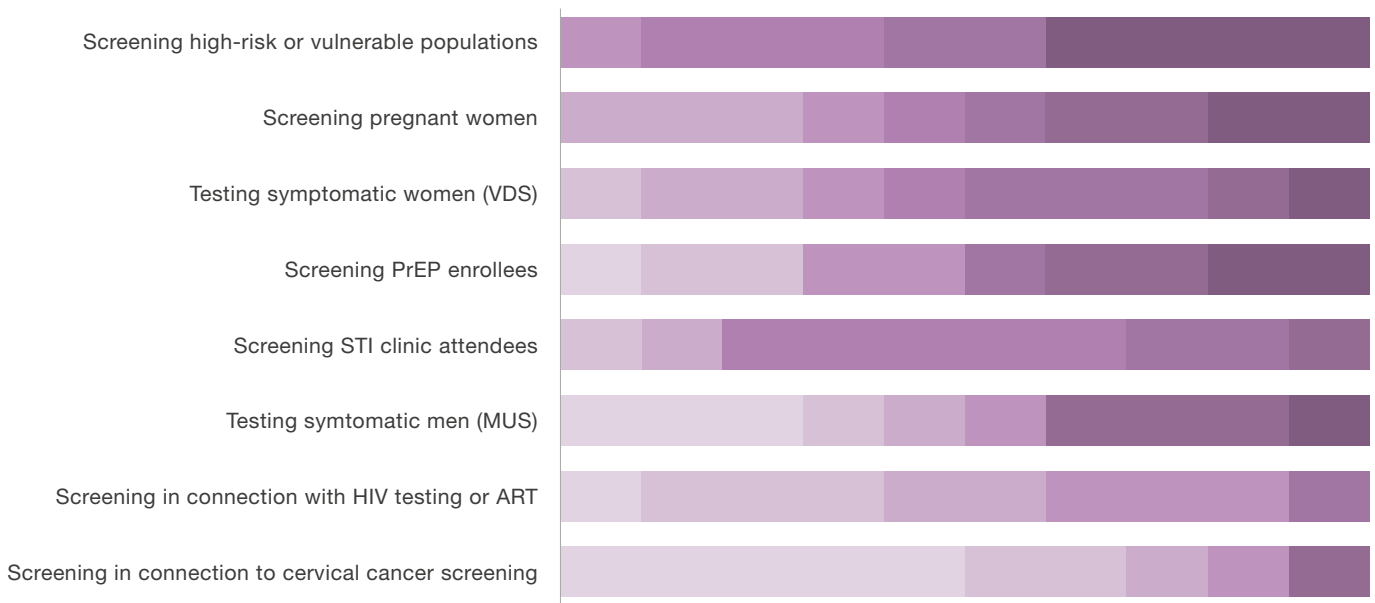


Figure 15: Ranking of eight different use scenarios for a POC NG/CT test (bar size is proportional to the number of times it was ranked)



Use scenario potential market sizes

The potential market size for commonly prioritized use scenarios was assessed and, despite the relative scarcity of data, the estimates provide a useful starting point for thinking about the potential market and access to NG/CT testing in South Africa. These market sizes represent the set of people for whom testing is potentially relevant, or who could be candidates for testing. As such, the figures represent the uppermost limit of the potential market size for any NG/CT test in South Africa.

Many assumptions were required to generate these “top down” estimates, derived from incidence and population size estimates. Often, additional

data points (e.g. derived from household surveys or clinic reporting) did not align well with the top down estimates, suggesting several limitations. Additionally, the estimates do not consider factors such as the choice of test (e.g. POC vs laboratory-based test), the actual availability of the test at the point of service, use of the tests by providers, and acceptance of the tests by patients. Additionally, the adoption of any test would ultimately be informed by cost and budget impact, and, as discussed below, in the current funding environment the NDoH would struggle to fund NG testing. Therefore, it is unlikely that demand would achieve these market potential estimates in the near term.

Note: Each use scenario is sized on its own; however, there could be substantial overlap in the patient populations targeted by the various use scenarios. Depending on which use scenarios were implemented, populations would then need to be subtracted from the estimate to avoid overcounting (e.g. a percentage of pregnant women would also fall into the high-risk/vulnerable population or the PrEP enrollees, and thus adjustments would need to be made if the use scenarios were combined).

Syndromic management

One of the primary motivations for developing a POC test for NG/CT is to improve care for STIs in symptomatic patients presenting to clinics, thereby targeting the treatment received to the etiology of the infection and reducing unnecessary antimicrobial use. Different methodologies can be used to estimate the potential number of patients presenting with MUS

and VDS, or for STI care, in South Africa each year. Depending on the approach used, these estimates range from 0.6 to 3 million cases per year:

- ▶ One approach builds on the Spectrum estimates for South Africa,⁶¹ resulting in an estimated 2.1 million cases of MUS presenting for care (range

1.1–3.2 million) and 1.2 million cases of VDS presenting for care (range 0.7–1.7 million).

- ▶ Using household survey data suggests there are 1.8 million cases of symptomatic STIs in South Africa each year; 1.2 million of these seek care, 1.1 million from professional healthcare providers (public or private).
- ▶ Case reporting by clinics totaled 310 921 MUS cases per year in the public sector.
- ▶ Extrapolation of sentinel site data suggests 383 640 cases of MUS and 209 460 cases of VDS are seen in the public sector each year.
- ▶ The NDoH reported that 1.5 million new STI syndromes are seen in the public sector each year; however, the proportion of MUS, VDS,

and “other” syndromes are not reported. A review of NICD etiological studies suggested that an assumption of one third each of MUS, VDS, and other syndromes would be reasonable, resulting in 500 000 cases each of MUS and VDS presenting each year.

As this exercise has illustrated, there is a significant range in the number of symptomatic patients that might present to care and be eligible for testing, and while we assume the majority will seek care in the public sector, private practice is also an important channel. These estimates rely on many assumptions, often made with limited evidence, and the existing data do not always allow for “apples with apples” comparison, rather some data are based on MUS/VDS while other data includes STI syndromes more broadly.

Screening use scenarios

Screening high-risk or vulnerable populations is another priority, and the table below provides a range of potential market sizes for priority use case scenarios. These estimates are based on target population size estimates, the estimated number of screenings per year, and assumptions about the coverage of the intervention, including what proportion of the target population can actually be reached, whether the test is available at the point of

service, and whether the provider and patient use the test.

Screening all priority groups is financially and pragmatically impossible. Additionally, it is important to note that there is overlap in these different populations and therefore summing any of them could result in an overestimation of market size.

Table 4: Screening use scenarios market size estimates

| Use case for a screening test | Population size estimate | Policy | | Coverage: Percentage of eligible population reached | | | | Assumptions and notes |
|----------------------------------|--------------------------|---------------------------------|------------------------|---|---------|----------------|----------------|--|
| | | Population recorded for testing | Number of tests a year | 20% | 40% | 60% | 80% | |
| PrEP | 44,000–85,000 | 64,750 | 2 | 25,900 | 51,800 | 77,000 | 103,600 | Population recommended for testing is average of current enrolled and target for 2021/22 |
| Sex workers | 150,000 | 150,000 | 2 | 60,000 | 120,000 | 180,000 | 240,000 | 60–75% know status, have done HIV test; ~20–30% FSW positive on ART |
| MSM | 299,000 | 299,000 | 1 | 119,600 | 239,200 | 358,800 | 478,400 | 25–55% have tested, know status; 22–40% on ART |
| Adolescent girls and young women | 1,141,530 | 1,141,530 | 1 | 228,306 | 456,612 | 684,918 | 913,224 | Female pop ages 15–24 using modern contraceptive accessed via public sector |
| Pregnant women | 1,126,572 | 1,126,572 | 1 | 225,314 | 450,629 | 675,943 | 901,258 | Assume high acceptance of testing. |

***Most likely assumption**



ONGOING DEBATE: SYNDROMIC VERSUS ETIOLOGICAL MANAGEMENT OF STIS AND ASYMPTOMATIC INFECTIONS

A desk review, interviews, and the online survey substantiate concerns about the limitations of syndromic management in South Africa and enthusiasm for the potential of emerging STI diagnostics; however, the path forward for diagnostics has yet to emerge.

Acknowledging the limitations of syndromic management

Increasingly, national publications about AMR, NICD reports, and NDoH STI programme publications acknowledge the limitations of syndromic management, especially for women. For example, the current STI strategy mentions that “the syndromic approach for vaginal discharge is poorly predictive of the presence of cervical chlamydial and/or gonococcal infections. There is also a concern with managing syndromically emerging microbial drug-resistant organisms, e.g. *N. gonorrhoeae*.” In its most recent etiological study of STI syndromes, the NICD affirmed the usefulness of syndromic management in MUS and acknowledged the complexity of VDS. Considering the poor performance of syndromic management for VDS, the national algorithms continue to be slightly modified in attempts to improve its performance.

The overwhelming limitation of syndromic management, emphasized by national institutions and academics alike, is the inability to detect asymptomatic infections, which comprise the bulk of STIs. Academics argue for moving away from syndromic management, not only because so many asymptomatic infections are missed but also because untreated infections increase the risk of acquiring HIV⁶². One expert said, “local studies have established that syndromic misses 25% to 75% of infections...” and that “while we know STI treatment will not control HIV, such high levels of inflammation are likely driving some of the HIV

incidence.” Other arguments against the syndromic approach include the effect of untreated HIV on STIs, i.e. increased risk of prolonged infection and severe consequences. While overtreatment and AMR were mentioned during interviews, as well as the need for quality surveillance data (possible through diagnostic confirmation of infection), these were generally not the main arguments used by advocates of a new approach to STIs, but rather supporting arguments.

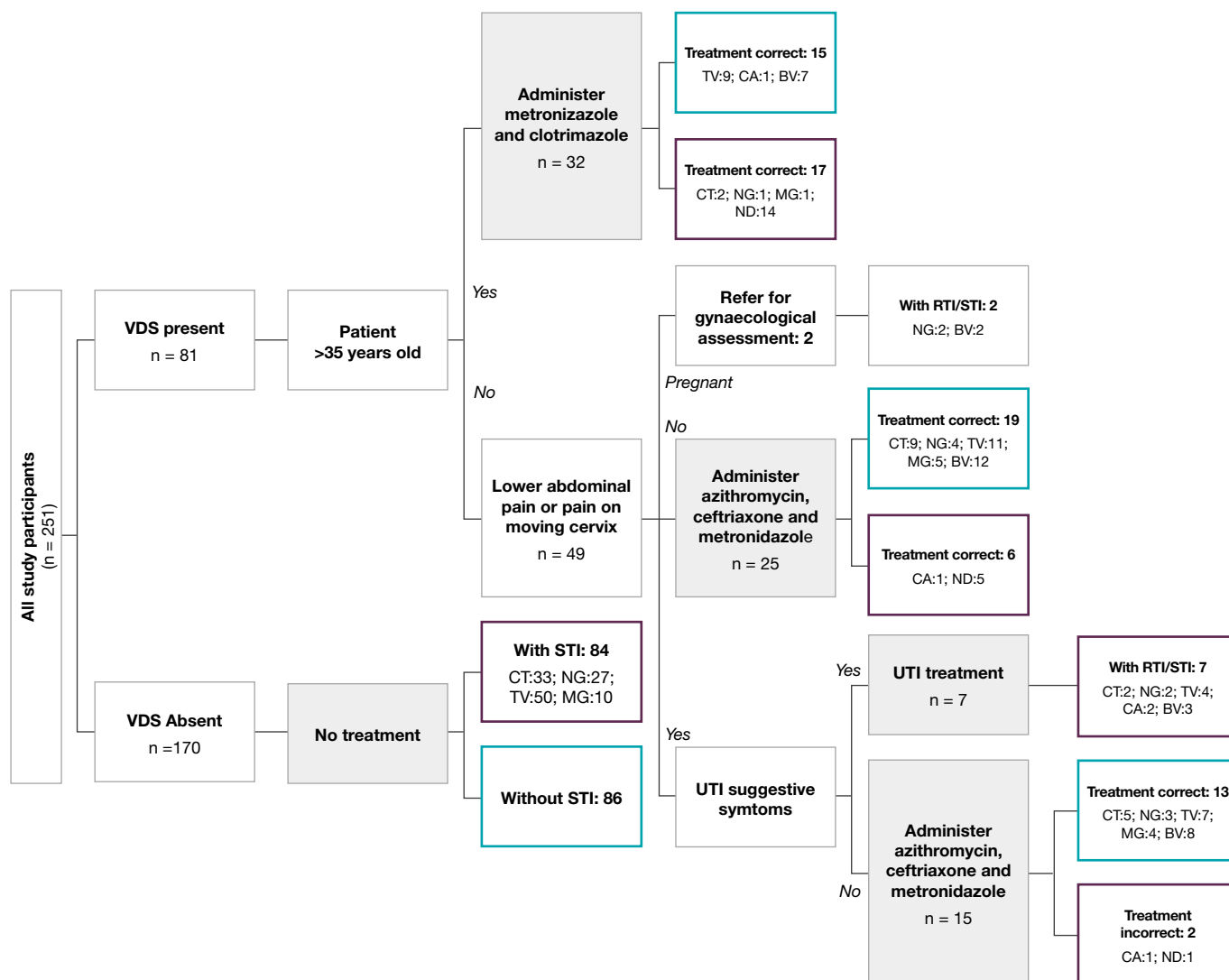
Indeed, some leading public health clinicians have echoed these concerns and are increasingly calling for a new approach to STI control. One modeller referred to a 2011 analysis of the impact of rolling out syndromic STI management in South Africa: while it led to a slight improvement in gonorrhoea prevalence, it had no effect on chlamydia and trichomoniasis prevalence⁶³. In 2016, CAPRISA hosted an STI workshop in KwaZulu Natal that gathered providers and policy makers to consider the STI epidemic and care provision and to review evidence for and against an etiological-based approach. The group concluded, and published a piece with the same name, that “syndromic management had reached its expiry date”⁶⁴. In addition to the limitations of a syndromic approach (e.g. inability to detect asymptomatic infections, overuse of antibiotics, lack of susceptibility testing, lack of surveillance data, and limited opportunity to notify partners), this group stressed the epidemiological and biological links between HIV transmission and STIs/BV, and the need to replace syndromic management in countries with a high prevalence of HIV.

Studies have assessed the performance of the syndromic management guidelines and generally concluded that significant improvement is not possible without diagnostic tests⁶⁵. The most recent

study illustrated the under- and over-treatment in syndromic management in women in South Africa⁶⁶. This study recruited 251 women who attended a mobile clinic for any service. The mobile clinic was staffed by a professional nurse and counsellor and provided health information as well as screening for HIV, TB, non-communicable diseases and cervical cancer. All the women, regardless of whether they

had STI-associated symptoms, were tested for STIs, and 53% tested positive for at least one STI. If the 2015 syndromic guidelines for VDS were applied, two thirds of the STI-infected women would be missed because asymptomatic infections would not have been detected. Additionally, 25 women would have been overtreated (with azithromycin, ceftriaxone or metronidazole) (Figure 16).

Figure 16: Evaluation of VDS management guidelines when applied to women visiting a mobile clinic for any care in South Africa.



Source: Hoffman et al. (2019), *Provision of STI services in a mobile clinic*.

Another recent study documented a high burden of untreated GTIs, including STIs, BV and Candida, among the youth in South Africa. Only 16% of young women and almost no young men reported symptoms, but diagnostic testing identified at least one GTI in 70% of females and 10% of males. Syndromic management would have low sensitivity in this situation and leave the young at increased risk of HIV acquisition. The study authors, including the head

of the Medical Research Council in South Africa, concluded: “We strongly recommend policy changes to replace syndromic management with innovative public health approaches, inclusive of widespread diagnostic testing to reduce GTI burden and HIV-associated risks among youth.... In the context of evolving and less costly GTI diagnostic capabilities, exploring new approaches to implementing youth-focused GTI services is warranted”⁶⁷.

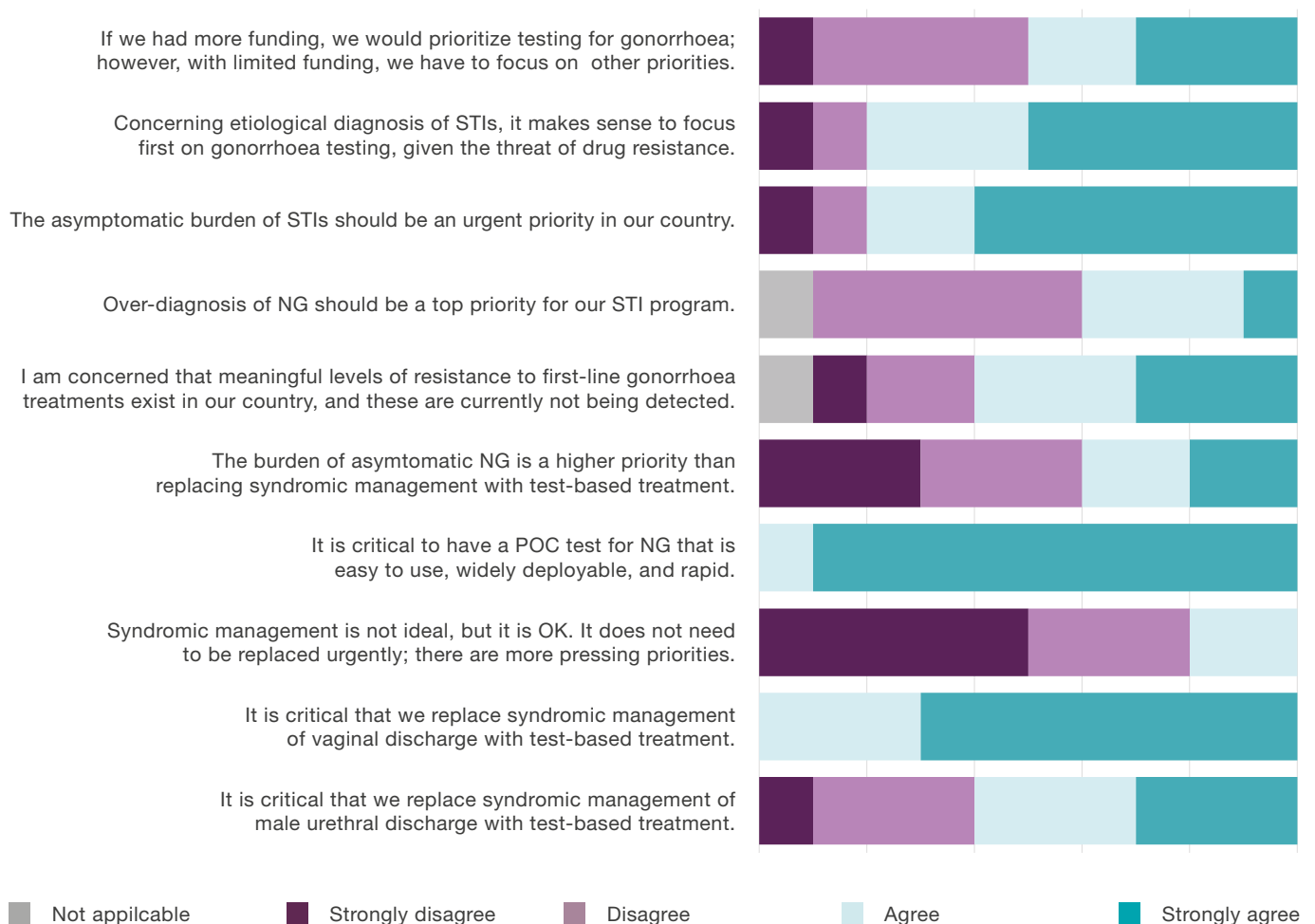
Not yet ready to completely abandon syndromic management

Despite the limitations of syndromic management, South Africa does not yet appear ready to abandon it completely. The current national strategy upholds that the syndromic approach remains the most appropriate STI management approach in South Africa. This is because the country lacks laboratory facilities and the capacity to diagnose STIs etiologically in PHC facilities, and because of the need to prevent loss to follow-up of patients.... “Integrating the syndromic approach to STI care provides greater accessibility, reduced costs, and can avoid the social stigma associated with specialized STI clinics....” The strategy acknowledges that in choosing the syndromic approach it must also address quality of care, and hence the plan stresses provider training and sensitization.

The online survey (Figure 17) and several interviewees also questioned the urgency of

moving away from syndromic management, particularly considering the HIV epidemic. For example, one provider said, “given the urgency of our HIV epidemic, we can’t afford to have people walking around with an STI” and pointed to risk assessment questions in the guidelines intended to improve the targeting of STI treatment. Other providers suggested that syndromic management “is OK, it’s not bad” and that if “90% of MUS is caused by NG, then do we need to move away from syndromic?” Similarly, a large NGO has been wrestling with whether it is wise to move away from syndromic management and considers that the contribution of this management approach to resistance is likely minimal, “since the treatment is a stat dose.” Another expert indicated that testing symptomatic patients was “a nice to have, but not a priority”, given South Africa’s relatively well-validated syndromic system.

Figure 17: Online survey, level of agreement with statements



A mixed approach is likely

Research suggests that South Africa is likely to pursue a hybrid approach, which combines syndromic management and selected etiological testing. This is supported by documents produced by NICD and NDoH. A 2017 NICD report suggests that there is a case for “a selective screening approach for asymptomatic STIs in high-risk/key populations. These populations need to be clearly defined and may include MSM, sex workers, mobile populations, adolescent girls and young women. Sexual risk screening tools could be developed and validated for each key population group”. The NICD is currently conducting a questionnaire study to identify young women attending family planning who are most at risk for STIs, because “it is impossible to screen each and every adolescent woman” attending clinics. Tools such as this questionnaire aim to limit who is tested given affordability concerns. As of early 2020, the NDoH, the University of Witwatersrand, and other stakeholders were mobilizing resources to pilot STI testing in PrEP clinics.

The STI strategy lays out a similar approach; however, if tests are not available, then presumptive treatment is a possibility for key groups: “The key game changer for STIs is to introduce methods that allow for the identification of people with asymptomatic STIs to allow for early treatment. In the absence of capacity for etiological laboratory screening, the approach involves doing a sexual history or a risk assessment, and for those at risk, providing presumptive periodic treatment based on data from STI surveillance”. The STI strategy cites a 2013 review of priority interventions to reduce HIV transmission in sex work settings in sub-Saharan Africa (Chersich et al.⁶⁸) where presumptive STI treatment in sex workers was predicted to reduce HIV incidence by 20%. The STI strategy notes that an etiological approach is not yet feasible but alludes to emerging POC tests that would be “especially important in asymptomatic infections that account for most STIs”. Interviewees confirm that the idea of presumptive STI treatment in certain populations is often discussed by NDoH, for example, if a third of PrEP enrollees had an STI, presumptive treatment might be considered.

Emerging research on diagnostics-based management of STIs

At least two published studies have validated the NG/CT GeneXpert test in South Africa, and another is underway⁶⁹. Other lab-based systems (e.g. BD) are also being considered.

Additionally, there are several small implementations of “POC” STI testing, using the GeneXpert test. In one, CAPRISA evaluated diagnostic testing and expedited partner therapy for reducing the STI burden. Their proof of concept study found a high acceptance of POC STI testing, immediate treatment, and expedited partner therapy in a group of HIV-negative, high-risk young women ($n = 267$), 88% of whom were seeking care for genital symptoms.⁷⁰ Another recent study by the Foundation for Professional Development and partners looked at the acceptance and feasibility of STI testing during the first ANC visit by HIV-positive women. Acceptance was high, 40% had an STI, and 92% received same-day treatment.⁷¹

The CAPRISA group also analysed the impact of POC STI, HIV and TB testing⁷² on clinic flow to assess the value of new POC tests (as described above). They found that while patients received their diagnosis sooner, their waiting times at the clinic were longer, and many patients did not receive same-day results despite rapid testing. The authors concluded that in addition to investing in the development of new POC test technology, investment in improving patient flow and care models is also needed to make any new test a success.⁷³ An interviewee echoed this finding, noting that GeneXpert is “poorly used for TB at busy PHCs” because while it is near-patient, the results are not immediate and often not available on the same day. Logistical challenges around space, reagents, staff and batching also prevent such “near-patient” testing from being POC.

ACCEPTANCE, TRAINING AND COMMUNICATION

Provider perspective

Generally, the interviews suggested that clinicians lack sensitization around NG resistance; they did not see it as an urgent issue or one that required their attention. Their concerns centered around identifying and treating infections, and they considered drug resistance for STIs to be a surveillance and NDoH issue. While they were quite familiar with drug resistance (e.g. TB, ARVs), they assumed the NDoH monitors it at sentinel sites, and when certain thresholds are reached, would simply introduce a new first-line treatment. Unless prompted, providers did not raise concerns about the overtreatment of STIs or antibiotic resistance of STIs. While the providers interviewed generally had a sense of the limitations of syndromic management, they had little sense of the actual sensitivity and specificity of syndromic guidelines, making it somewhat difficult for them to assess how a test would outperform existing practice.

Interviewees suggested that healthcare providers, largely nurses, are likely to initially resist any change in practice such as the introduction of a new test, but with time and consideration of the workflow, testing would be accepted. Nurses accept STI management as part of their scope of practice; however, STI consultations are usually quick, and providers will need a reason to perform a test that increases work and extends the consultation time.

The CAPRISA study of clinic flow for POC testing for STIs, HIV and TB in a busy urban clinic included qualitative interviews with staff. These staff expressed concerns about workloads, especially in light of South Africa's ambitious HIV test and treat plan, and this contributed to some "hesitancy to accept POC tests" as this could further increase their workload.⁷⁴ Staff at this clinic had good access

to a central laboratory and suggested that POC tests were critical for rural areas where it can take days or weeks to get laboratory results back (likely referring to HIV and TB test experiences). They indicated that even with POC tests on site (GeneXpert), results for samples collected in the afternoon would not be available that day, i.e. "the patient must return and the purpose of POC is defeated."

The interviews also revealed that while standard treatment guidelines for PHC are updated regularly through established processes, it takes time for these updates and training on them to reach providers, if they ever do. Dissemination of guidelines is a challenge, those who are sent to training sessions are often not necessarily the best messengers, and providers do not have time in their schedule to study the new guidelines. One researcher working with the national STI programme reported that recently there has not been much training on STIs.

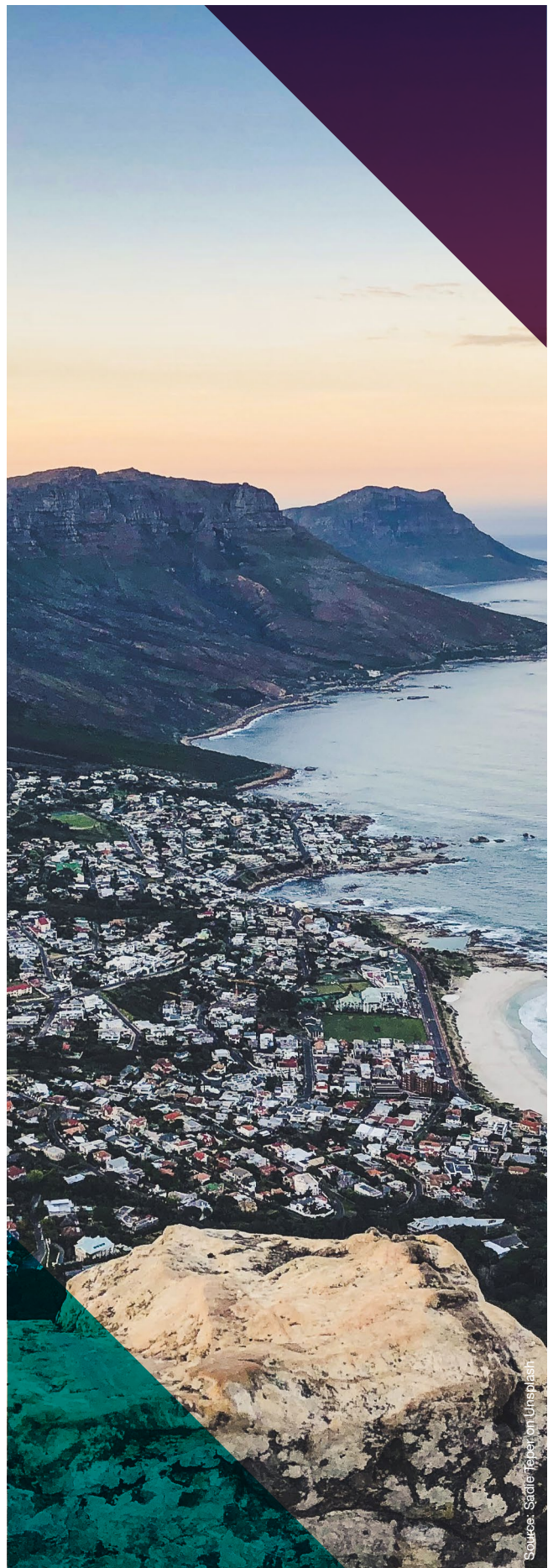
Patient perspective

Most interviewees felt that patients would be receptive to testing. A few researchers implementing STI testing have been surprised at the rapid uptake among the youth in particular, and of the receptivity of family and local communities to initiatives framed as sexual and reproductive health initiatives for the youth (as opposed to HIV initiatives for the youth). One expert said, "young women in South Africa want to know the cause of infection, they want a diagnosis."

More than one expert indicated that self-collected vaginal swabs are being used and are acceptable, although a urine test would be preferable. Interviewees suggested that for men urine would be the only acceptable sample, as men are unlikely to self-swab, and providers would avoid having

to swab them. One interviewee thought that implementing nurse provider-performed vaginal swabs at scale would be problematic, as speculum examinations are not performed for a variety of reasons, and swabbing would require a special training programme for nurses, similar to what has been done for Pap smears. Overall, there is plenty of precedent for urine testing at PHC (urine dipsticks and increasingly the urine lipoarabinomannan (LAM) assay). A study of STI testing in HIV-positive pregnant women investigated sample types and found that 12% of women preferred a urinary specimen, 44% preferred a vaginal specimen, and 44% had no preference. They also found that more women preferred a self-collected vaginal swab: 64% of women preferred to self-collect a vaginal swab, 11% preferred a nurse-collected swab and 25% had no preference.⁷⁵

Most of the STI testing studies described used molecular methods (e.g. GeneXpert or other PCR tests) and require patients to wait for or be called with the results. Loss to follow-up is a challenge, yet there is insufficient experience to conduct an analysis of its impact. One interviewee suggested that for asymptomatic screening a 20-minute turn-around time is the maximum and stressed the need to provide results when the patients are at the clinic.



Source: Saatchi & Saatchi/Unsplash

FINANCING CONSIDERATIONS

In the public sector, assuming the patient follows the correct chain of referral for their condition, primary care services, including for STIs, are free, and any out of pocket payments are relatively small (e.g. opening a file when attending a hospital outpatient department instead of their local clinic). The South African government funds most of the public sector healthcare, apart from the HIV and TB programmes. In 2016/17, the government funded US\$ 1.34 billion of the HIV response, with PEPFAR contributing US\$ 490 million and the Global Fund US\$ 54 million.⁷⁶ Overall, interviewees reported that the South African health systems budget is

shrinking, and only “exceptional” new interventions will be considered.

South Africa’s National Strategic Plan for HIV, TB and STIs includes information on historical spending as well as high-level cost estimates for each objective. Overall, the cost of implementing the STI objectives is estimated to be US\$ 100–127 million per year and includes HPV vaccination and cervical cancer screening, as well as significant funding for diagnostics (Table 5). Despite the cost estimates, interviewees confirmed that the STI programme remains largely unfunded.

Table 5: Estimated STI resource needs for implementing the NSP (USD)⁷⁷

| | 2017/18 | 2018/19 | 2019/20 | 2020/21 | 2021/22 |
|--|--------------------|--------------------|--------------------|--------------------|--------------------|
| Prevention NG/CT/syphilis, (other than HPV vaccination) | 1,700,000 | 1,496,000 | 1,564,000 | 1,564,000 | 1,564,000 |
| HPV vaccination Detection, diagnosis, treatment | 45,968,000 | 52,360,000 | 53,040,000 | 53,788,000 | 54,468,000 |
| Screening and diagnosis | 43,044,000 | 47,532,000 | 54,060,000 | 57,800,000 | 63,580,000 |
| Total | 100,912,000 | 112,268,000 | 122,332,000 | 127,772,000 | 135,932,000 |

Source: *South Africa’s National Strategic Plan for HIV, TB, and STIs 2017-2022*⁷⁸

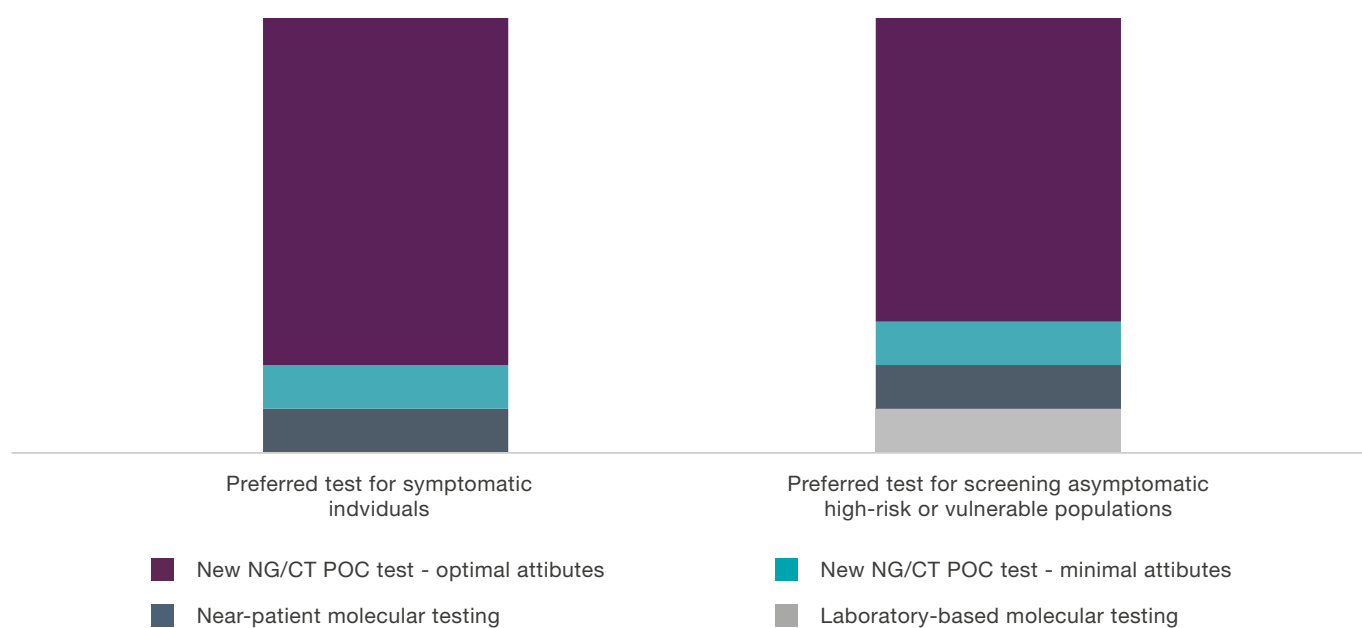
While not the primary market, the private sector is also a potential market for new STI tests; many insured as well as uninsured people likely access South Africa’s private GPs for STI care. Interviewees mentioned that working people, even without insurance, would currently pay around 200 rand (US\$ 15) to see a GP for STI symptoms, so it is possible that they would be willing to pay for a

less expensive test (e.g. US\$ 3). One interviewee mentioned that medical aid schemes do not reimburse POC testing in South Africa, so even insured patients would pay out of pocket; therefore, uptake of a more expensive test (e.g. US\$ 13) is likely minimal. Another interviewee said, “even with a \$3 test, when the medicine is less than US \$2, people may forgo testing.”

NG/CT POC TEST ADOPTION

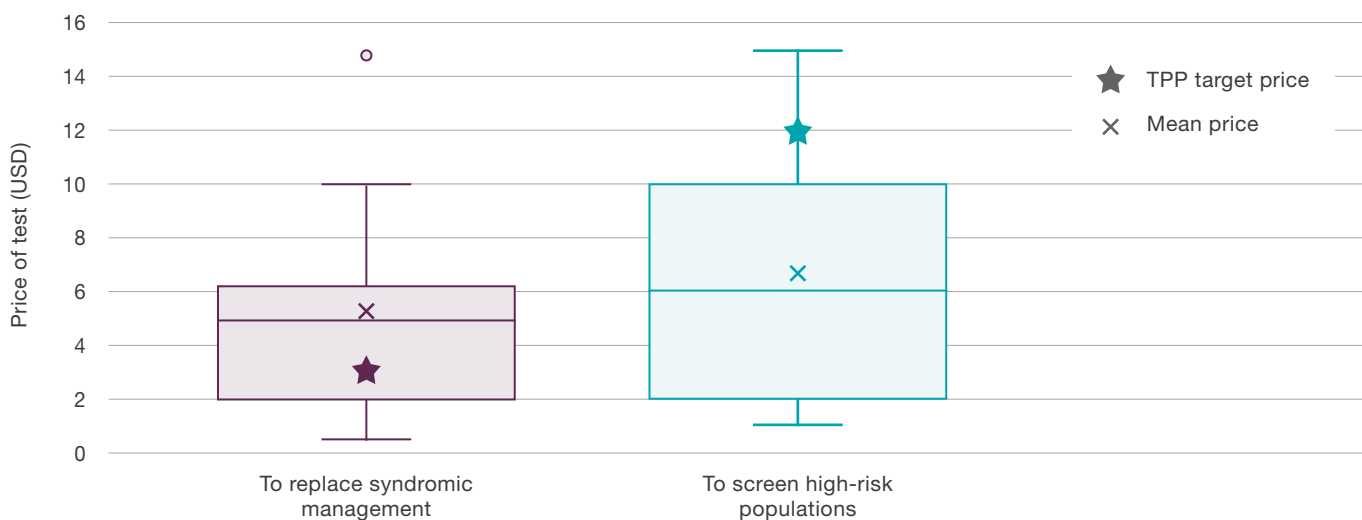
Interviewees overwhelmingly stressed the importance of cost, suggesting that the cost of testing would be the ultimate driver in any public sector consideration of adopting a new test. The test that ultimately becomes available, minimal or optimal, and the associated potential use scenarios, would also be a factor in any decision-making around adoption.

Figure 18: Preferred tests for symptomatic individuals and for screening



The optimal test was preferred by online survey respondents (Figure 18) for both symptomatic individuals as well as for screening. This tests also aligns well with the country's STI strategy, which includes STI screening in selected asymptomatic populations. The cost of this test, however (US\$ 12), exceeds the maximum most survey respondents would recommend the NDoH pay (Figure 19).

Figure 19: Maximum price the NDoH should pay for an NG/CT POC test



The use cases for the minimal test are limited to symptomatic patients (VDS, MUS and lower abdominal pain syndrome) presenting for care. The main argument for inclusion of a test in syndromic management would be to reduce overtreatment for NG. Currently, this scenario is not prioritized in any national strategic documents; therefore, the scope for introducing this test may be limited, at least until resistance to the current first-line treatment emerges. Cost is also a factor. While survey respondents recommended pricing that was in-line with the TPP target price, interviewees expressed doubts about whether etiological management with a test like this would be adopted under current conditions. One interviewee explained that even for a middle-income country like South Africa, at US\$ 3 per test, without an imminent threat of resistance, for a disease that is not killing people or infecting health workers, an external donor would likely be required. None of the three AMR experts interviewed were optimistic about adoption of a minimal test, unless the first-line treatment began to fail and a change to more expensive treatments was required

Unlike in many other countries, the strong centralized testing network of the NHLS factors into decision-making about the adoption of any new tests in South Africa. The NDoH often prefers centralized testing rather than rapid, POC tests because the centralized network is robust and efficient. If etiological STI management policies were to be adopted, cost-effectiveness analysis comparing POC testing and centralized testing (including potential to leverage the GeneXpert platform that is widely rolled out for TB) would likely inform decision making.



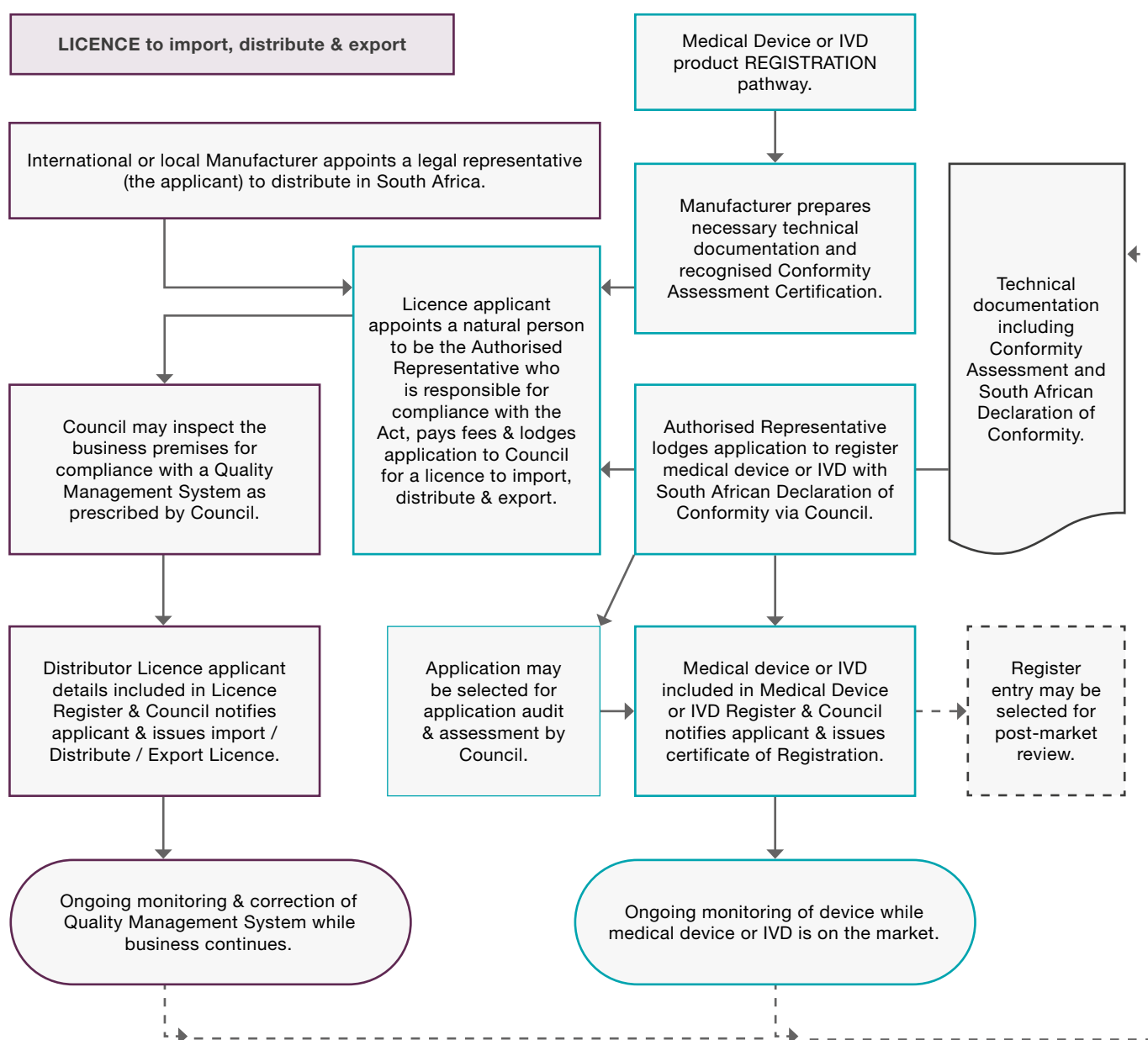
Source: Simon Greenwood on Unsplash

REGULATORY

Until recently, South Africa did not have a comprehensive regulatory framework for diagnostics, and often looked to NHLS for guidance. In 2016, the government established SAHPRA (South African Health Products Regulatory Authority), a semi-autonomous body for medicines, devices and diagnostics regulation. The approach SAHPRA takes

in relation to diagnostics is expected to be similar to Europe's Confirmatory Assessment process (Figure 20); however, our desk review suggested that the registration of diagnostics has yet to commence, as the documents available on SAHPRA's website are not final drafts. Therefore, the information below would need to be confirmed in the future.

Figure 20: Pathways to import and register an in vitro diagnostic device (IVD) in South Africa



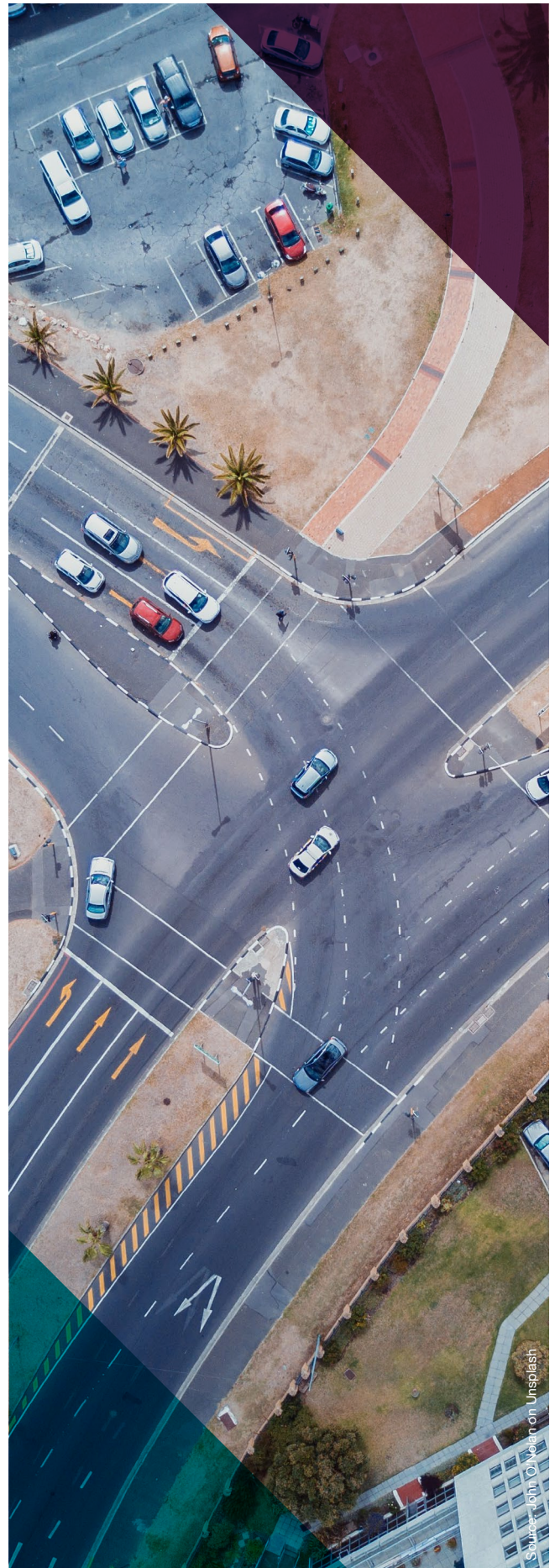
Source: SAHPRA, *General Guideline for Medical Devices and IVDs*, v2 Sept 2015⁷⁹

SAHPRA documents outline two requirements for diagnostics:

1. Establishment licensing. South African healthcare exporters, importers, distributors and manufacturers are required to register with SAHPRA, and only legally authorized local entities can approach SAHPRA for registration of a diagnostic test^{80,81}.
2. Test registration. The new regulations include a four-tier, risk-based classification system (Class A is low risk and Class D is high risk). Draft guidelines from SAHPRA indicate that STI tests would be considered Class C, or moderate-high risk.⁸² It appears that SAHPRA will look to or rely on other recognized verifications (e.g. from Australia, USA, EU, Brazil, Canada and Japan)⁸³.

While SAHPRA is currently operational, its regulatory functions for diagnostics are new and not yet fully implemented. Status updates include:

- ▶ Licensing of medical technology establishments will be required starting in October 2019, and backlogs have been cleared⁸⁴.
- ▶ Registration of diagnostic tests will begin in 2019/2020, in a phased manner.⁸⁵ According to a recent update from the medical devices industry, SAHPRA will publish updated regulations and fee schedules, expand its diagnostics staffing and publish a phased call-up plan for the registration of devices (e.g. details on priority devices, such as HIV self-test kits and high-risk products).

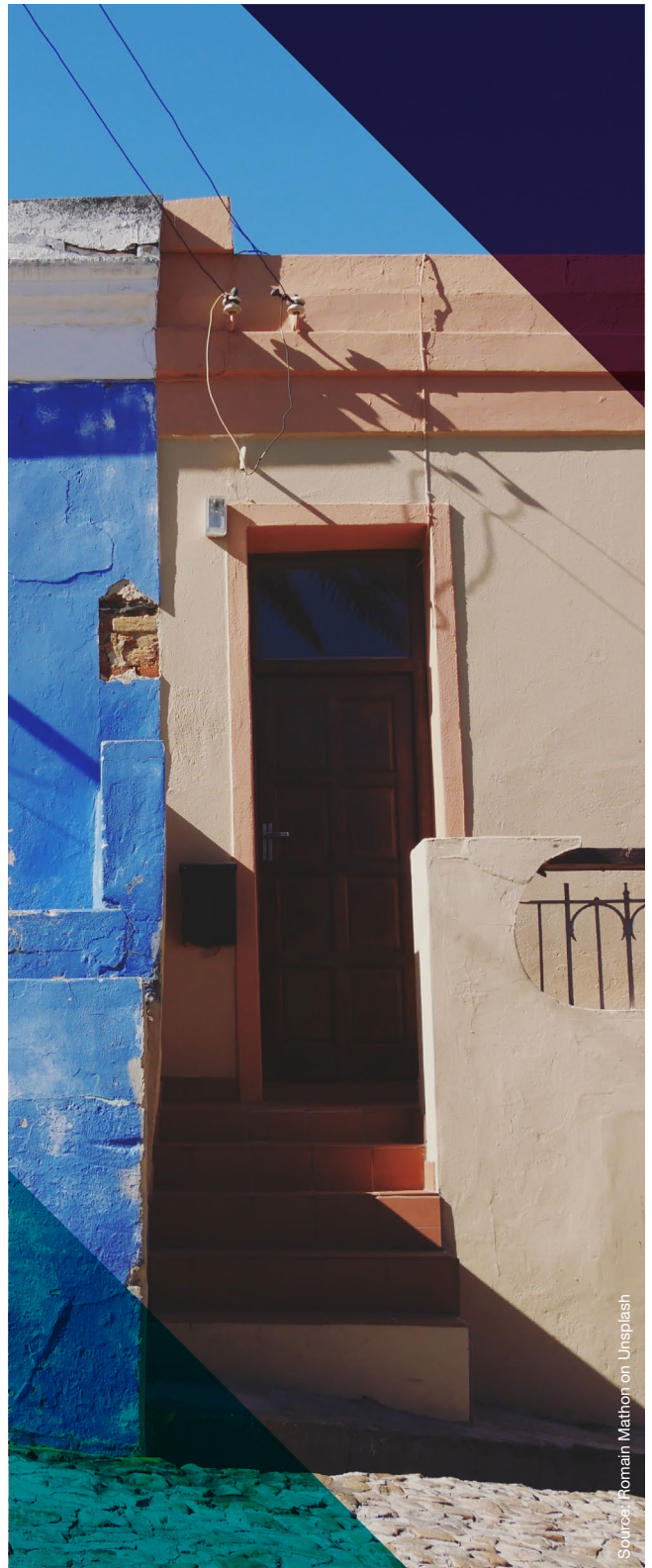


TEST INTRODUCTION AND DISTRIBUTION

A new NG/CT POC test would likely be considered by the NDoH primary care treatment guidelines and essential medicines list group, in consultation with members of the STI programme and possibly NHLS. The test would need to be included in the STI guidelines and standard treatment guidelines for the PHC level, as well as the recently developed essential diagnostics list for the PHC level in South Africa. That said, one interviewee suggested that decision-making around a new test for PHC level is likely to be “a mission”, because there was no clear focal point for POC testing at this level, with it not being clearly within the remit of NDoH primary care or NHLS. The role played by NHLS in rapid tests is often minimal, and NDoH may procure rapid tests without input from NHLS.

For the public sector, standardized tendering processes exist at NDoH (Central Procurement Agency), NHLS and provincial levels. Which entity would procure NG/CT POC tests is not clear. However, generally, a tender must be advertised, with bids examined by a tender board. The process may be weighted to support local products and companies with good Black Economic Empowerment processes. Usually, an award is given to one supplier of a given product for 2 years. For rapid tests, South Africa has relatively well-developed distribution systems in both the public and private sectors. In the public sector, diagnostics are often sent to a central depot and then distributed to provincial depots. From there they are distributed to healthcare facilities.

In the private healthcare sector, test selection is largely in the hands of individual providers, although some managed care interventions (such as formularies and treatment guidelines prescribed by funders) do exist, and for centralized testing, providers contract with one of the three major laboratory companies.



Source: Romain Mathon on Unsplash

CONCLUSION

The diagnostic testing market in South Africa is highly centralized, with NHLS performing the bulk of testing in centralized laboratories. NG, and STI incidence more generally, is poorly understood, and this hampers evidence-based decision making around STIs. Additionally, the HIV and TB epidemics have overshadowed the response to STIs, although this is slowly changing.

While symptom awareness and care seeking for STIs could be improved, experts and data both seem to suggest some improvement has occurred in recent years. Although care for general illness is predominantly sought in the public sector, there may be a greater proportion of patients seeking care for STIs from private GPs, who operate independently and are unlikely to be adhering to national guidelines. From a market perspective, while the private GP channel represents an opportunity to reach patients with a new test, it is likely one that would be difficult to implement outside of other concerted efforts (e.g. NDoH is considering delivering PrEP via private GPs, and STI diagnostics could form a part of this). The public sector is more likely to be an easier market to penetrate initially, although it is not without challenges.

Within the public sector, there is a strong imperative for change in STI management, but the path forward is unclear. Data on the high rates of untreated, asymptomatic STIs continue to emerge and, ethically, a response focusing on this asymptomatic burden is likely. The case is perhaps stronger in South Africa than in other countries, given the high HIV burden and the desire to prevent further HIV infections by reducing any potential transmission risk caused by STI-related inflammation.

There is an undeniable interest in implementing STI diagnostic testing among leading clinicians, and presumably NDoH, with funding and targets included in the NSP and the STI strategy. However, while they are aligned with WHO global strategy, as with the

global strategy, these commitments are not currently funded. The preferred NG/CT test would certainly be one capable of detecting asymptomatic infection, i.e. the more expensive, optimal NG/CT TPP.

In South Africa, unlike many low-resource countries, any new POC test would need to compete with central laboratory testing, as well as near-patient platforms such as GeneXpert. The adoption of any new test will heavily depend on how NDoH weighs the risk of loss to follow-up, and the impact of having an immediate result on the epidemic, i.e. through expedited partner therapy, which researchers are beginning to trial. One advantage of the TPP1 Optimal test compared with a near-patient option is the cost: the TPP target is US\$ 13/test, which is below the current cost of GeneXpert. The price of central laboratory platforms, however, would likely be less expensive, and the competitive response of Cepheid and other central laboratory suppliers needs to be considered. It is quite likely that the available budget, along with the cost of the test, will dictate the number of tests procured each year, and the potential target populations.

Today, the potential market in South Africa for a test like TPP 1 Minimal is less compelling. There is less urgency around replacing syndromic management, and its major limitation in the eyes of many is not overtreatment but missing cases. The investment case for testing in lieu of syndromic management is difficult to make with today's treatment prices; first-line treatments are less expensive than the proposed TPP1 Minimal test price. There may be scope for testing in women only, given the etiological data on the diverse causes of VDS, especially if there is potential to detect more infections; however, this would likely be more of a "screening" intervention, as many women who are infected do not report symptoms. The picture will certainly change if first-line treatment resistance in NG begins to emerge, as groups within NDoH are quite engaged with ABS,

and ceftriaxone is an important medicine commonly used for pre-referral and in-hospital treatments. However, even if resistance began to emerge, due to budget constraints, testing might initially be reserved for people who return with persistent symptoms, or only adopted when NDoH is forced to switch to a more expensive first-line treatment (when these become available).

There is a clear preference for self-collected vaginal swabs and/or urine testing and a rapid turn-around time, especially with a screening test. In terms of

positioning, STI testing as part of sexual health and fertility makes a compelling argument for the general population. Then, within NDoH, positioning these services as an entry to HIV care could be attractive.

Overall, although the market presents several challenges (e.g. lower priority of an ABS test and competition from central laboratory and near-patient tests), given the high burden of STIs in South Africa, the public health impact of testing could be quite compelling and therefore it is likely worth engaging further in this market.



Source: Annie Spratt on Unsplash

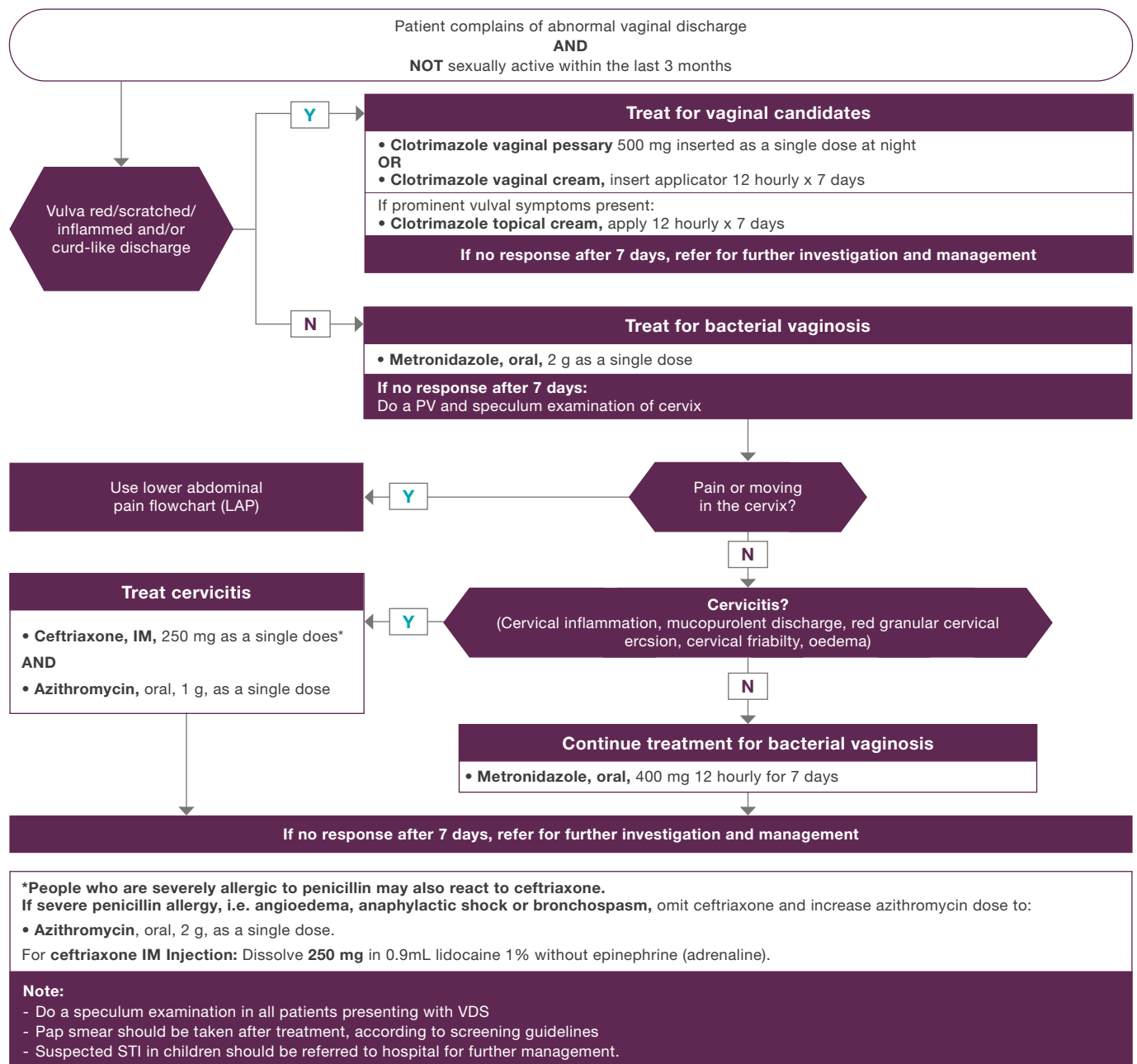
ANNEX 1: STI GUIDELINES (2018)

Note, while the 2018 Guidelines have been developed, they have yet to be widely rolled-out.

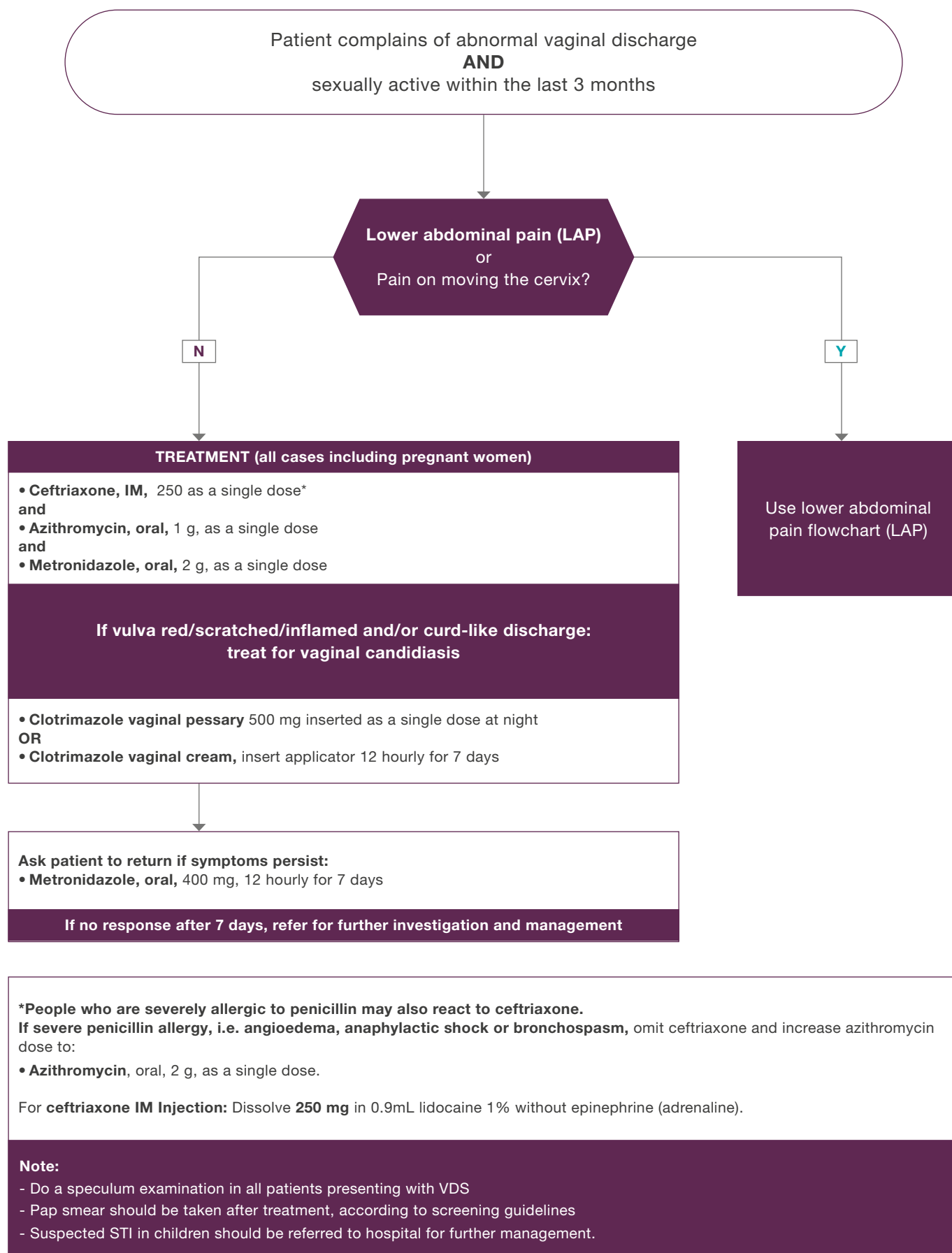
Vaginal discharge syndrome (VDS)

B37.3/N76.0/N89.8

Sexually non-active women

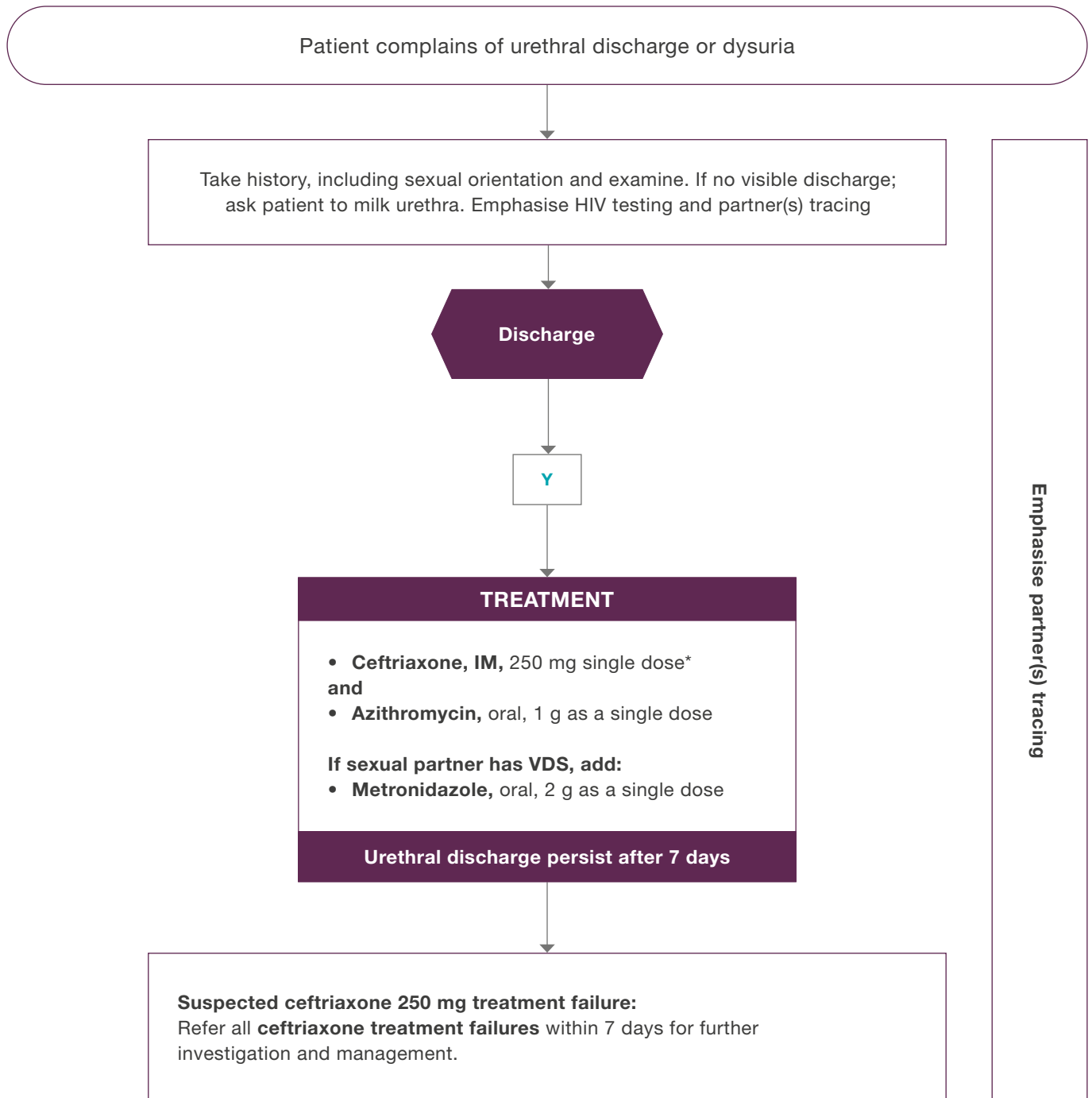


Sexually active women



Male urethritis syndrome (MUS)

A64 + N34.1



***If severe penicillin allergy, i.e. angioedema, anaphylactic shock or bronchospasm, omit ceftriaxone and increase azithromycin dose to:**

- **Azithromycin**, oral, 2 g as a single dose.

For ceftriaxone IM injection:

- Dissolve ceftriaxone **250 mg** in 0.9 mL lidocaine 1 % without epinephrine (adrenaline).

ANNEX 2: INDIVIDUALS CONSULTED AND SURVEY RESPONDENTS

Table 6: Individuals consulted

| | |
|-----|--|
| 1. | Microbiology, UCT, MAC member |
| 2. | STI research, Foundation for Professional Development |
| 3. | Provider, Program Manager, MSF |
| 4. | Provider, Anova |
| 5. | Epidemiologist, CIDER, modelling group at UCT |
| 6. | Adult Infectious Disease, UCT, MAC chair |
| 7. | Africa Health Research Institute |
| 8. | Provider, Anova |
| 9. | NICD, focal point for ABS, Head of WHO Collaborating Center |
| 10. | Head of STI section, NICD |
| 11. | STI research, Anova, (currently Foundation for Professional Development) |
| 12. | Clinician guideline expert, UCT primary care expert |
| 13. | University of Witwatersrand, member of STI Technical Working Group |
| 14. | National Department of Health, HIV/PrEP program |

Ten experts, including six of the interviewees, also responded to an online survey (Figures 21 and 22). Respondents included staff from the local WHO office and NHLS, as well as two academics.

Figure 21: Online survey respondents' areas of focus/expertise

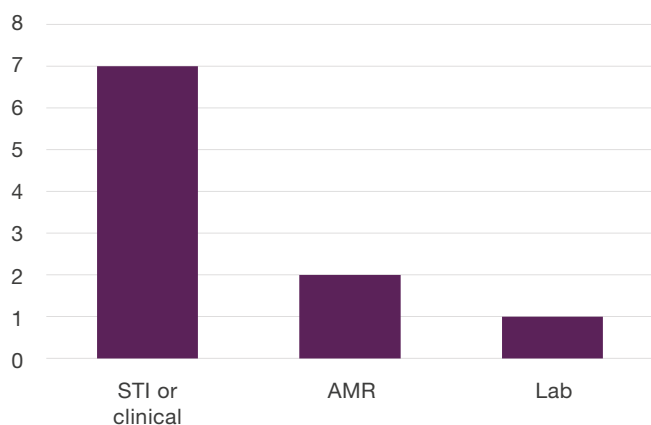
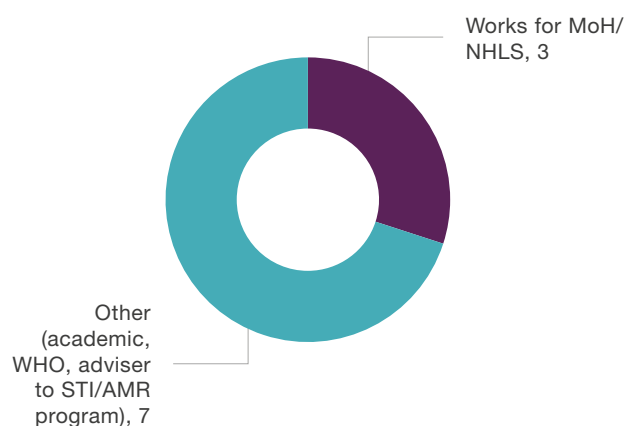


Figure 22: Online survey respondents' institutional affiliations



ANNEX 3: SOUTH AFRICA MARKET SIZING

Figure 23: NDoH reports of STI syndromes/year + NICD etiological studies on STI syndromes

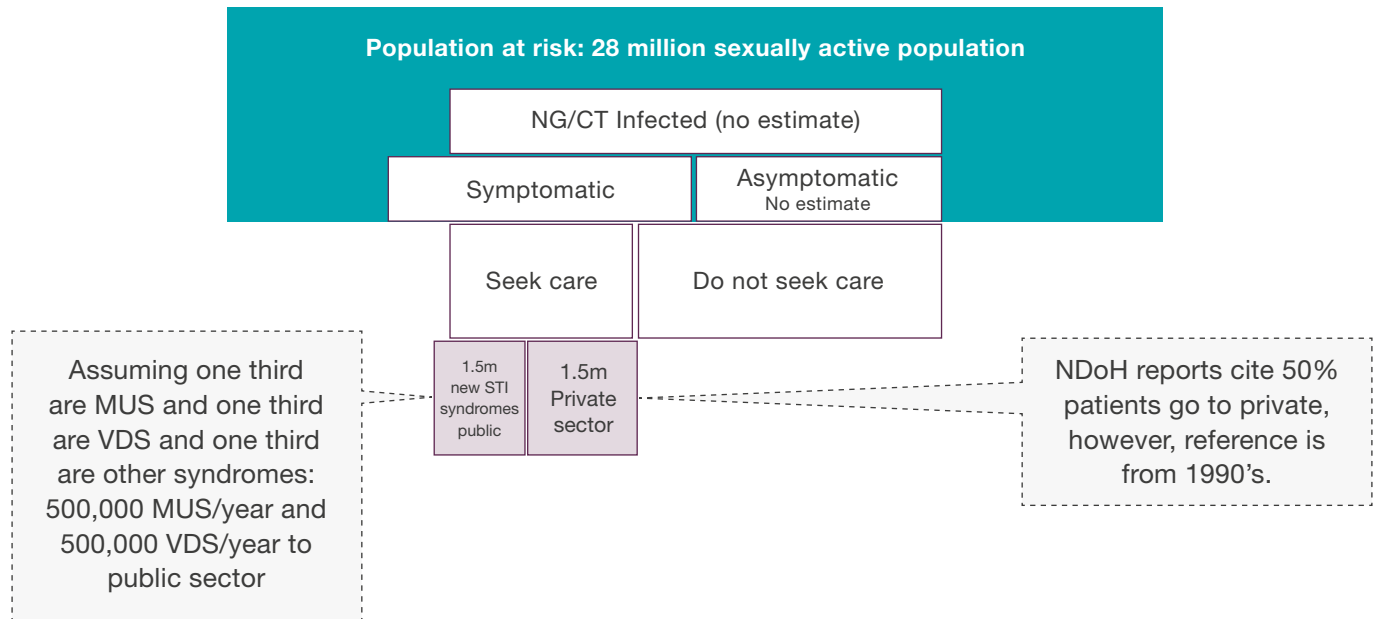
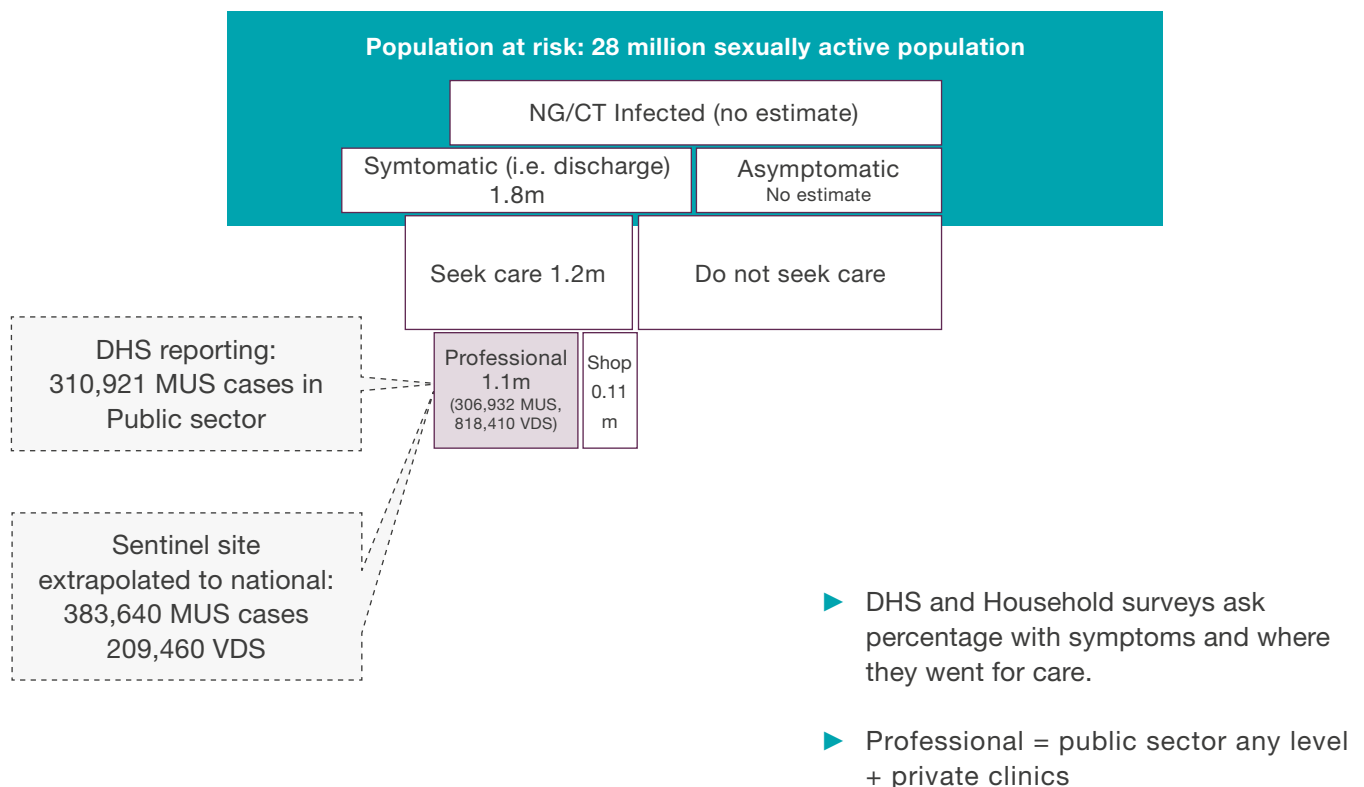


Figure 24: Household survey-derived estimates



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