Unitaid
SAVE LIVES FASTER

Gonorrhea point-of-care diagnostics technology and market

Landscape report

Executive summary

Unitaid's mission is to expand access to high-quality health products in low- and middle-income countries by investing in innovative approaches that ensure affordability and availability. This report, aligned with Unitaid's 2023-2037 strategy, highlights the critical need for improved sexually transmitted infections (STI) diagnostics in low- and middle-income countries (LMICs) and identifies potential opportunities for improving the management of gonorrhea and STI management, focusing on point-of-care (POC) solutions that enable same-day treatment.

The findings and recommendations aim to guide further discussion and action on a complex yet important issue: improving STI management in resource-limited settings and supporting global efforts to curb the spread of gonorrhea and its associated public health impacts. As this report lays out, gonorrhea touches on many public health priorities, including STIs, antimicrobial resistance (AMR), HIV, reproductive health, and maternal and newborn health.

Methods and limitations

This landscape report was developed by extensively reviewing publicly available data, expert consultations, and discussions with diagnostics developers. It utilizes the Unitaid framework to assess market shortcomings in various areas: innovation, availability, quality, affordability, demand, adoption, supply and delivery of STI diagnostics. The gonorrhea diagnostics landscape is dynamic, with over 75 point-of-care tests identified; this report focuses on a selection of these to illustrate current market offerings and pipeline products. The recommendations are not specific to Unitaid, but relevant to the broader global health community.

Public health challenge

Gonorrhea, caused by the bacterium Neisseria gonorrhoeae (NG), is a common STI with significant global health implications. The World Health Organization (WHO) estimated 82 million new cases of gonorrhea in 2020, with increasing rather than declining trends in new infections. The impact of STIs is not equally distributed globally, with many vulnerable populations and LMICs bearing a disproportionate burden.

Gonorrhea poses several critical public health challenges:

- High disease burden: The infection rate is inversely correlated with country income status, with the WHO African

and Western Pacific Regions having the highest burdens.
- Asymptomatic nature: Many infections, particularly in women, are asymptomatic, leading to untreated cases and ongoing transmission.
- Severe complications: Untreated infections can lead to pelvic inflammatory disease, infertility, ectopic pregnancy, and increased risk of HIV transmission. Gonorrhea can be passed to babies during birth, potentially causing severe eye infections and blindness if untreated.
- Antimicrobial resistance (AMR): Gonorrhea has a distinctive biological ability to rapidly mount antibiotic resistance. Penicillin, tetracycline, and ciprofloxacin have been effective in the past, but now all of the estimated 82 million annual cases are resistant to one or all of these, and there is only one recommended treatment, ceftriaxone, remaining effective. Underinvestment in diagnostics and surveillance challenges efforts to counter drug resistance. Although there are two new clinical trial-stage treatments, prices are expected to be several times the cost of existing treatments.

The cornerstone of gonorrhea control is early detection combined with prompt and effective treatment. While etiological diagnosis is optimal, the lack of affordable, rapid, point-of-care diagnostic tools renders it infeasible in most settings, and as a result low-resource settings rely on syndromic management. This approach involves making treatment decisions based on observed signs and reported symptoms, treating each of the common causes of the syndrome without confirming the specific pathogen causing the infection. While syndromic management has improved access to treatment, it has several disadvantages, including low specificity, resulting in substantial overtreatment. In 2021, the WHO recommended a shift to etiological management using diagnostics where possible. Given the substantial burden of asymptomatic infections, the WHO is also expected to issue guidance in 2024 for screening high-risk populations.

Global response and targets

The WHO prioritizes gonorrhea as one of the three major STIs of global concern, alongside syphilis and human papillomavirus (HPV) infection. Global targets for gonorrhea are ambitious, aiming to reduce new infections from 82 million in 2020 to 8.2 million by 2030. However, the global response is not on track to meet these targets, primarily due to limited visibility, funding, and implementation support.

Access gaps

The significant gaps in access to quality, diagnostics-informed care for gonorrhea vary based on whether individuals experience symptoms and how they seek care. A major issue is the high number of missed gonorrhea infections, as over half of the cases are asymptomatic, and there are currently no strategies for screening at-risk populations, contributing to long-term complications and serving as a reservoir for ongoing transmission.

Conversely, access to quality, diagnostics-informed care is a challenge for symptomatic individuals. Firstly, stigma, privacy concerns, and general access issues prevent many individuals from seeking care from accredited health services. For those seeking professional care, syndromic management results in overtreatment for infections they do not have. For example, without diagnostics, symptomatic women are likely to receive at least two and possibly four treatments. Although the WHO recommended a shift to etiological management in 2021, adoption is low, partly because fit-for-purpose, affordable tests are not available. The lack of testing also reduces visibility around STI prevalence and drug resistance, reducing the efficacy of syndromic protocols and complicating efforts to address these issues effectively.

These diagnostic access gaps result in both undertreatment and overtreatment, contributing to permanent health problems, ongoing transmission, and potential drug resistance. The gaps particularly affect women and key populations, with critical implications for reproductive, maternal, and newborn health, and HIV transmission. As drug resistance puts the last effective treatment at risk, etiological STI management and strengthened efforts to decrease incidence become increasingly important.

Technology landscape

There has been tremendous progress in developing POC diagnostics for gonorrhea and other STIs in the past five years. With over 75 POC and near-POC gonorrhea tests at various stages of development, many of the novel tests will surpass current diagnostic methods. While laboratory-based nucleic acid amplification tests (NAAT) are the gold standard for gonorrhea, their high costs and incompatibility with same-day treatment limit their utility. Though effective for urethral discharge, the microscopic review of Gram-stained smears lacks performance in other specimens and is challenging to implement consistently. Given these shortcomings, the global STI community has prioritized POC tests, and the WHO has developed target product profiles (TPPs), highlighting the importance of rapid turnaround times to enable within-visit treatment.

There are three POC and near-POC tests cleared by the U.S. Food and Drug Administration (FDA), and the pipeline includes a few antigen-detecting rapid diagnostic tests (RDTs), and several molecular options, including instrument-

free tests, small device-based systems using disposable test cartridges, and near-POC systems requiring more infrastructure, but with simple test processing steps. The tests in development rely on a variety of novel sample processing, amplification, and detection systems.

Key advances include rapid turnaround times (less than 30 minutes), enabling, for the first time, treatment based on test results during the patient's visit. Test performance is high, some on par with central laboratory tests. Self-collected vaginal swabs and urine samples improve ease of use. Multiplexing capabilities are also available, often combining tests for gonorrhea and chlamydia. These advances in STI POC test technology could have a transformative effect on STI control, improving antimicrobial targeting and reducing incidence by enabling, for the first time, screen-and-treat programs targeting high-risk asymptomatic populations.

Preliminary work on LMIC markets for gonorrhea POC tests

Estimating demand for gonorrhea tests is difficult; preliminary estimates suggest there is a large unmet need for POC NG testing and sizable target populations. However, multiple adoption barriers exist, including limited ability to pay for STI care and proposed test pricing that is several times higher than the price of current treatment. For the public sector, STI testing may be hard to prioritize if there is a substantial burden of other high-mortality diseases.

Most STI programs suffer from years of underinvestment, and as a result, countries often lack surveillance data, STI strategies, and up-to-date guidelines. Additionally, given many competing priorities, some STI programs are forced to focus narrowly on a singular sexually transmitted disease or population (e.g., congenital syphilis elimination). Underinvestment in STI programs has also reduced dedicated resources; often, national STI coordination is performed by a single focal point within national HIV programs. This approach contrasts with the reality of STI control, which encompasses many pathogens, risk groups, and providers, who, depending on the country, could include primary care nurses and specialists (e.g., dermatologists and urologists).

Another barrier to adoption relates to evidence: the morbidity caused by untreated gonorrheal infections and the impact of overtreatment on antimicrobial resistance are difficult to demonstrate. For example, gonorrhea and other STIs can be asymptomatic and transient, a proportion resolves without treatment. Sequelae, such as pelvic inflammatory disease and infertility, may have causes other than gonorrhea and may only present years after infection, making it difficult to attribute cause. Similarly, for overtreatment, without evidence of the adverse outcomes of gonorrhea infection and overtreatment, countries struggle to make the investment case for testing. Undoubtedly, testing symptomatic people allows for pathogen-specific treatment. However, the counterfactual, direct evidence of overtreatment's effect on resistance, is difficult to establish.

Given resource constraints, very few LMICs are rolling out gonorrhea testing broadly (i.e., both to all symptomatic patients and routinely screening high-risk populations), and it is likely that testing will initially focus on selected populations. As a result, the approach to STI testing is unlikely to be uniform across countries and will take time to emerge.

Partner landscape

Many partner efforts focus on developing POC technologies relevant to high-income countries (HICs) and LMICs. Few partners work on downstream activities, such as clinical trials or product introduction in LMICs. While program donors may support testing in focus populations (e.g., key populations), these donors are unlikely to support widespread testing in the near term.

Market shortcomings and challenges

Despite the robust POC pipeline and the tremendous STI burden in LMICs, several barriers prevent tests from reaching those who need them most.

Availability. Despite the dynamic and robust pipeline for POC gonorrhea and STI tests, products may not be optimal for the diverse LMIC use cases. While lateral flow tests with additional enhancements have shown promising performance, these enhancements add cost and can reduce access (e.g., additional operator steps for sample concentration, fluorescent detection requiring a reader). Additionally, few evidence-supported products are ready for introduction. While many STI tests are in late-stage development, delays in validations and regulatory clearances are common, and costs are often higher than developers anticipate. Finally, despite their critical importance, POC tests with extra genital sampling are not prioritized for development.

Quality. In 2024, WHO began drafting Technical Specifications for NG POC NAAT and antigen-detecting tests suitable for use in LMICs. However, the evidence requirements and timelines for opening prequalification (PQ) for NG tests are uncertain. Additionally, in-country quality assurance and quality control for POC STI testing are open questions.

Affordability. Both consumers and LMIC governments have limited ability to pay for STI care, and no large-scale funding is available to support STI programs. On-market test prices and indicative prices from developers suggest that affordability will be a significant adoption barrier for LMICs. The current gonorrhea treatment is inexpensive, below the cost of gonorrhea tests, providing no financial incentive to test. As treatment becomes more expensive due to resistance, the financial incentive to test may increase. However, there is little certainty about the recommended use of novel treatments (i.e., positioned as "reserve" or "first-line" treatments) and whether their use will require a diagnostic.

Financially, large screening interventions at current test prices are likely cost-prohibitive for low-resource settings. Moreover, while experts believe screening and treating is worthwhile in high-risk groups, it is difficult to build evidence for this use case because it is pragmatically very difficult to directly attribute the intervention (additional infections identified and treated) to health outcomes (e.g., infertility, poor birth outcomes, or reducing drug pressure) or to cost savings.

Demand and adoption. Few LMICs have adopted etiological testing policies for a variety of reasons. First, there are few affordable fit-for-purpose tests: on-market near-POC assays are unaffordable, and true POC tests are unaffordable and not commercialized in LIMCs. Second, LMIC policymakers generally find it hard to prioritize gonorrhea, as chronic underinvestment in surveillance has limited visibility of the burden, and morbidity data is difficult to attribute directly to gonorrhea. The investment case for testing is challenging to make without direct evidence of the harm from syndromic management and evidence of the effectiveness of testing across different use cases, including the opportunities to detect and treat asymptomatic infections. Lastly, when resources are limited, higher mortality diseases may take precedence over STI diagnostics.

Supply and delivery. The near-term lack of gonorrhea POC test demand and uncertainty about future demand disincentivize suppliers from registering and commercializing tests in LMICs. Most test developers lack the resources to commercialize in high-, middle-, and low-income countries simultaneously and will first focus on establishing their technology in high-return markets. The costs and timelines associated with being a "first mover" in LMIC markets (e.g., educating policymakers, supporting local studies, navigating registrations) may further discourage engagement.

Given the long-standing practice of syndromic management, when testing is adopted, the transition to new approaches will take time for both health workers to implement and for patients to accept. Additionally, in many settings, stigma around STIs and discrimination of affected populations continue to be barriers to dignified care and care-seeking more generally.

Opportunities for intervention

Opportunities to support NG POC testing focus on creating demand for gonorrhea testing in LMICs and incentivizing suppliers to commercialize in LMICs. It is important to appreciate that even with support, the initial uptake of gonorrhea POC tests is likely to be limited; testing for all who need it is only likely to emerge when there are lower-cost tests and more compelling evidence demonstrating the value of testing. Nevertheless, laying the groundwork for gonorrhea testing is an important global priority considering the burden disproportionately affecting vulnerable populations, as well as the threat of extensively drug-resistant gonorrhea and, with it, substantial treatment cost increases.

To address the market challenges and increase access to STI diagnostics in LMICs, several gonorrhea-focused diagnostics opportunities have been identified, including:

- While large-scale demand is not expected to materialize quickly in LMICs, there are likely small customer segments interested in gonorrhea testing who may be able to pay. Identifying and supporting the adoption and uptake of POC tests in these nascent market segments will send an important signal to the market.
- Refine LMIC demand forecasts and explore dual pricing strategies. Building on work to support nascent demand (above) more refined estimates of LMIC demand are needed to inform work with suppliers to reduce LMIC test prices and to evaluate the role of time-limited market shaping interventions.
- Fund product development for diverse user needs, including a chlamydia rapid diagnostic test, extra genital sampling, and eventually self-testing.
- Fund product validations and clinical trials in LMIC markets to incentivize suppliers to engage in these markets. Focusing on early adopter countries and linking trial participation to access terms (e.g., country registration, WHO PQ, and price), could accelerate access to POC STI tests.
- Creative approaches to demonstrating the benefits of testing are needed to build the investment case for policymakers and funders. Studies are needed to generate data on health outcomes, impacts, and testing costs. This data could inform cost-benefit studies and discussions around optimal target prices for STI testing in LMICs.
- Providing time-limited support for expanding STI focal points in ministries of health (MoHs) may accelerate test adoption and rollout. New test introductions are resource-intensive, particularly for STIs, as the diversity of target populations and providers, as well as a multitude of delivery channels, presents a challenge. Therefore, programs

would benefit from support in developing implementation models that take into account the nuances of testing in different environments, including different populations, infrastructure, and provider workloads.
- A centralized procurement mechanism to consolidate demand across a fragmented market, including many low-volume buyers and private buyers, would reduce transaction costs and ease suppliers' ability to serve small and fragmented demand.

Several priority opportunities to integrate gonorrhea and STI testing into other interventions have also been identified, including:
- STI testing should be included in integrated POC molecular initiatives. The increasing availability of POC molecular platforms in LMICs could be leveraged to ensure commitment to NG/CT test registration and access pricing.
- Strengthening POC diagnostics implementation in antenatal care (ANC) settings. Comprehensive POC testing (e.g., malaria, anemia, HIV, syphilis, and increasingly hepatitis B, and possibly STIs) alongside malaria prevention efforts can support healthy pregnancy and birth outcomes.
- Intensify integrated delivery of STI and HIV care. STI care can be an entry point for HIV care and has the potential to improve the engagement of hard-to-reach populations. Similarly, incorporating STI testing into services for patients already in HIV care is an effective means of expanding access to take advantage of frequent contact with health facilities.
- In many countries, stigma, social norms, and laws discourage identification as a key population member. New approaches to safely delivering care, for example, through STI clinics, might reach key populations without requiring individuals to identify as such.

Conclusion

The growing threat of drug-resistant gonorrhea and the advent of more costly next-generation antibiotics underscore the need for effective, affordable gonorrhea diagnostic tools. The emergence of POC gonorrhea tests represents a potentially transformative advance in STI management, and several products are already available or nearing market readiness. Despite the need and the promise of new technologies, significant market challenges impede test accessibility in LMICs. There is a high risk that products will become readily available in well-resourced settings and remain largely inaccessible in LMICs.

Addressing this disparity requires concerted efforts to generate demand for testing by heightening the perceived value of testing among stakeholders at all levels and improving the affordability and availability of fit-for-purpose tests.

Despite obstacles, it is imperative to advance POC gonorrhea testing markets in LMICs, even on a limited scale initially. Transitioning from syndromic to etiologic diagnosis will be a gradual process, heavily dependent on the availability of affordable and suitable diagnostics. Acting now, as tests become available, is an essential signal for a nascent market. Early work to implement testing will provide valuable evidence and experience and undoubtedly improve STI outcomes, especially for vulnerable populations that will benefit from diagnostics-guided care, reduce transmission, and extend the lifespan of effective antibiotics.

The growing threat of drug-resistant gonorrhea and the advent of more costly next-generation antibiotics underscore the need for effective, affordable gonorrhea diagnostic tools.

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- Numerous technology developers who participated in discussions and shared information on their products.
- Many partners and researchers who engaged in insightful conversations with us.

Their collective expertise has been instrumental in shaping this report and advancing our understanding of the field.

Abbreviations

AN	antenatal care
AMR	antimicrobial resistance
ART	antiretroviral therapy
AVAC	AIDS Vaccine Advocacy Coalition
BV	bacterial vaginosis
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CE IVDR	European Conformity In Vitro Diagnostic Regulation
CLIA	Clinical Laboratory Improvement Amendments (U.S.)
COGS	cost of goods sold
COVID-19	SARS coronavirus disease 2019
CT	chlamydia trachomatis
EGASP	Enhanced Gonorrhea Antimicrobial Surveillance Program
FDA	Food and Drug Administration (U.S.)
FIND	Foundation for Innovative New Diagnostics
FSW	female sex workers
GARDP	Global Antibiotic Research and Development Partnership
GASP	Gonococcal Antimicrobial Surveillance Program
HIV	human immunodeficiency virus
HPV	human papillomavirus
IPTp	intermittent preventive treatment in pregnancy
LBW	low birth weight
LFA	lateral flow assay
MG	mycoplasma genitalium
MoH	ministry of health
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NG	Neisseria gonorrhoeae
OTC	over-the-counter
PID	pelvic inflammatory disease
POC	point-of-care
POCT	point-of-care testing
PQ	prequalification
PrEP	pre-exposure prophylaxis
RFP	request for proposals
RTI	reproductive tract infections
STI	sexually transmitted infection
TB	tuberculosis
TPP	target product profile
TV	trichomonas vaginalis
UDS	urethral discharge syndrome
VDS	vaginal discharge syndrome
WHO	World Health Organization

1. Introduction

Unitaid's mission is to expand the reach of the best health products for those who need them most, designing and investing in innovative approaches to make quality health products available and affordable in LMICs. Unitaid accelerates the introduction and adoption of essential health products, using market-shaping approaches to enable suitable, affordable, quality supply. The Unitaid Strategy for 2023-2027 includes increasing screening and treatment for STIs as a programmatic priority. This work links to many cross-cutting areas of focus for Unitaid, including women's health, AMR, integrated diagnostics, and HIV and coinfections.

This landscape report intends to inform potential opportunities to improve the management of gonorrhea and STIs in LMIC populations, acknowledging the foundational role of diagnostic tests. Gonorrhea touches on several different public health priorities, including STIs, AMR, HIV, reproductive health, and maternal and newborn health. Work to strengthen gonorrhea testing provides an important avenue for advancing many of these priorities.

1.1 Methods and limitations

This report was prepared primarily by reviewing information in the public domain, including policymaker and partner reports, webinars, and peer-reviewed publications. Expert, partner, and diagnostics developer discussions supplemented this desk review.

Over 15 experts and partner representatives were consulted on a variety of topics, including the diagnostic test landscape, priority populations, the impact of testing and treating, the challenges of STI management and antimicrobial resistance, and public health priorities. Conversations with over 10 diagnostics technology developers and manufacturers provided more detail on specific products and technical and market challenges.

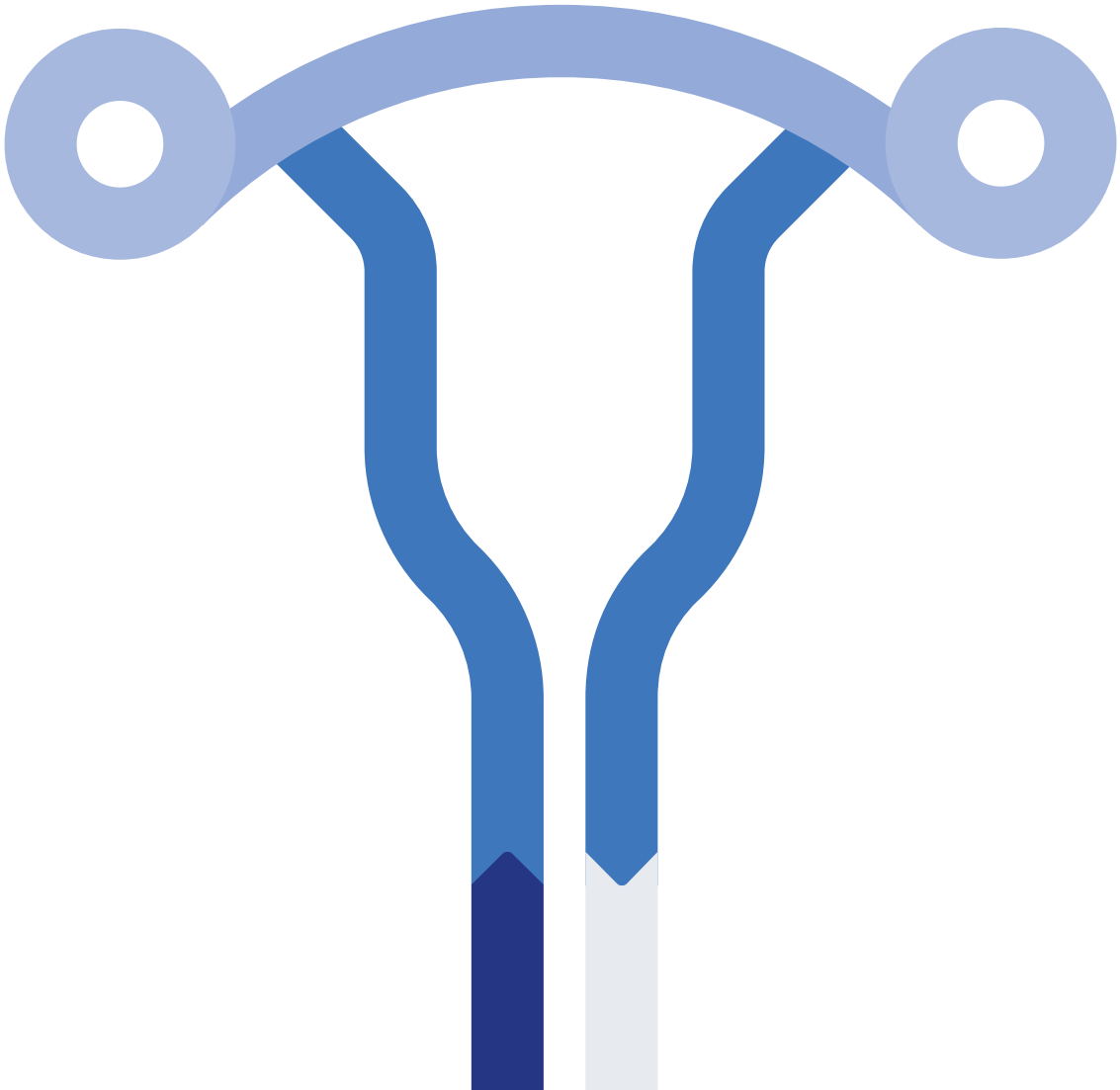
The market shortcomings analysis uses the Unitaid framework to consider gaps in innovation and availability, quality, affordability, demand and adoption, and supply and delivery. Several potential opportunities for advancing STI diagnosis and management are described. These opportunities are not specific to Unitaid, but are general recommendations meant to stimulate further discussion of this complex yet important public health priority.

Unitaid's priorities influence the scope of diagnostics landscaping activities, including its focus on decentralized delivery and person-centered care. Tests in scope include those that can be implemented where patients present for care in LMICs. For gonorrhea and other STIs, there is an emphasis on same-day treatment, which precludes sending samples to an offsite laboratory for testing. Hence, POC solutions were explored exclusively. Additionally, this report builds on other efforts. Notably, many on-market laboratory tests were reviewed in two WHO 2023 publications, WHO diagnostic landscape for sexually transmitted infections (1) and the WHO STI Laboratory and POC diagnostic testing for STIs, including HIV (2).

Tests for drug susceptibility and antimicrobial resistance were not a focus of the technology landscaping, although some of the tests do include a marker of resistance, typically ciprofloxacin. However, surveillance data, albeit incomplete, suggests high levels of ciprofloxacin resistance in LMICs (3) (4), and ciprofloxacin resistance tests are most useful where some portion of gonorrhea infections are still susceptible to ciprofloxacin, primarily in the United States (U.S.) and Europe. Commercialized tests with genetic markers of ceftriaxone resistance are not yet available.

The diagnostics technology landscape is dynamic. While pandemic-related funding accelerated platform development, the volatility in COVID-19 test demand has resulted in an unsettled market. The landscaping identified over eighty gonorrhea diagnostics; a selection is described in this report to illustrate the types of products on the market and in the pipeline. Other partners also conduct landscaping (e.g., WHO, GARDP, FIND) with varying scopes and technical and commercial details. Given the high number of products in the pipeline and other partner efforts in this space, for this landscape, developers and manufacturers were engaged and profiled based on convenience, i.e., existing relationships, partner introductions, and internet searching. Not all of the developers contacted responded.

All prices are ex-works, unless otherwise specified.



2. Public health challenges

2.1 Gonorrhea disease burden

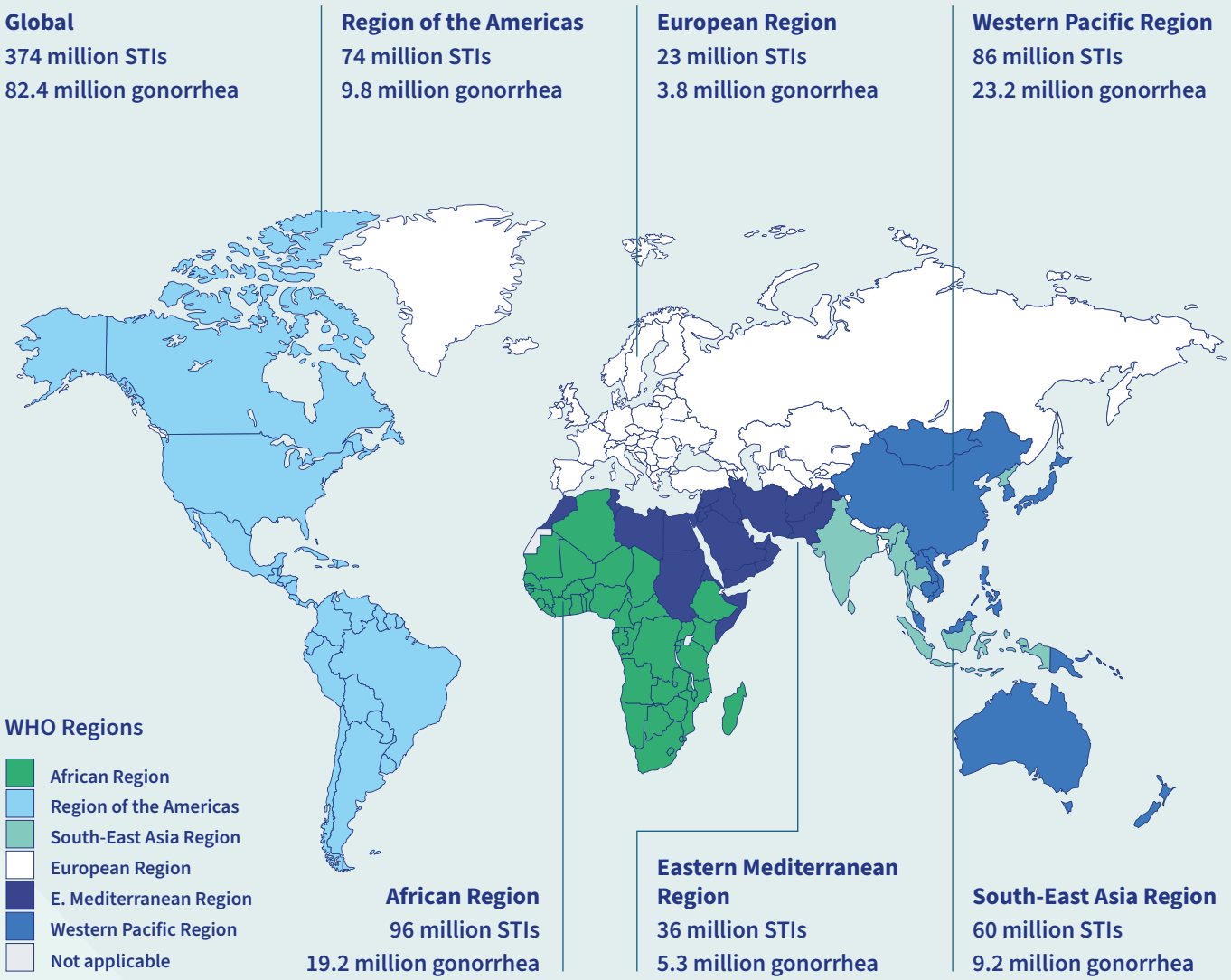
Gonorrhea is a common STI caused by the bacterium Neisseria gonorrhoeae (NG). It is an important public health concern for several reasons: the magnitude of infections and potential complications, an increased risk of HIV associated with infection, and extreme propensity for drug resistance resulting in potentially untreatable infections.

The WHO estimated 82 million new cases of gonorrhea occurred in 2020, (5) with increasing rather than declining trends in new infections[1] (6). The precise burden of gonorrhea infection is difficult to establish due to insufficient surveillance, underreporting, limited testing, and asymptomatic infection.

Globally, the impact of STIs is not equally distributed, it is more concentrated in some regions than others. Gonorrhea incidence correlates inversely with country income status. Additionally, WHO estimates that African and Western Pacific Regions have the highest burdens (Figure 1). Populations at risk vary by context as well, but generally high-risk populations include men who have sex with men (MSM), sex workers and their clients, and adolescents and young people. In high-burden HIV settings, there is mounting evidence of high STI incidence in young and pregnant women. (4) (7) (8)

1 Estimates from countries with well-established STI surveillance systems show increasing rates of gonorrhea cases **(6)**.

Figure 1. Incident cases of four curable STIs, including gonorrhea, among adults (15-49 years old), by WHO region, 2020
Syphilis (Treponema pallidum), gonorrhoea (Neisseria gonorrhoeae), chlamydia (Chlamydia trachomatis) and trichomoniasis (Trichomonas vaginalis)



Region	Adult gonorrhea prevalence
African Region	1.40%
Region of the Americas	0.50%
South-East Asia Region	0.70%
European Region	0.30%
Eastern Mediterranean Region	0.50%
Western Pacific Region	0.80%

Source: Adapted from WHO (9)

Gonorrhea is transmitted mainly through sexual practices and infects mucosal surfaces of the cervix, urethra, rectum, pharynx, and conjunctiva. Like many STIs, gonorrhea often has no symptoms, and untreated infection can lead to infertility and other reproductive health complications. Moreover, this substantial asymptomatic reservoir contributes to ongoing transmission. Additionally, prior gonorrhea infections do not confer protective immunity, and reinfection is possible.

The primary site of infection and clinical presentation differ markedly by sex (Table 1): in men, gonorrhea infects the urethra, while in women, it infects the cervix. These biological differences result in women bearing a disproportionate burden of morbidity, as many female infections are also asymptomatic and go untreated. The majority of urethral infections will become symptomatic (e.g., urethral discharge, painful urination), and, as a result, men are more likely to seek treatment. (10) Two-thirds of infections in women are asymptomatic and unlikely to be treated. While a proportion resolves without treatment, a meaningful proportion of gonorrhea infections will lead to health problems. In women, these include pelvic inflammatory disease (PID), ectopic pregnancy, infertility, miscarriage, and premature labor. Gonorrhea can be passed to babies during birth, resulting in severe neonatal eye infections that can cause blindness if not treated. In men, untreated gonorrhea can cause painful inflammation near the testicles and, rarely, infertility.

When clinical symptoms are present, they overlap with other diseases. In men, gonorrhea and chlamydia are the main causes of urethritis. In women, abnormal vaginal discharge can indicate sexually transmitted infections, such as chlamydia and trichomoniasis, causing 128 million cases and 156 million cases, respectively, in 2020 (5), as well as common conditions that are not sexually transmitted, such as bacterial vaginosis and vaginal candidiasis, caused by overgrowth of vaginal flora or yeast. Extragenital infections in both sexes are often asymptomatic and can occur with and without urogenital infection. As a result, many extragenital infections are missed if the throat and rectum are not screened, contributing to ongoing transmission.

Despite its potential for long-term irreversible outcomes (e.g., infertility), high-quality evidence on the frequency of adverse health outcomes from gonorrhea infection is limited, partly because it is difficult to attribute a specific health outcome directly to a gonorrhea infection. Gonorrhea and other STIs are often asymptomatic and transient. Sequelae, such as pelvic inflammatory disease and infertility, may have causes other than gonorrhea and may only present years after infection, making it difficult to attribute cause. Coinfection is also common; for example, 10-40% of individuals with gonorrhea infection are coinfected with chlamydia (10), further confounding efforts to estimate the health outcome of any one disease.

The situation is similar for pregnancy: significant observational data suggests that gonorrhea is among the STIs and reproductive tract infections (RTIs) that contribute to preterm birth and low birth weight (LBW). However, because there are many potential causes of LBW (e.g., infections, smoking, nutrition), attribution is difficult.

Gonorrhea infection also increases a person's chance of acquiring or transmitting HIV.[2] A recent study among youth in Zimbabwe confirmed a higher prevalence of gonorrhea in youth living with HIV than among those who were not HIV-infected (8.9% vs 2.6% gonorrhea prevalence) (15). As such, the WHO, with its partners, is advocating for stronger and integrated STI management in the effort to reach HIV targets, including ending AIDS by 2030.

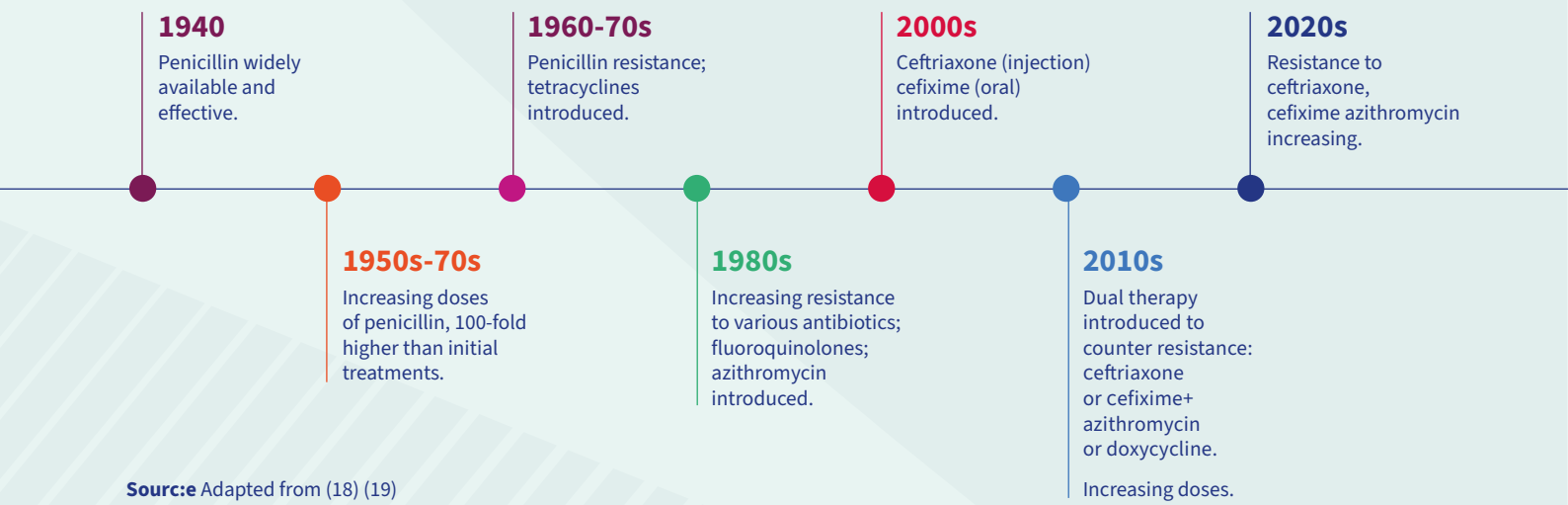
2 While there is strong observational evidence indicating that STI infections, including gonorrhea, facilitate both the transmission and acquisition of HIV (75), trials measuring the impact of implementing STI treatment on HIV prevalence have had mixed results. Experts attribute the mixed evidence to a range of factors, including the HIV epidemic maturity, STI prevalence, and the services offered (76) (77).

Table 1. Summary of gonorrhea infection clinical presentation and priority concerns

Population	Primary site of infection	Estimated proportion symptomatic and asymptomatic	Primary symptoms	Priority concerns for untreated infection (individual level, not population)
Female	Cervix	34% symptomatic 65% asymptomatic	Some women notice abnormal discharge	Some infections will resolve after 5-6 months with no lasting health problems. Experts suggest that up to half of infections ascend to reproductive organs causing pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain, and infertility. Multiple STI infections likely increase infertility risk.
Male	Urethra	60% symptomatic 40% asymptomatic	Discharge; painful/ difficult urination; pain	Most cases of untreated urethritis resolve spontaneously after several weeks, some cause epididymitis.
Male and female	Rectum	Most are asymptomatic	Proctitis (inflamed rectum), pain	Increased risk of HIV transmission resulting from inflammation and increased viral shedding.
Male and female	Pharynx	Majority are asymptomatic	Mostly asymptomatic, some have sore throat	Increased risk of drug resistant infection.
Newborns	Eyes	Transmission rates are ~ 30-50% to the unborn baby.	Conjunctivitis	Blindness, the standard of care is ointment applied to eyes at birth to prevent.

Sources: (10) (16) (17) and expert discussion. Note: estimates of symptomatic vs. asymptomatic vary, and require additional refinement and study.

Figure 2. Timeline illustrating resistance-induced changes in gonorrhea treatments: penicillin, tetracycline, and ciprofloxacin have been effective in the past, but now all of the estimated 82 million annual cases are resistant to one or all of these.



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Today, there is only one remaining recommended gonorrhea treatment, ceftriaxone, and it is at risk.

2.2 Drug-resistant gonorrhea

Gonorrhea is a major public health concern because of its rapid ability to mount resistance to antibiotics. Over time, gonorrhea has consistently developed decreased susceptibility, followed by resistance to available antibiotics, requiring dose modification of existing drugs and introduction of new treatments (Figure 2). On top of gonorrhea’s inherent biological tendency to mutate rapidly, poor quality antibiotics (20), unrestricted access to antibiotics, inappropriate selection and overuse of antibiotics contribute to selection pressure, resulting in drug resistance.

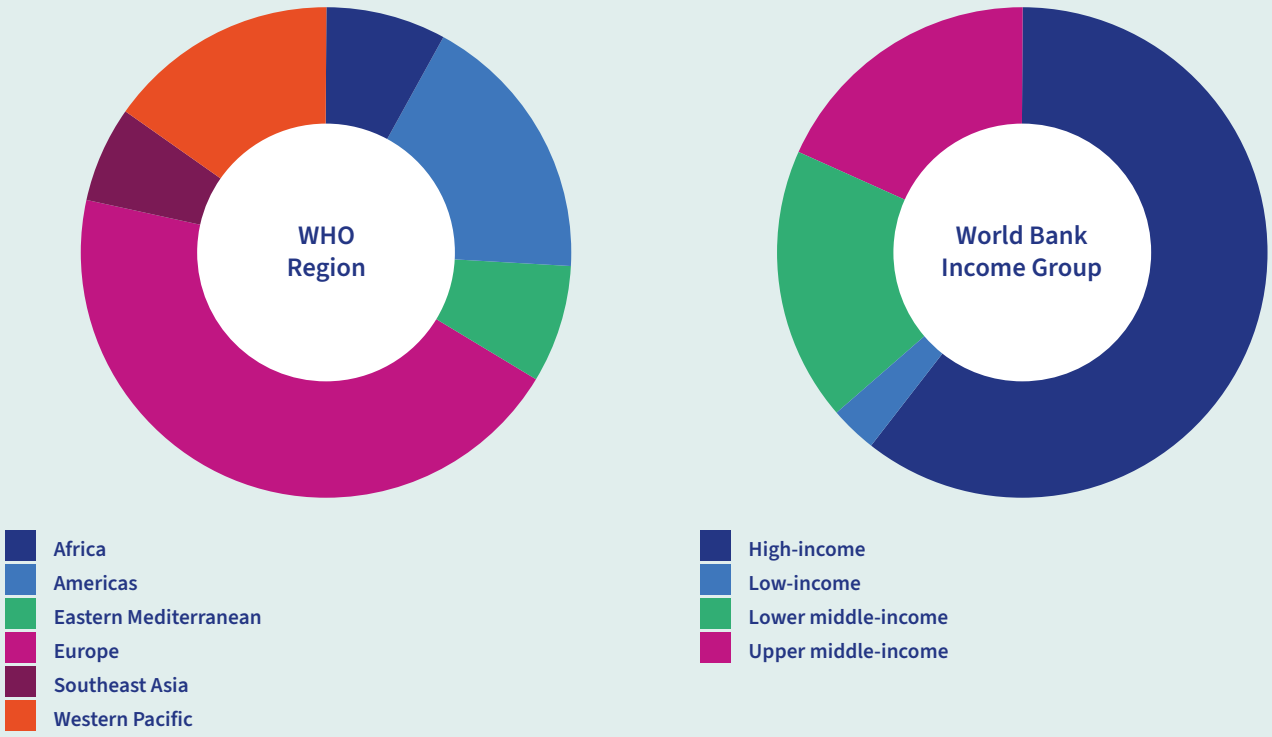
Today, there is only one remaining recommended gonorrhea treatment, ceftriaxone, and it is at risk. In the past decade, drug resistance to ceftriaxone has emerged, and several treatment failures have been reported. There is mounting evidence of international spread (21) (22) and considering the high global gonorrhea prevalence, ceftriaxone resistance may exist undetected due to lack of surveillance.

In response to a rapidly evolving resistance landscape, in July 2024, the WHO updated its treatment recommendation for gonorrhea by increasing the treatment dose of injectable ceftriaxone from 250mg to 1 gram (23), in order to delay the development of resistance to this last-line treatment option. Acceptance by patients is a concern; the WHO suggests the increased ceftriaxone dose may be painful and to consider lidocaine with the injection for pain relief. Additionally, the WHO has dropped a former recommendation for dual therapy with ceftriaxone and azithromycin, preferring to reserve azithromycin for emerging STIs.

The WHO classifies ceftriaxone as a “watch” antibiotic. Generally, “watch” antibiotics should be monitored to avoid overuse as they have a high potential for selection of drug resistance and are critical for managing sicker patients, e.g., ceftriaxone is often a pre-referral treatment or used in hospital facilities. (24)

The WHO Gonococcal Antimicrobial Surveillance Programme (GASP) monitors resistance globally (Figure 3). However, the global picture is incomplete, partly because of the low availability of microbiological culture, which is essential for drug susceptibility studies. Additionally, available drug resistance surveillance data often has limitations, e.g., insufficient sample size, gaps in the representativeness of the isolates tested, and too few antibiotics included (Table 2). (25) In response, WHO has developed standard surveillance protocols and is expanding support to 14 sentinel countries (Thailand, the Philippines, Cambodia, Uganda, South Africa, Malawi, Viet Nam, Côte d’Ivoire, Zimbabwe, Indonesia, Brazil, Argentina, India, and Qatar) to improve surveillance through the Enhanced Gonorrhea Antimicrobial Surveillance Program (EGASP) (26).

Figure 3. 66 countries reporting to WHO Gonococcal AMR Surveillance Programme in 2018, by WHO Region and World Bank income group



Source: Analysis of WHO Gonococcal AMR Surveillance Programme data

Table 2: WHO Gonococcal AMR Surveillance Programme 2017 and 2018 data

Treatment	Proportion and number of countries reporting decreased susceptibility or resistance
Ceftriaxone	31% (n=68)
Cefixime	47% (n=51)
Azithromycin (used with Ceftriaxone or Cefixime)	84% (n=61)
Ciprofloxacin	100% (n=70)

Source: September 2021 The Lancet Microbe published the latest results from a retrospective observational study of WHO's global antimicrobial resistance surveillance (GASP/GLASS (1)) for Neisseria gonorrhoeae isolates from 2017-2018

Current approaches to treating patients with drug-resistant gonorrhea vary and may involve increasing dosages, combinations of antibiotics and intravenous antibiotics. Drug-resistant gonorrhea can prolong infection when initial treatments do not work, increasing the likelihood of long-term complications and transmission of drug-resistant strains. When resistance is present in a population, guidelines and treatments must be updated, additional testing is required to confirm infections have been cleared ("test of cure"), and contact tracing stepped up.

Resistance is of special concern in sexual networks that have high gonorrhea transmission, such as MSM and female sex workers (FSW). Experts also believe that oral pharyngeal infections contribute disproportionately to resistance; other *Neisseria* species are common in the oropharynx, and gene transfer occurs in these sites. Additionally, most oropharyngeal infections are asymptomatic and can last approximately 15 weeks, serving as a transmission reservoir for drug-resistant strains (27).

Although crucially needed, the pipeline for new affordable antibiotics is limited (see novel treatments section below). Gonorrhea vaccines are also in early stage of development. Vaccine efforts include WHO development of preferred product characteristics, trialing the effect of existing meningitis B[3] vaccines to reduce gonorrhea infection, a GSK investigational vaccine that received FDA fast track status in 2023, and several other preclinical vaccine candidates. (28)

2.3 Gonorrhea current standard of care, global guidelines

2.3.1 Moving from syndromic management to etiological diagnosis

The cornerstone of gonorrhea treatment is early detection combined with prompt and effective treatment to cure clinical symptoms, prevent complications and reduce onward transmission.

While etiological diagnosis is optimal, the lack of affordable, rapid, POC diagnostic tools render it infeasible in many low resource settings, and as a result the WHO introduced syndromic management for STIs over three decades ago (29) (30). Syndromic management involves making treatment decisions based on signs observed by the clinician and symptoms reported by the patient. Common signs and symptoms are associated with syndromes, and treatment is based on the most common pathogens causing a syndrome. Gonorrhea is a potential cause of urethral discharge syndrome (UDS), vaginal discharge syndrome (VDS), and rectal discharge syndrome. For each syndrome, WHO develops flowcharts and treatment recommendations to guide clinicians. WHO recommends that programs periodically validate and customize the flow charts and treatment recommendations by conducting local etiology[4] and drug susceptibility studies.

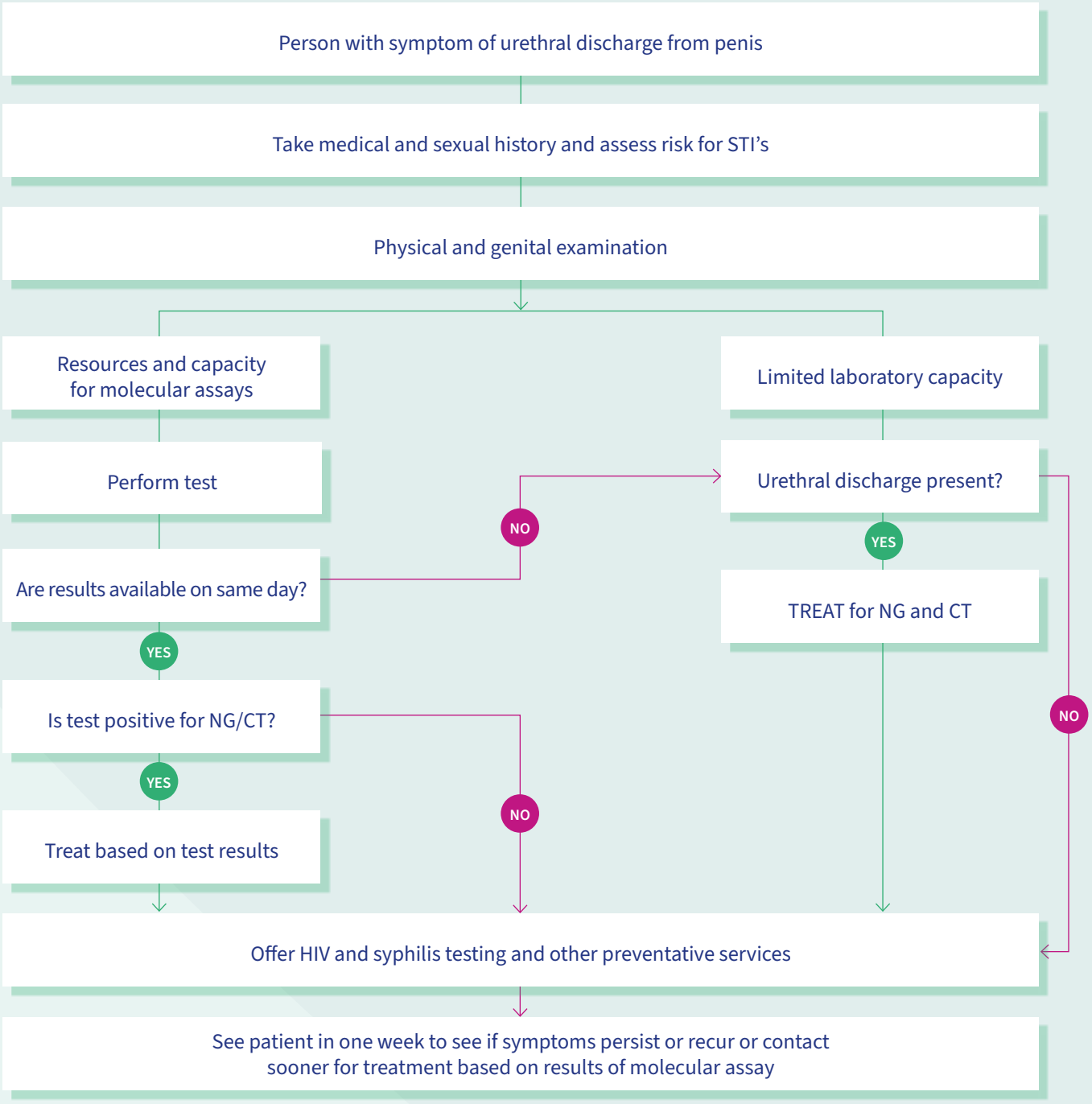
Today, syndromic management flow charts are the standard of care in most low-resource settings and remain a cornerstone of STI treatment based on their scalability, efficiency, and ability to treat immediately (i.e., during the consultation). However, syndromic management has disadvantages: First, the specificity of syndromic management is low, resulting in substantial overtreatment, especially in women. Second, many infections are asymptomatic, resulting in missed opportunities to detect and treat infection in high-risk populations. Third, syndromic regimens are usually single dose, which provides suboptimal treatment for some infections and may result in treatment failure. Finally, there is limited guidance on treatment of people with persistent or recurrent symptoms who may require a different treatment. Thus, the long-term public health priority is an etiologic diagnosis, especially as POC diagnostics come to market, STI burdens increase, and antimicrobial susceptibility threatens effective and simple treatments.

In 2021, the WHO (31) recommended incorporating etiological management where testing is feasible and available, i.e., recommending syndromic management if same-day diagnosis and treatment is impossible. (Figure 4 and Figure 5).

For men with UDS, molecular testing is recommended to confirm gonorrhea or chlamydia infection, with treatment based on the test results. If a molecular test is not available, then syndromic management, wherein both gonorrhea and chlamydia are treated, is recommended. Most experts suggest that syndromic management of urethral discharge is relatively

3 A pathogen closely related to NG.
4 Etiology studies are carried out in representative populations to determine, using diagnostic tests, the most common infections contributing to the syndrome.

Figure 4. WHO flow chart for the management of urethral discharge from the penis



Source: (30)

NG, N.gonorrhoeae; CT, C. trachomatis.

* If molecular assay was performed and results were not available on the same day, revise the syndromic treatment initially provided according to the test results when available.

If test is negative but urethral discharge is present, treat for non-gonococcal/nonchlamydial urethritis (such as M. genitalium, T. vaginalis or herpes simplex virus).

effective, especially if well-informed by an understanding of the local prevalence of gonorrhea, chlamydia, and other STIs contributing to urethral infection.

The flowchart for VDS is complex, and syndromic management is the default. There are four different options based on the diagnostic test and clinical examination capacities (e.g., RDT or molecular test availability, staffing and training, and suitable setup for speculum exam). Molecular testing is recommended, but if unavailable, the guidelines recommend a gonorrhea/chlamydia RDT with a minimum sensitivity of 80% and specificity of 90% to confirm or exclude gonorrhea and chlamydia.[5] If neither test is available, a speculum exam is recommended to inform the decision to treat cervical infections (i.e., gonorrhea and chlamydia). However, speculum exams are infrequent in low-resource settings because of time and space constraints and limited patient acceptance. Absent testing and speculum exams, WHO recommends syndromic management for VDS.

Unlike UDS, there are five common causes of VDS, and often multiple of these are present. Gonorrhea and chlamydia, bacterial vaginosis (the most common cause vaginal discharge), trichomoniasis, and candidiasis must be considered. As a result, several treatments are recommended: a single dose of injectable ceftriaxone for gonorrhea, a week of twice-daily oral doxycycline for chlamydia; oral metronidazole for seven days for trichomoniasis and bacterial vaginosis; and treatment for yeast infections. While syndromic management expands access because it is inexpensive and easy to implement, a 2019 review of studies examining the diagnostic accuracy of basic VDS flow charts reported 28% sensitivity and 57% specificity.(32)

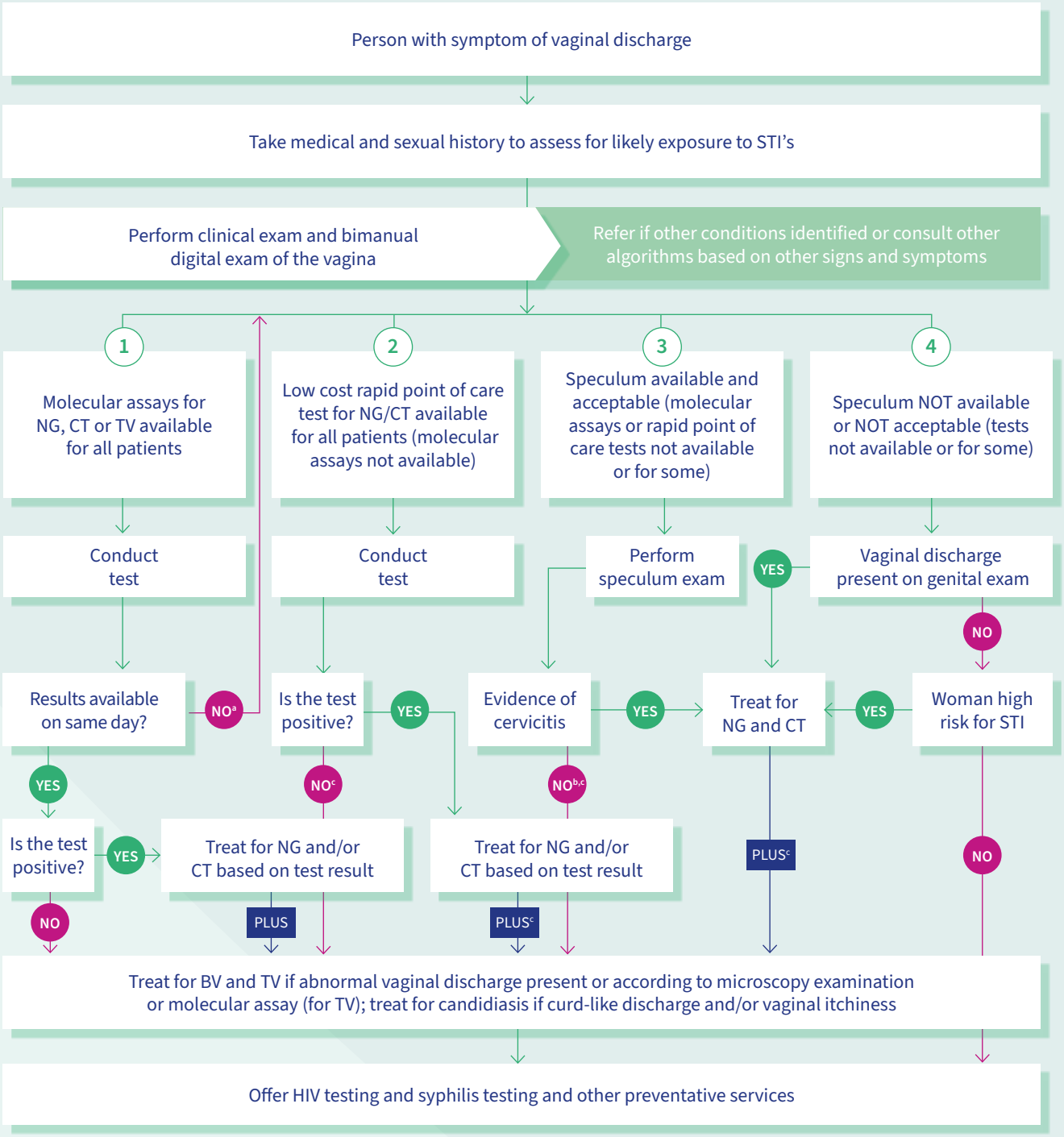
Effective STI case management includes notification and treatment of sexual partners to break the chain of infection. Often, sexual partners are unaware of their infection, given high rates of asymptomatic infection. There are many options for notification: the infected person may deliver contact-tracing cards to their partner(s) referring them to a clinic; health care workers can attempt to notify partners; or treatment for sex partners can be given to the index case ("expedited partner therapy"). Partner notification is resource intensive and not always implemented. In the absence of diagnostics, providers struggle to implement partner notification for women because they cannot determine whether the syndrome is caused by a sexually transmitted infection or by one that is not transmitted sexually (i.e., bacterial vaginosis, candidiasis).

For male and female patients whose symptoms do not resolve, clinicians must discern if the patient was reinfected, if the infection is drug-resistant, or if the symptoms are caused by a disease other than those covered in the syndromic flow chart. WHO provides some additional guidance for these scenarios.

The long-term public health priority is an etiologic diagnosis, especially as POC diagnostics come to market, STI burdens increase, and antimicrobial susceptibility threatens effective and simple treatments.

5 These cut-offs are derived from modeling studies that suggest that a test with these characteristics will lead to fewer missed and falsely treated people compared to syndromic management or no treatment.

Figure 5. WHO flow chart for health care providers to manage vaginal discharge according to local availability of resources and preferences.



Source (31)

NG, N.gonorrhoeae; CT, C. trachomatis; TV, Trichomonas vaginalis; BV, bacterial vaginosis.

[a] If molecular assay was performed and results were not available on the same day, revise the syndromic treatment initially provided according to the test results when available.

[b] Perform rapid point of care test or molecular assay if available to confirm NG/CT and treat if positive; if negative do not treat and ask woman to return if symptoms recur.

[c] If woman complains of recurrent or persistent discharge refer to a centre with laboratory capacity.

2.3.2 Asymptomatic infections and anticipated guidance updates

Considering that the syndromic approach will not address many gonorrhea infections, the WHO is considering the evidence for screening in specific populations (e.g., high-risk groups, pregnant women). New guidance is expected in late 2024. Currently, WHO recommends STI screening in pre-exposure prophylaxis (PrEP); however, a recent review of national PrEP guidance found that one-third did not mention STI services (33). Periodic NAAT testing for urethral and rectal gonorrhea and chlamydia infections is recommended for MSM, trans and gender diverse people (34) and periodic gonorrhea, chlamydia and syphilis screening is recommended for sex workers (35).

WHO is also currently reviewing evidence on the use of doxycycline as post-exposure prophylaxis (doxy-PEP) for STIs in high-risk populations (e.g., MSM and transgender women who have had bacterial STI in the past year) (6). Trials have recently shown doxycycline taken after sex can reduce syphilis and chlamydia infections by >70% and gonococcal infections by approximately 50% (36).

2.3.3 Novel gonorrhea treatments

The pipeline of novel antibiotics is limited, and includes two clinical-trial stage treatments (37). In November 2003, Innoviva and Global Antibiotic Research and Development Partnership (GARDP) announced positive Phase III trial results for zoliflodacin, a new single-dose oral antibiotic indicated specifically for gonorrhea, (38) suggesting that a 2025 U.S. FDA submission is plausible. In April 2024, GSK announced favorable phase III trial results for gonorrhea treated with two oral doses of gepotidacin, an antibiotic also being developed for uncomplicated urinary tract infections. (39)

While novel treatments for gonorrhea are urgently needed, policymakers are grappling with several challenges regarding their use. On the one hand, there is a desire to conserve the efficacy of the new treatments by reserving them for drug resistant infections. On the other hand, widespread use (i.e., adoption as the first line) would enable lower prices through scaled production. It would also strengthen the supplier's incentive to register and commercialize the new treatment in LMICs. Affordability is a critical concern: current first-line gonorrhea treatments are < US$2, while novel treatment prices will likely exceed US$25. Without market intervention, LMIC demand will be limited at high prices. Additionally, over the counter use with poor stewardship is a concern, as are the formulations (one is a powder, another is a multiple-dose treatment).

Consequently, several approaches to new antibiotic introduction are possible, and many open questions remain. For example, treatment could be reserved for confirmed resistant cases. However, without advanced diagnostics, it is difficult to document failure. Alternatively, (or eventually) a country could adopt the new antibiotic as the first-line treatment for gonorrhea once a certain threshold (e.g., 5%) of resistance to the current first-line treatment is surpassed. In this scenario, whether the new treatment requires a confirmed gonorrhea diagnosis or could be used in syndromic management is a critical open question for diagnostic markets.

Individualized treatment based on genetic resistance markers might be possible using POC NAAT tests that include gonorrhea and resistance markers.[6] In some countries where infections are susceptible to older drugs (e.g., ciprofloxacin in the U.S.) and POC tests with resistance markers are available, treatment may be guided by test results. However, developers have not prioritized genetic markers for ceftriaxone drug resistance – the most relevant marker for LMICs – and the availability of low-cost tests is prerequisite for consideration of an individualized approach in LMICs.

6 While culture can provide drug susceptibility information, it is not routinely available, and results take several days. In settings where drug resistance surveillance data is available, programs can select genetic resistance markers for the most common forms of drug resistance and use the results to guide treatment.

2.4 STI care seeking and delivery

Data on STI care seeking and delivery of care have not been systematically captured at the national or global level. However, to improve monitoring of the STI response, in July 2024, the WHO released a framework for STI monitoring which recommends 11 policy, programmatic, and impact indicators (40). Because this information is not yet available, the overview below draws on expert interviews and one-off efforts (e.g., household surveys, academic studies, or market research).[7]

In all settings, due to stigma, privacy, and confidentiality concerns, many patients avoid the public sector, preferring private clinics, traditional healers, pharmacies, or drug shops. Experts suggest that many individuals attempt traditional medicine or self-medication via pharmacies before seeking professional medical care, especially if the individual has been treated previously for similar symptoms.

Generally, in sub-Saharan Africa, STI care is integrated into primary care. In urban areas, there may be other options, such as public and non-profit key population clinics or STI clinics housed in referral hospitals. Syndromic management is used in African countries at almost every level except at referral hospitals, which may perform testing, especially for referred individuals who have not responded to treatment.

In the Indian public sector, care is delivered through STI clinics where syndromic management is well established and simplified through the use of color-coded pre-packaged treatments corresponding to a particular syndrome. STI counselors and peer educators frequently dispense treatment.

In other regions, STI care is available at the primary level, but specialty clinics (e.g., STI, dermatology, urology, or gynecology) see most patients. Etiological testing policies exist in some countries (e.g., Thailand and Viet Nam), and the diagnostic used is Gram-stained microscopic slides. However, Gram stain does not perform well in women, and staffing and workloads often preclude timely results, leaving providers to treat based on syndromes. Even in countries with etiologic policies, syndromic management is expected at the lower tiers of the health system as infrastructure, staffing, and workloads preclude performing Gram stain.

2.5 Global response and targets

Due to its high burden and potential for resistance, the WHO prioritizes gonorrhea as one of the three major STIs of global concern, alongside syphilis and HPV infection (41). Global targets for gonorrhea are ambitious: reducing new gonorrhea infections from 82 million in 2020 to 65.8 million in 2025 and 8.2 million in 2030 (41). Despite calls for reenergizing and reframing the global response, it is not on track to meet these targets, primarily due to limited visibility, funding, and implementation support (42).

A WHO Global Action Plan guides efforts to monitor and control gonorrhea drug resistance (43). Strengthening surveillance is a priority, and in 2021, 38% of countries reported data to the WHO surveillance program, GASP. Significant effort will be required to achieve the target of >70% of countries reporting by 2030 (6). The WHO's AMR response also prioritizes drug-resistant gonorrhea, considering it among the "high priority" drug-resistant bacterial pathogens (44). While many LMIC national action plans for AMR include gonorrhea in their scope, national action plans are often underfunded, and gonorrhea is usually in the latter phases of work.

7 For example, FIND and AVAC have each conducted studies in several countries. See: https://www.finddx.org/tools-and-resources/access-and-implementation/market-and-landscape-insights/and https://avac.org/resource/results-from-sti-landscaping-analyses-in-east-and-southern-africa-parts-1-and-2/

3. Access gaps

The gaps in access to diagnostics-informed quality care for STIs differ by whether the individual experiences symptoms and how they seek care, as described below. (Figure 6)

3.1 Many missed gonorrhea infections

More than half of the estimated 82 million annual gonorrhea infections are asymptomatic. There is little high-risk population screening; infected individuals are at risk for long-term complications such as infertility. At the population level, asymptomatic untreated infections serve as a reservoir for ongoing transmission.

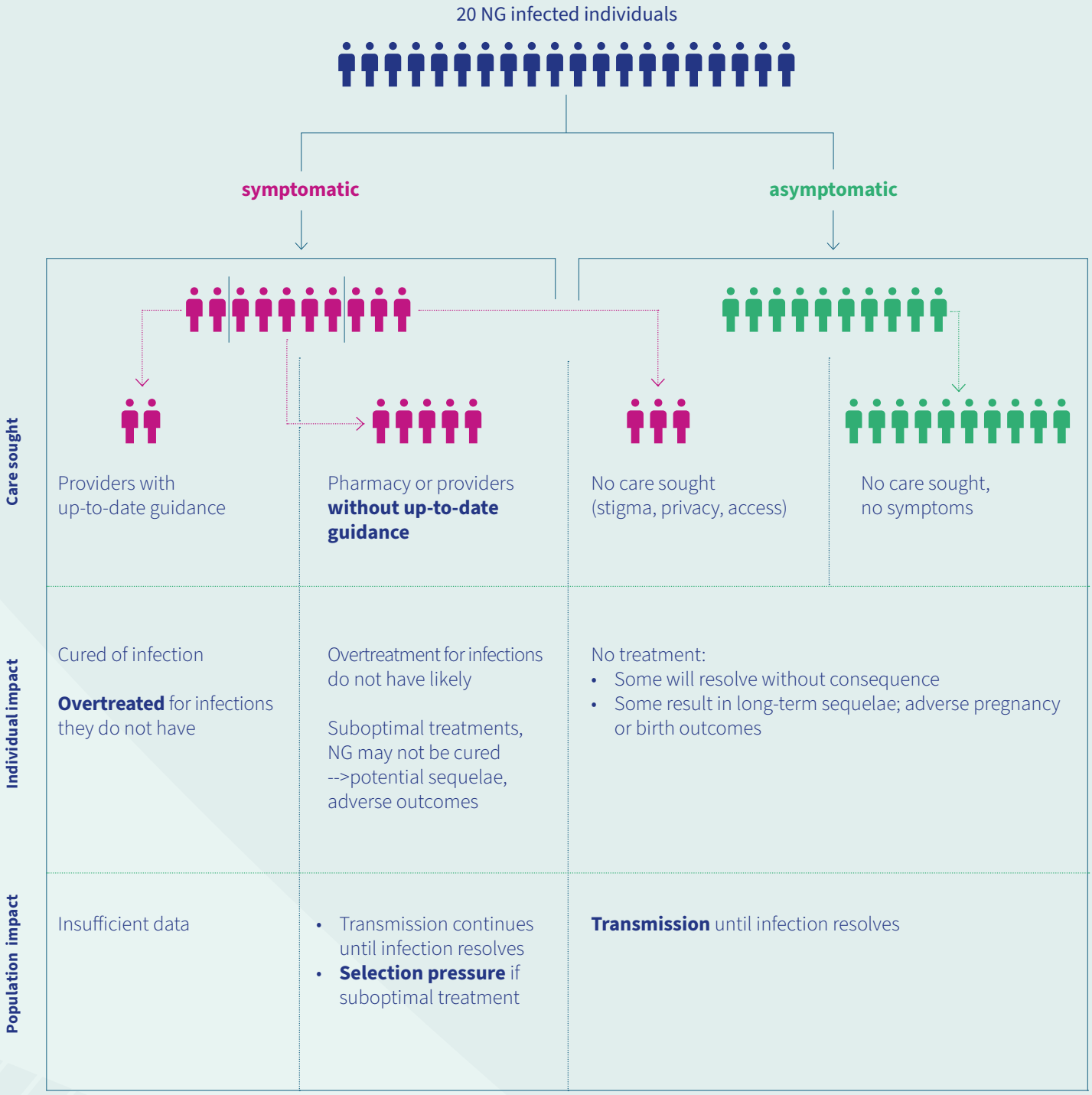
More than half of the estimated 82 million annual gonorrhea infections are asymptomatic. There is little high-risk population screening; infected individuals are at risk for long-term complications such as infertility.

3.2 Uninfected, symptomatic individuals are overtreated

The 2021 WHO guideline recommending etiologic management has not been widely adopted: most case management continues to be syndromic, apart from a few sites such as higher-level facilities and private urban hospitals.

Without diagnostics, uninfected individuals with STI symptoms (e.g., vaginal discharge, urethritis) are overtreated. These individuals may have another STI (e.g., CT, trichomonas vaginalis (TV)) or reproductive tract condition (e.g., bacterial vaginosis (BV)). Without diagnostic tests, they receive unnecessary ceftriaxone, putting them at risk for allergic reactions and antibiotic side effects, as well as less well-understood harms from antibiotics, for example, the killing of bystander organisms and microbiome impacts. At the societal level, unnecessary use contributes to drug selection pressure and resistance. Additionally, in the countries that have not recently conducted etiological studies, syndromic STI management could also result in individuals receiving several treatments that do not cover their infection (undertreatment).

Figure 6. Illustrative care paths and outcomes for gonorrhea-infected populations when testing is not available



3.3 Poor management of symptomatic gonorrhea infections

For individuals with STI symptoms, accessing quality STI care is challenging. First, stigma, privacy concerns, and general access issues (e.g., low awareness, cost, distance, convenience) prevent many from seeking care at all. In some countries, it is unsafe for key populations to access treatment as doing so requires identifying as a member of a criminalized population group.

Many symptomatic individuals seek care from providers using syndromic guidelines. While they are likely to receive effective treatment for their gonorrhea infection, under syndromic management they will also be overtreated for several infections they do not have. In the many countries that have not recently conducted drug susceptibility studies to update their treatment guidelines, individuals may not actually receive effective treatment for their strain of gonorrhea (because of drug resistance).

Other symptomatic individuals access care through informal providers, pharmacies, and drug shops. Little is known about STI management practices in these settings, but diagnostics and the recommended gonorrhea treatment (e.g., injectable ceftriaxone) are usually unavailable, resulting in both use of less effective gonorrhea medications and unnecessary treatments.

3.4 Impact of diagnostic access gaps

Collectively, the lack of access to NG diagnostics and quality case management for STIs in LMICs results in undertreatment and overtreatment, contributing to permanent health problems, ongoing gonorrhea transmission, and potential drug resistance. Asymptomatic infections are a major gap, particularly affecting women and key populations. Untreated gonococcal infections have critical reproductive, maternal, and newborn health implications, including amplifying the risk of HIV acquisition and transmission. Additionally, overtreatment can harm patients and contribute to drug resistance. Etiological STI management becomes increasingly critical as the number of effective antibiotics decreases, because drug resistance prolongs infection duration, increasing treatment costs and the burden of gonorrhea. While novel treatments are in late-stage development, their cost is high. Finally, the lack of testing reduces visibility around STI prevalence and drug resistance.

> **The 2021 WHO guideline recommending etiologic management has not been widely adopted: most case management continues to be syndromic.**

4. Point-of-care gonorrhea test landscape

4.1 Summary of methods and existing tests

The WHO recently updated its STI and HIV diagnosis manual (2), including a review of available methods for diagnosing gonorrhea. These methods include microscopy, culture, and many NAAT tests.

Microscopic examination of Gram-stained smears is sufficiently sensitive and specific for gonorrhea diagnosis in symptomatic men with urethral discharge. However, it lacks sensitivity and specificity in cervical secretions and extragenital samples, and it requires training, equipment, quality stains and supplies, and electricity. Notably, the WHO 2021 guidelines do not recommend microscopy in UDS, based on modeling results showing no improvement in syndromic management's performance. (31) Practically, however, some facilities use Gram stain as there are no other affordable options.

Culture and NAAT are feasible in larger laboratories. Culture is moderately sensitive and specific but has many drawbacks, including a >2-day turnaround time and the need for microbiology-trained technicians working within strong quality assurance systems. Because NG is extremely sensitive to environmental conditions, successfully culturing it depends on careful sample collection, transport, and culture methods to maintain viability. Despite these challenges, as drug resistance threatens available treatments, microbiologic culture capacity must be supported, as it is the only method that can provide drug susceptibility information, especially for ceftriaxone, the current cornerstone of treatment.

Because of its superior sensitivity, NAAT has supplanted culture as the "gold standard" for gonorrhea detection. Additionally, NAATs can accommodate a variety of specimen types. Several commercial FDA-approved NAAT kits and in-house polymerase chain reaction (PCR) methods detecting NG DNA/RNA are available, and POC NAATs are rapidly becoming available. While in-house methods can be more affordable than commercial kits, quality control and comparability are challenging. Usually, gonorrhea and chlamydia are multiplexed in NAAT assays, and other STIs and genetic resistance markers may be included. Research to identify genetic markers associated with reduced ceftriaxone susceptibility and assay development for these markers is ongoing. (45)

A few gonorrhea-detecting RDTs have been commercialized, although some are no longer on the market. The WHO does not recommend their use, as studies show they do not meet WHO minimum characteristics for performance[8] (2), have not undergone stringent regulatory authority review, and are not optimized from an ease-of-use perspective (46).

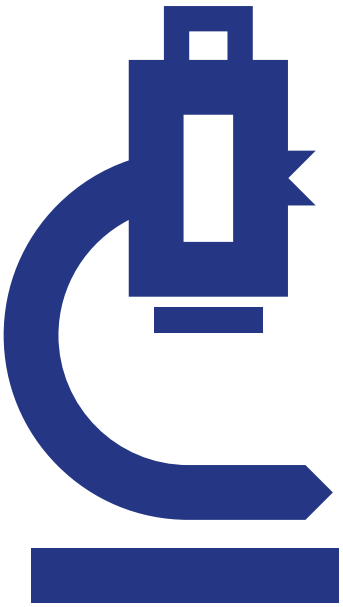
8 Many RDTs claim high performance. However, validations often compared them to culture, which overestimates RDT sensitivity. NAAT testing is the preferred reference standard. The recent pre-clinical data of an LFA developed by FIND does meet the WHO criteria in symptomatic infections (54).

4.2 Specimens

Specimen sampling and processing are a major technical challenge for gonorrhea (and chlamydia) test development. Given the various sites of infection, several specimen types are relevant. Some types are better suited, depending on the individual being tested, the technology platform (e.g., RDT, culture, NAAT), and the intended use (e.g., symptomatic vs. asymptomatic patients). Usually, specimens with the most concentrated organism burden are less acceptable to patients. For example, urethral swabs have the highest concentration of bacteria load (superior sensitivity) but are uncomfortable; most men prefer a urine sample, especially if asymptomatic. For women, gonorrhea infects the cervix, but genetic material pools in the vagina, making vaginal swabs suitable. However, the vaginal sample may require additional processing to ensure accurate detection. Recently, self-collected vaginal and rectal swabs have been shown to have high acceptance and performance (47).

Few tests are licensed for extragenital samples. Specificity in extragenital samples can be challenging due to cross-reactivity with other organisms in these specimens (e.g., Neisseria meningitis in oropharyngeal specimens). Depending on risk, one individual may require a genital, pharyngeal, and rectal swab. Each of these would warrant another test. Methods for pooling an individual's samples to increase efficiency and reduce cost have been explored. (48)

Testing for STIs other than gonorrhea using the same specimen is beneficial, but multiplexing adds technical complexity. Chlamydia is often paired with gonorrhea, given similar symptoms and frequency of coinfection. However, CT's bacterial load is lower than NG's, and because it is an intercellular organism, it is difficult to isolate and detect.



> **"The long-term public health priority is an etiologic diagnosis, especially as POC diagnostics come to market, STI burdens increase, and antimicrobial susceptibility threatens effective and simple treatments.**

4.3 WHO target product profiles

In 2006, WHO introduced the REASSURED criteria for point-of-care tests: real-time connectivity, ease of specimen collection, affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end users. Although notable progress has been made, no tests meet all these criteria (49).

To accelerate the development of STI POC tests, WHO facilitated landscape analyses (1) and several target product profile (TPP) development meetings. A TPP for a gonorrhea POC test was developed in 2014 and updated in 2023 (49). WHO and FIND also developed TPPs in 2019 to improve antimicrobial stewardship (50) (51).

These gonorrhea POC test TPPs align in many areas: the intended use includes case management, including at primary care/lower-level health clinics, and potentially screening high-risk populations. There is a preference for single-use, disposable tests; however, the TPPs acknowledge the necessity of a reader or some instrumentation, provided it is small, portable, and chargeable for eight hours. The TPPs differ slightly in preferences for specimen type, but generally, a vaginal swab and urine for men are minimal requirements, with rectal and pharyngeal specimens as optimal. Both stipulate minimal sample preparation/test processing steps,no cold chain, and similar shelf life (12 months minimal, 18 months optimally).

Notable differences in the TPPs include:

- Performance.
  - One TPP requires 90% sensitivity, with 98% being optimal. The other TPP has different requirements based on the technology platform. For simple tests like RDTs, the minimal sensitivity is 80% (>90% is optimal). Although 80% seems low, modeling shows improvement over syndromic management; a test meeting this TPP's sensitivity and specificity characteristics will reduce overtreatment with ceftriaxone, especially in women. This TPP requires 90% sensitivity for molecular tests (>95% is optimal).
  - The specificity requirements range from 90% to 95-98%.
- Timing. TPPs have different minimal turnaround times: <60 minutes or <30 minutes, but are relatively aligned on the optimal time to results (<10 or <15 minutes).
- Price.
  - One TPP specifies ex-works pricing <$5, optimally <$1.
  - The other TPP differentiates between low and high-complexity tests. Low complexity tests (i.e., RDTs achieving > 80% sensitivity and > 95% specificity) should be < $3. High complexity tests (i.e., single-use disposable molecular tests, achieving 95% sensitivity, 98% specificity) should be <$12.

While there are only a few antigen-detecting RDTs in development, several molecular efforts exist, including disposable, instrument-free tests, small device-based systems using disposable test cartridges, and near-POC systems.

4.4 Landscape of on-market and pipeline POC gonorrhea tests

Globally, despite many laboratory-based testing options, public health institutions have been increasingly prioritizing rapid POC testing for STIs. Rapid turnaround times enable within-visit treatment, reducing loss-to-follow-up and potential onward transmission. A definitive diagnosis also enables better counseling and expedited therapy for partners.

Developers have responded to the need for faster results; research for this report uncovered >75 POC and near-POC gonorrhea tests, among them three FDA-cleared tests. While there are only a few antigen-detecting RDTs in development, several molecular efforts exist, including disposable, instrument-free tests, small device-based systems using disposable test cartridges, and near-POC systems.[9]

An illustrative selection of tests is described below.

4.4.1 RDTs, lateral flow tests

Given relatively low organism loads and the desire for less invasive sample types (urine and vaginal swabs), traditional lateral flow technology is unlikely to achieve WHO TPP performance requirements. To enhance performance, RDT developers must identify well-conserved antibodies and consider additional steps to concentrate the sample, lengthen the reaction time, or amplify and strengthen the signal.

BioLytical, a Canadian rapid test manufacturer of the Insti HIV tests in LMICs, is developing an NG/CT test for its iStatis lateral flow platform. BioLytical expects to begin trials in 2024, with regulatory submissions to follow. The intended use is symptomatic patients, and a professional test is likely to launch first, followed by a self-test. The test will use vaginal and urethral swabs, and be similar to other RDTs in terms of processing and turnaround times. While bioLytical expects to offer preferential pricing for LMICs, the prototype test cost is higher than HIV tests. BioLytical has recently completed a manufacturing facility dedicated to producing iStatis lateral flow assays (LFAs).

FIND is supporting the development of an NG-only fluorescent RDT. DCN Dx developed the test; it has undergone initial validations and acceptance studies (52) (53) and is being transferred to manufacturing partners for commercialization. The RDT detects NG antigens and uses europium-based labels to provide a fluorescent signal, requiring a simple RDT reader. The test has been validated in urine (men) and vaginal swab specimens; extra-genital specimens have yet to be assessed.

Processing steps include mixing urine with buffer or eluting the vaginal swab in a small buffer tube and transferring several drops to the lateral flow cassette. A qualitative result is available after 20 minutes by inserting the cassette into a reader. The reader is lightweight and powered by an external battery that requires charging once every 3-4 weeks (in a study). Results can be downloaded from the reader as well, but it does not have inbuilt connectivity.

FIND and its commercial partners are targeting <$3 test and <$50 for the reader, as per TPP requirements, however FIND is negotiating lower prices at <2$ test and <$ 25 for the reader Pre-clinical study results from South Africa showed promising performance for an LFA, meeting several optimal sensitivity and specificity requirements (54). FIND is now managing the test transfer to a commercial partner to perform clinical studies for regulatory submissions.

An NG test alone does not replace syndromic treatment; rather, it optimizes syndromic management because CT (and, in some settings, TV) are still treated empirically. FIND's work to develop a CT RDT is ongoing.

GIFT, the Genital Inflammation Test, is a rapid diagnostic test being developed by a team from the University of Cape Town in South Africa and the Burnet Institute in Australia. Unlike other tests profiled in this landscape, GIFT does not diagnose specific STIs. Instead, it detects biomarkers of genital inflammation caused by STIs and bacterial vaginosis. By detecting and treating the inflammation, the GIFT team aim to prevent HIV acquisition, reduce reproductive health complications, and minimize adverse pregnancy outcomes that can result from untreated STIs. Specifically, the test can be used to screen women, including those without symptoms, for inflammation. If detected, the woman is treated, either empirically for several potential causes (similarly to syndromic management) or etiologically if further diagnostic testing is available. The test has been designed to be affordable, making it suitable for HIV prevention efforts in

9 Tabletop instruments that may accommodate more than one cartridge at a time.

low resource settings. GIFT is currently in the pre-commercial testing phase.

4.4.2 Disposable POC molecular tests

Fuse Diagnostics is an early-stage UK start-up founded in 2022. It is developing low-cost, disposable molecular testing. In 2024, CARB-X funded its proof-of-concept and feasibility work for an NG/CT test.

Lucira Health was a U.S.-based start-up founded in 2019 that commercialized the first over-the-counter (OTC) disposable molecular COVID-19 test in the U.S. The disposable molecular platform comprises a sample tube and a palm-sized battery-operated device. The technology is LAMP-based and returns a result in 30 minutes. In September 2022, Lucira announced favorable interim results of a pilot evaluation of their combined NG/CT test. However, the company soon filed for bankruptcy due to low COVID-19 test demand, and Pfizer acquired its technology. The STI test status is unclear. The COVID/flu test retails for US$43 (55).

Visby Medical, a U.S.-based start-up, launched the first disposable, instrument-free, handheld PCR-based test that uses lateral flow technology for detection. The Visby Medical Sexual Health Test detects NG/CT/TV and is a Clinical Laboratory Improvement Amendments (CLIA)-waived professional use test for women. After connecting the device to a reusable power supply using a provided adaptor, the operator elutes a self-collected vaginal swab specimen in a media tube and transfers the sample to the device. The result is available in less than 30 minutes. The first version of the test received clearance in 2021, and a second-generation test received FDA clearance in March 2023. Visby had just completed NG/CT test trials when the COVID-19 pandemic began. After focusing on respiratory tests for several years, it returned to its STI test in 2021 and with CARB-X support is developing a test for men using urine samples, and gonorrhea drug resistance markers (56). Visby has an automated production line, its second-generation test included redesigns for more efficient manufacturing and cost reduction, yet ex-works pricing exceeds US$100.

4.4.3 POC molecular tests using reusable, small instruments

Aptitude Medical Systems is a U.S.-based start-up that has developed the Metrix system, a LAMP-based molecular platform with electrochemical detection. The system comprises a reusable palm-sized reader and assay cartridges. Aptitude is targeting both self-testing and professional testing, the design draws on blood glucose technology to achieve lower costs. Currently, it has an OTC FDA-cleared COVID-19 test on market; it is developing a broader respiratory test, followed by an NG/CT/TV test. The STI test uses self-collected vaginal swabs and penile meatal swabs. The testing process requires inserting the swab into a container, shaking the container, and snapping on another part before inserting it into the reader. Results are available in 30 minutes; the readout currently uses LED lights; connectivity via an app is planned. The Metrix COVID-19 test retails for US$25, and the reusable reader for US$50 (57).

Binx Health, a U.S. and UK start-up, developed the Binx io platform gaining regulatory clearance in 2019. The fully automated, CLIA-waived molecular system comprising a small desktop instrument and single-use cartridge, uses PCR amplification and electrochemical detection, with results available in about 30 minutes. The first assay on the platform is a dual test for the simultaneous detection of gonorrhea andchlamydia, which are FDA-510(k) cleared and CLIA-waived. The platform is the first POC NG/CT test accepting both vaginal swabs (FDA 510(k) August 2019) and male urine (FDA 510(k) April 2020). The testing process includes adding the sample to a preservation buffer and using a disposable fixed-volume pipette to transfer the sample to a test cartridge. Once loaded, the cartridge is placed in the instrument which runs the test automatically, with a qualitative read-out of test results on the instrument. Results are stored on the device or can be printed or transferred directly to electronic medical records systems. The device, which is not stackable, requires power. Binx has worked on several additional indications to add to the platform and may seek a female urine claim next, which could facilitate asymptomatic screening, potentially expanding the market size. Additional tests for the platform are under consideration, likely focused primarily on sexual and women's health for the near term. Binx is continuing its commercial roll-out with customers across multiple key verticals (urgent care, student health, emergency departments, STI clinics etc.) with the majority of platforms having been placed under multi-year reagent rental contracts.

Guangzhou Pluslife Biotech, a Chinese start-up founded in 2017, has commercialized the Pluslife mini-dock system, a palm-sized device that, along with test cards, utilizes their patented RNase Hybridization Assisted Amplification (RHAM) technology. In 2023, Pluslife launched a STI testing solution, available in two formats: a NG/CT/ ureaplasma urealyticum (UU) test and a streamlined NG/CT test. This test accepts both provider-collected vaginal swabs and urethral swabs. Pluslife is also developing a CT/NG/TV Combo Test, and a preliminary validation with urine samples is complete. The testing process involves sample collection, two minutes of hands-on time (e.g., mixing and an incubation period), and transfer of the sample to a test card, which is inserted into the testing device. Results are available within 35 minutes, via LED lights on the device. Additionally, the device has Bluetooth connectivity, allowing data transfer to a computer or mobile app. The test has been validated in China, and Pluslife is

exploring European Conformity In Vitro Diagnostic Regulation (CE IVDR) certification to expand into international markets, pending suitable clinical trial opportunities. The company is also investigating the potential for using urine samples to broaden the test's applicability. The Mini Dock instrument, which supports these tests, is priced below US$150, with each test costing between US$5-8. The system is portable and has a rechargeable battery. For higher throughput, Pluslife also offers the Pluslife Dock Pro 8 analyzer and docking stands for up to five instruments. Pluslife's current test menu includes: COVID-19, flu, TB, mycoplasma pneumonia, and HPV, among others.

MagIC Lifescience, a U.S. start-up, is developing the MagChipR™ (mag-chip-er), a compact, affordable POC platform that delivers multiplex pathogen and antimicrobial resistance results in under 20 minutes. MagChipR's proprietary PCR amplification and on-chip giant magnetoresistive (GMR) detection methods enable fast results and low costs while increasing multiplexing capacity. GMR detection overcomes the limitations and high costs compared to commonly used fluorescence-based detection. The first MagChip panel in development detects CT, NG, TV and mycoplasma genitalium (MG) and genetic drug resistance markers for positive NG and MG samples. Upon launch in high-income countries, the MagChipR analyzer and MagChip™ cartridges will be priced between US$3,000-3,500 and US$40-50, respectively. Eventually, MagIC Lifesciences expects economies of scale to enable lower MagChip pricing for LMICs. The company is raising its Series A Round and expects to begin clinical studies in 2025.

Novel Microdevices, a U.S.-based start-up, is developing an NG/CT/Cipro resistance assay for its Novel Dx system. The system comprises test cartridges and a portable, fully integrated real-time PCR analyzer using magnetic bead-based sample processing technology and real-time detection. A respiratory panel, followed by the STI test, are planned. Novel Microdevices expects to achieve design lock and pilot manufacturing in 2024. Vaginal swabs and urine are being developed, with swabs inserted into a transport buffer and transferred to a cartridge using a disposable pipette. The results will be qualitative and available after 15 minutes. The device is battery-powered and portable. Novel Microdevices is enthusiastic about LMIC markets and expects ex-works instrument pricing of approximately US$500 and assay prices of <US$5.

Prominex is a U.S.-based start-up, founded in 2018, with proprietary molecular chemistry that it combines with lateral flow detection using a digital reader. The system comprises a small reusable device and cassettes containing a reaction tube and lateral flow strip. Prominex aims to deliver results in 6-7 minutes at low cost. There is no sample prep; crude vaginal and penile meatal swabs are the expected sample types. Prominex began the development of NG/CT assays before the pandemic but shifted to COVID and is currently working on a RADx-funded COVID-19/Flu assay with enhanced accessibility and OTC status.

Prompt Diagnostics is a U.S.-based start-up, developing a hand-held POC PCR system based on a technology spun out of Johns Hopkins University. The system uses cartridges to perform sample processing, heating and fluorescent based detection. The first test being developed is for NG and ciprofloxacin resistance. The developers aim to run at least 20 tests per day on battery power and return results in less than 15 minutes. Anticipated cartridge pricing is US$3 each. In 2024, CARB-X granted Prompt funding to transition from a prototype device to an instrument and to optimize shelf stability and cost. Prompt expects to begin clinical studies in 2026 (58).

Roche is developing an NG/CT test for its cobas Liat system which it expects to submit to FDA and CE IVDR in 2024. Liat comprises a small, fully integrated real-time PCR analyzer and Liat assay tubes. On-market tests include respiratory tests and a *C. diff* assay. Several additional tests are in development. The test will be professional use, and Roche anticipates clearance for vaginal swabs (collected by providers or self-collected) and urine (men and women). The testing process involves collecting a swab, inserting the swab into a media-containing tube, transferring the sample solution to the Liat assay tube using a disposable pipette, and inserting the test into the analyzer. Results are available in 20 minutes.

Scout is a U.S. based start-up, developing a point of care molecular test for NG/CT. The system comprises a portable instrument, test kits, and a mobile app and is based on a proprietary Loop-de-Loop isothermal technology. Results are available in 30 minutes. The company obtained an FDA emergency use authorization for its COVID test, and in 2024 a CARB-X grant for feasibility work on its STI test. Scout is targeting low costs, and potentially self-testing. (59)

Sefunda is a Swiss start-up, founded in 2019, focusing on AMR. Its first diagnostics test is for NG/CT/LGV[10] and a marker of ciprofloxacin resistance. The system uses simplified PCR technologies and cartridges. The first sample types will be cervical, rectal, and urethral swabs; urine in men and self-collected vaginal swabs will follow.

10 Lymphogranuloma venerum (LGV) is an STI caused by specific strains of Chlamydia. It is most common in tropical climates but is increasingly reported in MSM in HIC, manifesting as genital ulcers.

The assay is in the prototype stage and Sefunda is targeting the U.S. market first.

Talis Biomedical, a U.S. start-up, was founded in 2010 and went public in 2021, yet it appears to be shutting down, announcing in November 2023 the layoff of most staff. It had developed the Talis One system, which was based on real-time LAMP amplification using a small instrument and cartridges. After withdrawing from the COVID-19 and respiratory markets, Talis was focused on the women's and sexual health markets, and NG/CT tests were among its priorities. Funding from its public offering went to building in-house manufacturing capacity. However, both technical and manufacturing delays seem to have challenged the company, and its assets are being sold.

4.4.4 FIND and RIGHT Foundation support for POC molecular gonorrhea/chlamydia tests

In April 2024, FIND launched a request for proposals (RFP) targeting developers of true POC NG/CT molecular tests (60). Through the RFP, FIND intends to encourage and support developers with product development and optimization, and evaluation in LMIC sites. The RFP covers both genital and extra-genital samples. The RFP asks for <US$10/test pricing and awardees must commit to cost of goods sold (COGS)-plus-pricing for LMICs. The timelines contemplate awarding the RFP by the end of 2024 and supporting product development in 2025/2026 or, for sufficiently advanced technologies, conducting performance evaluations starting in April 2025-2026. Korean-based companies can also apply to the RIGHT Foundation to co-fund this initiative.

4.4.5 Near POC molecular

Near POC tests generally have a footprint that would preclude testing in an exam room; they require a small laboratory area. Additionally, their turnaround times tend to be longer than some of the "true" POC tests. Many of these existing tests are covered extensively in other landscapes (e.g., the WHO STI test landscape (1) and the WHO lab manual (2)) so only a few examples are described here for illustrative purposes.

Cepheid's Xpert® CT/NG test performed on the GeneXpert® system was FDA-cleared in 2012. The GeneXpert system is a fully automated and integrated PCR-based testing system with over 20 FDA-cleared tests. The Xpert CT/NG test takes 90 minutes and accommodates urine, vaginal swabs (provider or patient collected in a clinical setting), endocervical swabs, pharyngeal swabs, and rectal swabs. The test was initially cleared for urogenital specimens; extragenital specimens were FDA-cleared in 2019 through a study coordinated by a U.S. NIH-funded program using a master protocol to assess the diagnostic accuracy of multiple commercially available NAATs for NG and CT in throat and rectal sites. (61) Public sector LMIC buyer pricing is US $16.20/cartridge and sample collection devices are US $1.52.[11]

SD Biosensor, a Korean company, is developing an STI panel for its M10 near-point-of- care molecular system. This system uses cartridges and modular instruments that can be configured in sets of eight. M10 performs isothermal amplification and real-time PCR in under an hour. On-market tests include respiratory panels, TB assays, an arborvirus panel, a *C. difficile* test, and sexual health assays including HPV, STI panel and CT/NG test. SD Biosensor has a CT/NG/NG-AMR test in development, clinical studies are planned for the first half of 2027 followed by regulatory submissions in 2027. Pricing is expected to be competitive with GeneXpert. SD Biosensor has a newly established, fully automated production facility for M10 diagnostics cartridges in Korea.

> **"The POC gonorrhea tests perform well compared to central laboratory tests and offer < 30-minute turnaround times, enabling, for the first time, treatment based on test results during the patient's visit. This advance could have a transformative effect on STI control,**

11 Pricing as of August 2024. Instrument pricing and various support and warranty plans also need consideration; see: https://dxc-marketplace.finddx.org/pages/cepheid-accessible-pricing, https://aslm.org/diagnostic-pricing-database/

4.5 Technology summary and outlook

From a technology standpoint, there has been tremendous progress in developing POC gonorrhea and other STI diagnostics in the past five years. Current on-market, FDA-cleared NG/CT tests include near-POC, instrumented POC, and disposable POC options (respectively GeneXpert, Binx io, and Visby). The pipeline is abundant and dynamic, and many more products are expected to come to market in the next five years, including at least one disposable lateral flow test and several molecular POC tests using a variety of novel sample processing, amplification, and detection systems.

The POC gonorrhea tests perform well compared to central laboratory tests and offer < 30-minute turnaround times, enabling, for the first time, treatment based on test results during the patient's visit. This advance could have a transformative effect on STI control, reducing both antimicrobial overuse and stopping the spread of STIs by making screen-and-treat programs possible.

Additionally, the emerging POC tests are relatively easy to use, and many developers seek CLIA waivers[12] or even self-testing/OTC status. Another notable advance is easier specimen collection. In women, older diagnostic methods require cervical swabs, which are uncomfortable, collected only by trained health providers, and require space equipped for speculum exams. Vaginal swabs, which are provider or self-collected, have proven effective, especially in NAAT testing. Urine samples in men are increasingly replacing painful urethral swabs as well. Multiplexing is also increasingly the norm for NAAT tests, e.g., NG/CT ±TV, ± resistance markers.

Many of the instrument-based tests offer data connectivity options, and a few can be battery-operated, which is essential in many LMICs where power is unstable. While assays are designed to avoid cold chain storage requirements, many POC tests are designed with relatively well-resourced settings in mind. For example, health clinics in HICs where the environment is dust-free and ambient temperature and humidity are maintained. The performance and durability of the new POC tests under LMIC conditions will need to be evaluated.

Despite the sizable number of pipeline products and these many advantages, some attrition is expected, and development timelines will extend. Diagnostic test development can take ten or more years, and although pandemic resources accelerated many technology platforms, developers report more normal R&D funding levels now. Several companies interviewed for this report are looking for funding to support STI assay development and trials, and their launch timelines depend on fundraising success. While their test menus are based partly on market needs, developers are also opportunistic, advancing specific assays according to funding opportunities.

Ultimately, some gonorrhea technologies profiled here will not be commercialized. Even during the research for this report, a few developers (e.g., Talis, Lucira) were acquired or wound down their operations. Often, these developers invested heavily in manufacturing and commercial teams during the pandemic, anticipating high COVID-19 test demand. When COVID test demand dropped, it challenged their financial viability.

Clinical trials for gonorrhea multiplex tests can be time-consuming and expensive, also contributing to overall delays in product launch timelines. Typically, multi-site clinical trials are needed to assess performance in i) a variety of populations (low and high prevalence), ii) symptomatic and asymptomatic patients, and iii) several specimen types. Developers must be strategic in sequencing the validation of different specimen types. They often balance market needs and potential competitive advantages with the cost and complexity of validating multiple specimen types at once. As a result, most developers phase their regulatory clearances for different specimen types, i.e., they first validate the most common specimens and add additional specimen types later.

12 A CLIA waiver is available from the US FDA for tests that are simple, with insignificant risk of error. These tests do not require a highly trained laboratory technician to perform the test.

5. Preliminary work on LMIC markets for gonorrhea POC tests

5.1 Use cases

Within the broad categories of symptomatic and asymptomatic individuals, a more nuanced segmentation by populations and reasons for testing is beneficial (Table 4). Depending on the target population, the rationale for testing and value proposition for testing may vary – for instance, women with VDS may prefer to minimize the number of medicines they take, HIV programs might test for STIs as a marker of risk, while antenatal programs might introduce STI screening to improve pregnancy outcomes.

Additionally, STI care availability and delivery are not uniform across LMICs, and populations benefiting from gonorrhea testing could be tested at a variety of sites. Thus, these high-level use cases might be further segmented by the settings and capabilities available at the site.

From a product perspective, different features' relative importance (e.g., specimen types, performance, price, number of tests performed in a day) will vary based on the use case, and different POC technologies will better suit some of these use cases than others. Across all of the use cases, ensuring that results are available during the consultation is critical. However, there are varying needs for other features, including:

- The importance of multiplex tests (i.e., CT, TV, MG, resistance markers) may depend on the population being tested and local epidemiology.
- For device and instrument-based testing, the other tests available on the same platform may matter (e.g., leveraging a platform that has been established for COVID-19), as might the personnel and infrastructure requirements (e.g., space for storage, equipment, waste, and temperature).

Table 4. High-level summary of use cases for gonorrhea POC testing

Population	Rationale for testing	Key test attributes
Symptomatic women seeking care	• Quality of care: increasing the specificity of syndromic management → to avoid unnecessary medications that may be harmful. • Improve partner notification: with more confidence in the diagnosis of an STI vs. RTI providers might give oral cefixime as expedited partner therapy - efficiently reducing reinfection rates and onward transmission. • Engage in HIV care: confirmed NG (or other STI) is a marker of HIV risk, and presents an opportunity to engage in HIV prevention/ treatment services. • Reduce long term complications if symptoms persist.	• Fast. Result turnaround time that enables same day treatment (e.g., <30 min) • Variety of testing throughputs may be needed depending on the typical patient volumes across different sites. Ease of use and incorporation into clinic flow. • Additional STIs tested using same sample. NG only test directs use of injectable ceftriaxone. With additional STIs (e.g., CT/TV) can reduce overtreatment, provide more confidence in partner management. • Low price, as syndromic management and treatments are inexpensive. • Vaginal swab, self or provider collected • Lower sensitivity may be an acceptable tradeoff for increased access.
Symptomatic men seeking care	• AMR: Confirming NG to protect ceftriaxone, or before giving any novel NG antibiotic. • Engage in HIV care: confirmed NG (or other STI) is a marker of HIV risk, and presents an opportunity to engage in HIV prevention/ treatment services.	• Fast. Result turnaround time that enables same day treatment (e.g., <30 min) • Variety of testing throughputs may be needed depending on the typical patient volumes across different sites. Ease of use/ incorporation into clinic flow. • Low price, as syndromic management and treatments are inexpensive. • Urine
Recurrent/ persistent difficult cases	• Confirm etiology, reinforce partner notification	• High sensitivity & specificity for NG; additional STIs preferred • Ideally, have susceptibility/ceftriaxone resistance testing.
Surveillance/ AMR monitoring at sentinel sites (symptomatic populations)	• As above: improved quality of care/avoid overtreatment; improve partner notification; engage in HIV care. • More representative and efficient drug susceptibility surveillance: only patients with confirmed NG on a POC tests are further swabbed for additional sample collection via culture (men: urethral swab and women cervical swab)	• Fast. Result turnaround time that enables same day treatment and immediate collection of culture samples for surveillance. • High/moderate testing throughput is likely preferred. • May require additional STIs/RTIs tested using same sample
Symptomatic & high-risk self-treating (e.g., retail, on-line care seeking)	• Reduce transmission • AMR: reduce use of ineffective treatments, improper dosing, over-treatment	• Self-testing with linkage to treatment either on-site (pharmacy), telehealth, referral to clinic. • Additional STIs with same sample preferable. NG only test directs use of oral cefixime (injectable ceftriaxone usually requires clinician to administer). With additional STIs (e.g., CT/TV) can reduce overtreatment. • Affordability and financial incentive to test. For customers, lower price than treatment, or cost reimbursed through insurances. For retailers/ supply chain actors, incentives to stock and recommend testing.

Table 4. High-level summary of use cases for gonorrhea POC testing (continued)

Population	Rationale for testing	Key test attributes
ANC screening In high burden settings	• Reduce the burden of NG by treating many cases that are currently undetected and untreated. • Improve pregnancy and newborn outcomes. • Engage in HIV care: confirmed NG (or other STI) is a marker of HIV risk, and presents an opportunity to engage in HIV prevention/ treatment services.	• Easy to operationalize in ANC with other tests (e.g., HIV, syphilis, Hepatitis B malaria, anemia screening) • Fast: result turnaround time that enables same-day treatment (e.g., <30 min) • A variety of testing throughputs may be relevant, depending on the typical patient volumes across different sites. • Additional STI/RTIs using the same sample preferred confidence in partner management, STI test and treat may improve fetal growth • Low price, as volumes are high. • Minimally invasive sample: self-collected vaginal swab, urine
Screening in key pops (e.g., MSM, FSW)	• Reduce the burden of NG by treating many cases that are currently undetected and untreated. • Reduce AMR: reduce transmission in a population with disproportionate resistant cases. • Reduce HIV transmission and acquisition risk	• Fast: result turnaround time that enables same-day treatment (e.g., <30 min) • Additional STIs tested using the same sample preferred. • NAAT with pharyngeal and extragenital samples available, optimally • Self-collected samples (vaginal and rectal swabs, urine)
Screening AGYW (high burden settings)	• Decrease PID and its sequalae (ectopic pregnancy, infertility) • Reduce the burden of NG by treating many cases that are currently undetected and untreated. • Engage in HIV care: confirmed NG (or other STI) is a marker of HIV risk, and presents an opportunity to engage in HIV prevention/ treatment services. • Protect (early) pregnancy	• Fast: result turnaround time that enables same-day treatment (e.g., <30 min) • Self-sampling, vaginal swabs • Additional STIs tested using the same sample preferred • Low price essential for screening use case
Opportunistic screening for high-risk pops attending clinic (e.g., family planning)	• Decrease PID and its sequalae (ectopic pregnancy, infertility) • Reduce the burden of NG by treating many cases that are currently undetected and untreated. • Engage in HIV care: confirmed NG (or other STI) is a marker of HIV risk, and presents an opportunity to engage in HIV prevention/ treatment services.	• Fast: result turnaround time that enables same-day treatment (e.g., <30 min) • Self-sampling, vaginal swabs • Additional STIs tested using the same sample preferred • Ease of use/incorporation into clinic flow • Low price essential for screening use case
Screening in PrEP enrollees	• Decrease NG transmission • Reduce AMR if individual involved in a high-transmission network • Reduce HIV acquisition risk by treating NG	• Fast: result turnaround time that enables same-day treatment (e.g., <30 min) • Additional STIs tested using the same sample preferred

5.2 Estimates of unmet LMIC need

Estimating demand for gonorrhea POC tests is difficult, as there is limited gonorrhea epidemiological data and case reporting (both VDS, UDS, and confirmed gonorrhea infection) data is not always available or reliable and complete when it is. Preliminary estimates suggest there is a large unmet need for POC gonorrhea testing in LMICs (62). In 2020 FIND conducted market research in 6 LMICs (Kenya, the Philippines, South Africa, Thailand, Vietnam, and Zambia) (63). The studies included preliminary estimates of target population size for NG/CT POCTs. Generally, the potential number of patients seeking care for symptoms each year per country is in the low hundreds of thousands to single-digit millions each year. In some Asian countries, Gram stain is already used for men. The potential screening market size depends heavily on the targeted populations, how frequently testing is performed, and coverage. For example, FIND estimated that antenatal screening populations could range from a few hundred thousand patients annually to over 1 million tests/year.

5.3 Understanding LMIC test adoption and use barriers

WHO, AVAC, FIND, GARDP and academic researchers have conducted qualitative research to assess potential adoption and interest in gonorrhea POCT in LMICs and to map key barriers (64) (65) (66). Findings indicate that despite a significant unmet need and sizable target population, demand for tests in LMICs is uncertain due to various adoption barriers, among them:

5.3.1 Limited funding for STIs

Both consumers and LMIC governments have very limited ability to pay for STI care. Proposed prices for gonorrhea POC tests are nearly two times current gonorrhea treatment prices and three or more times the prices of other commonly used point-of-care tests (e.g., HIV, syphilis, malaria RDTs). In many countries, patients pay out of pocket for STI care, either because STIs are not free in the public sector or because they seek care outside of free channels for privacy reasons. Where STI care is covered by the government or insurance schemes, the budgets tend to be small i.e., likely insufficient to cover testing. In the public sector, gonorrhea testing is one of many health priorities competing for limited resources. In many countries, STI testing may be hard to prioritize, given the substantial burden of other high-mortality diseases.

5.3.2 Underfunded STI programs

Historically, STI programs were more robust than they are today, and they played an essential role in HIV prevention efforts in the early days of the HIV epidemic. In recent decades, however, attention and resources have moved to other health priorities, and STIs have been under funded. Often an STI a focal point is housed within the national HIV program, even though, STI care should be integrated throughout various health services and might be delivered through a range of providers, including primary care nurses as well as dermatology or urology specialists. Lack of resources results in infrequent guidelines updates, e.g., 40 of 99 countries reported to the WHO updating guidelines in last three years; 63 of 99 in the past five years. (6) given many priorities in STIs (e.g., stigma, integration with family planning and HIV programs, syphilis elimination), many programs are forced to focus narrowly on a singular sexually transmitted disease or population (e.g. congenital syphilis elimination).

5.3.3 Evidence gaps

Despite the growing burden of infection, the morbidity caused by untreated gonorrhea infections and the impact of overtreatment on antimicrobial resistance are difficult to demonstrate. Without evidence of the adverse outcomes of gonorrhea infection and overtreatment, countries struggle to make the investment case for testing, and cost-effectiveness cannot be assessed.

For gonorrhea (and many other treatable STIs), experts and observational data suggest that the many untreated infections contribute to significant and costly morbidity; however, trials of sufficient size and time horizon are challenging to conduct, and it is unclear, given gonorrhea's biology, that compelling evidence will emerge.

Studies looking at screening high-risk populations have not been conclusive. For example, researchers have prioritized studies looking at the impact of STIs in pregnancy on maternal and newborn outcomes. However, outcomes are difficult to document directly, given the number of confounding factors that affect a pregnancy. While observational data supports testing, the one major trial to date demonstrated a small positive effect for POC testing and treatment of gonorrhea, but not for chlamydia or bacterial vaginosis. (11) Additional studies are underway, but results may not be sufficiently compelling to spur large-scale test adoption (12) (13). Research also suggests that malaria treatment given during pregnancy (intermittent preventative treatment, IPTp, with sulfadoxine-pyrimethamine particularly) has some protective effect for birth outcomes, possibly by treating and preventing chlamydia infection, although the exact mechanism is not understood (14).

Undoubtedly, testing symptomatic people allows for pathogen-specific treatment, and there are many quality-of-care benefits. However, the counterfactual, direct evidence of overtreatment's effect on resistance, is difficult to establish. Limited drug resistance surveillance make it challenging to fully recognize the potential threat. Additionally, the lack of available alternatives, and the relative high cost of novel treatments, may reduce the perceived urgency of the issue. Without tangible evidence about the impact of overtreatment, the push to invest in more complex and costly management practices is not tenable for most public health systems in LMICs (67).

5.3.4 Evidence is needed to inform the prioritization of use cases and populations for testing

Given resource constraints, very few LMICs are rolling out gonorrhea testing broadly (i.e., both to all symptomatic patients and routinely screen high-risk populations). It is likely that, initially, testing will be considered for selected populations. There is general expert consensus that diagnostics should be prioritized for all women, asymptomatic men at high risk, and extragenital infections. However, within these groups, there is little evidence to inform prioritization, for example, between identifying causes in symptomatic patients so they receive proper care or detecting asymptomatic infections to reduce disease prevalence.

Overall, the approach to STI testing is not likely to be uniform across countries and will take time to emerge. Research conducted by FIND has found that generally, in Asia, there is a greater focus on drug resistance, as well as key populations. African stakeholders prioritize key populations in connection with HIV, pregnant women, and young/adolescent women--the latter related to concern about asymptomatic burden. In Africa, overtreatment of STIs and linkages to drug resistance are not immediate priorities as there is an absence of data suggesting they should be (68).

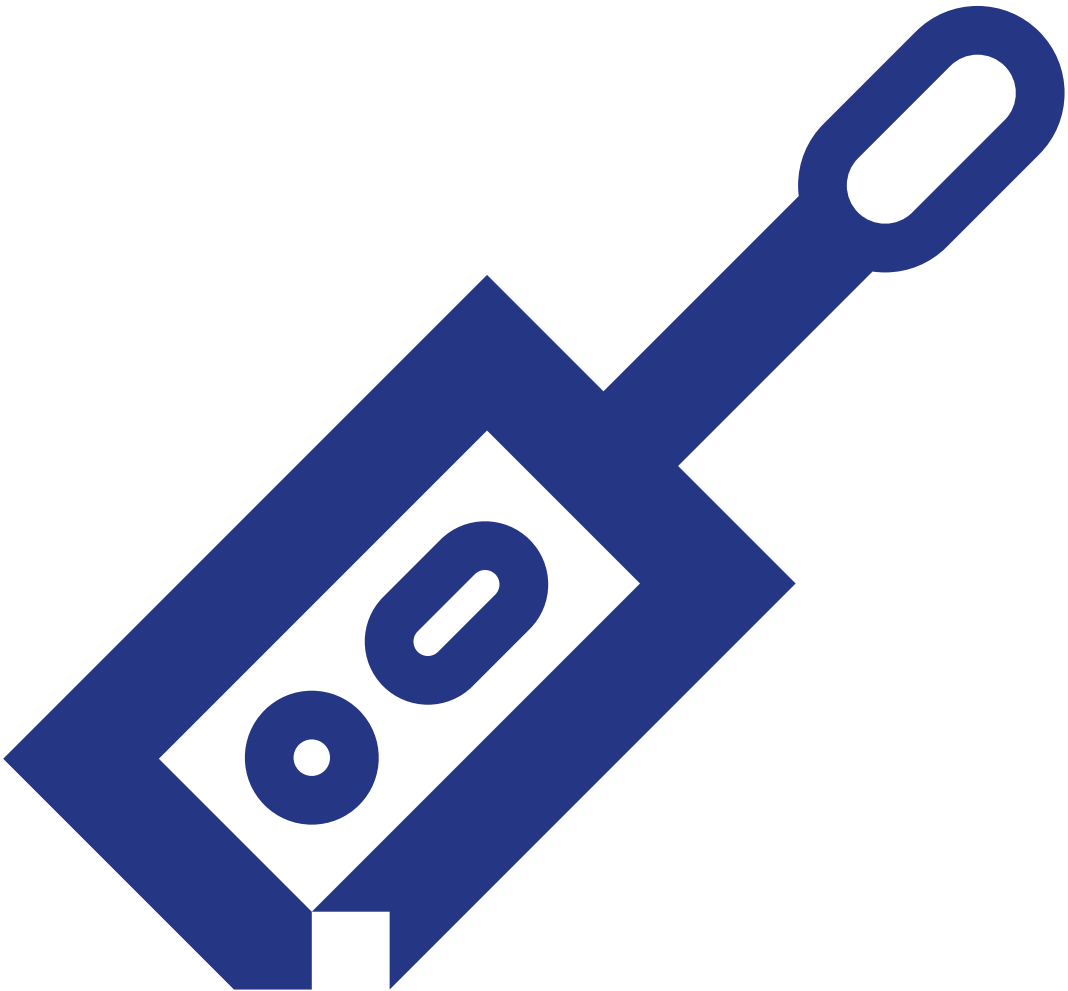
There is general expert consensus that diagnostics should be prioritized for all women, asymptomatic men at high risk, and extragenital infections.

5.4 POC testing market development in HICs

Although HIC markets are beyond the scope of this report, a high-level perspective is useful in considering how the POC STI test markets may evolve globally. STI rates have been increasing in HICs, and test reimbursement rates are attractive. In the past decade, studies have assessed the benefits of having results available during the patient's visit (69). As such, many POC test developers are prioritizing being among the first to market in high-income country markets to lock in market share. Thus, from a regulatory perspective, most developers prioritize US FDA clearance and CE IVDR, although a few describe processing backlogs in Europe. Currently, WHO PQ is not yet available for gonorrhea tests.

However, even in HICs, experts note that public health programs find novel tests unaffordable, and barriers to POC testing uptake exist, among them competition from lower-priced central lab testing (POC tests can be three to five times the cost of lab tests in the U.S.), albeit with longer turnaround times. Other barriers to POC STI testing in HICs relate to the introduction of testing into settings that have not previously performed testing, for example, obtaining site certifications for POC testing, validating tests, ensuring staff are available and proficient in testing (70), and adding billing and reimbursement capacities.

As a result, while HIC demand is growing, it will take time for companies pioneering these tests to become established. As they do, economies of scale and competition from new entrants could reduce prices. However, these conditions will take several years to materialize.



6. Partner landscape

Many partner efforts focus on developing POC technologies relevant to both HIC and LMICs (Figure 7). In addition to the FIND initiatives (above), the Bill & Melinda Gates Foundation, through its Women's Health Innovations initiative, is supporting several developers of true POC STI tests, including funding for product development, LMIC usability studies, and evidence generation. It is also conducting modeling. While not exclusively focused on LMIC settings, CARB-X and the Johns Hopkins Center for Innovative Diagnostics for Infectious Diseases (CIDID) also support several developers of POC gonorrhea tests for low-resource settings, both in developing and developed countries.

Notably, fewer partners work on downstream activities, such as clinical trials or product introduction in LMICs. Organizations such as Population Services International (PSI), JHPIEGO, AVAC, and several academic research groups with extensive experience in related fields (e.g., reproductive health, maternal health, HIV, hepatitis, cervical cancer) are collaborating with select test developers on early usability and field studies for new tests.

There is an absence of programmatic donor support for widespread gonorrhea testing. While some donors (e.g., the Global Fund to Fight AIDS, Tuberculosis and Malaria) are open to supporting gonorrhea testing, given different donor priorities (e.g., HIV prevention and key populations), this funding is likely to be directed at particular populations and not at comprehensive access to gonorrhea testing in symptomatic and high-transmission populations.

Figure 7. High-level partner landscape

7. Market shortcomings and challenges

Despite the robust POC test pipeline, the tremendous STI burden in LMICs, and concern about drug-resistant gonorrhea, many barriers stand in the way of gonorrhea POC tests reaching those who need them in LMICs. Chief among them are prices that are not affordable to LMICs, difficulties in establishing compelling cost-effectiveness evidence, and a lack of urgency and prioritization of STIs and AMR. These are discussed below, using Unitaid's market analysis framework.

7.1 Innovation and availability

There is a dynamic and robust pipeline for POC gonorrhea (and other STI tests), yet **products may not be optimal for the diverse LMIC use cases**. Multiplex, expensive technologies (e.g., POC molecular) dominate the pipeline compared to more affordable lateral flow tests. Generally, developers prioritize the attributes likely to sell well in HICs, where the market size and pricing are attractive, compared to LMICs, where the ability to pay is low and demand uncertain.

While a simple disposable rapid test format (e.g., akin to a syphilis test) is optimal for LMIC settings, the simplest lateral flow platforms are unlikely to achieve the required sensitivity and specificity. Lateral flow tests with additional enhancements have shown promise, but these enhancements add cost, and can reduce access (e.g., additional operator steps for sample concentration, detection requiring a reader). Developers report that there are few available antibodies for gonorrhea and chlamydia antigen detection, requiring investment in biomarker discovery and development work. This extends timelines and drives up product development budgets for lateral flow-based NG/CT tests.

Evidence-supported products are not yet ready for introduction. While many STI tests are in late-stage development, delays in validations and regulatory clearances are common, and costs are often higher than anticipated. Primary reasons include:

- Developers are optimizing across several sample types, (e.g., differing by site of infection). Unlike blood-based tests, each of these sample types must be validated. Multiple specimens and STI detection (e.g., NG, CT, and TV), also increase the complexity of clinical trials, for example, by requiring multiple samples and reference tests.
- Product development work usually relies on frozen or

contrived samples. When developers start using fresh samples, they may encounter differences that require additional product development.
- The evidence needed to support regulatory submissions is unclear. WHO PQ has not commenced for gonorrhea diagnostics, and technical specifications are still in development. The existence of separate performance requirements for molecular and antigen tests (50) (49) will likely increase WHO acceptance of lower-priced, more accessible POC test formats, even if they are not performing at the same level as NAAT tests. Acceptance of lower-performing tests in HIC markets remains to be seen, as high-income country regulators and stakeholders are accustomed to NAAT-level performance.

Despite their global relevance, POC tests with extra genital sampling are not prioritized for development. Developers typically prioritize sample types/specimens with larger markets (e.g., urine and vaginal swabs) ahead of extragenital samples. Reasons include technical challenges, particularly ensuring that the test does not cross-react with *Neisseria* species commonly found in the pharynx and the cost of additional trials and regulatory submissions. FIND has recently launched an NG/CT POC molecular test RFP that includes support to accelerate molecular platforms with extragenital sampling. (71) In HIC markets, extragenital specimen regulatory authorization required market intervention in the form of academic support and collaboration on studies, as there was little financial incentive for companies to seek these claims independently. (61) (72)

LMIC market introduction timelines are likely to be very long, as commercial efforts will focus on HIC markets first to meet return on investment targets; as new companies, most developers lack the resources to commercialize in LMICs simultaneously. Moreover, few have sufficient familiarity and experience with LMIC markets to inform plans around commercializing and distributing in these markets.

7.2 Quality

Although gonorrhea tests have been in WHO PQ expansion plans for many years, the COVID-19 pandemic delayed plans, and in 2024 WHO began drafting Technical Specifications for gonorrhea POC NAAT and antigen-detecting tests suitable for use in LMICs. **The timelines for opening PQ for gonorrhea tests are thus uncertain. Additionally, pragmatic quality assurance tools and schemes** for STI tests in LMICs are lacking; this is a common challenge for rapid tests in LMICs, especially as they are used in remote areas.

7.3 Affordability

There is a gap between sustainable prices for suppliers and affordable prices to LMIC customers (governments, donors, individuals, payers).

Although current information on prices for pipeline products is difficult to assess, **on-market test prices and indicative prices from developers make clear that affordability will be a significant barrier to gonorrhea test adoption and use in LMICs**. One of the WHO TPPs specifies a price of US$1/test (optimal) (49); however, current technology cannot achieve this pricing. While a US$1 test is possible for HIV and syphilis; these tests detect antibodies that are abundantly available in the blood using a well-established mass-produced lateral flow platform. For NG, and more so for CT, traditional RDT technology is not sensitive enough, given low organism burdens and accessibility of the pathogen in samples. As such, additional steps are typically required (e.g., sample concentration or signal enhancement), and these increase the costs. Pricing below one dollar is also highly dependent on economies of scale (e.g., ~100 million RDTs/year global market size); this level of POC gonorrhea test demand is not anticipated in the foreseeable future.

Molecular test costs exceed those of lateral flow tests, and while there are some lower-cost options, a US$5/test is likely a minimum and presumes scaled production. Most molecular test developers are not likely to achieve this pricing in the near term. Many test developers are start-ups initially targeting sales in HIC markets, and thus, they have not focused yet on optimizing test design and production in ways that might substantially lower unit costs.

There is little financial incentive to test. Current gonorrhea treatment is inexpensive (<US$1) compared to gonorrhea test costs (assay and device costs). Few governments, patients, and providers working in settings with limited resources are likely to consider testing when treatment is more affordable. A global stewardship related challenge is the difficultly weighing the tangible cost of testing vs more abstract concepts of potential drug resistance or, for individuals, the potential side effects of unnecessary antibiotics.

For asymptomatic infections, population **screening program costs are additive to existing health budgets**, e.g., introducing new test, treatment, and programmatic costs where there are currently none. To see an effect, screening must achieve high coverage in a population and be implemented over time. Financially, large screening interventions at current test prices are likely cost-prohibitive. Moreover, while experts believe screening and treating is worthwhile in high-risk groups, it is difficult to build evidence for this use case, because it is pragmatically very difficult to directly attribute the intervention (additional infections identified and treated) to health outcomes (e.g., preventing PID, infertility, poor birth outcomes, or reducing drug pressure) or to cost savings.

Both consumers and LMIC governments have limited ability to pay for STI care, and no large-scale funding is available to support STI programs. While targeted donor support is expected (e.g., testing in connection with HIV and key populations), countries may be reluctant to adopt testing for large populations due to concerns about the ability to sustain funding for testing if donor interest wanes. Additionally, because STIs are relevant to many different health initiatives (e.g., HIV, AMR, maternal and child health, sexual and reproductive health), there may be an opportunity to leverage multiple programs and funding sources to support NG testing. However, this requires coordination and may present challenges around maintaining clear accountability and ownership.

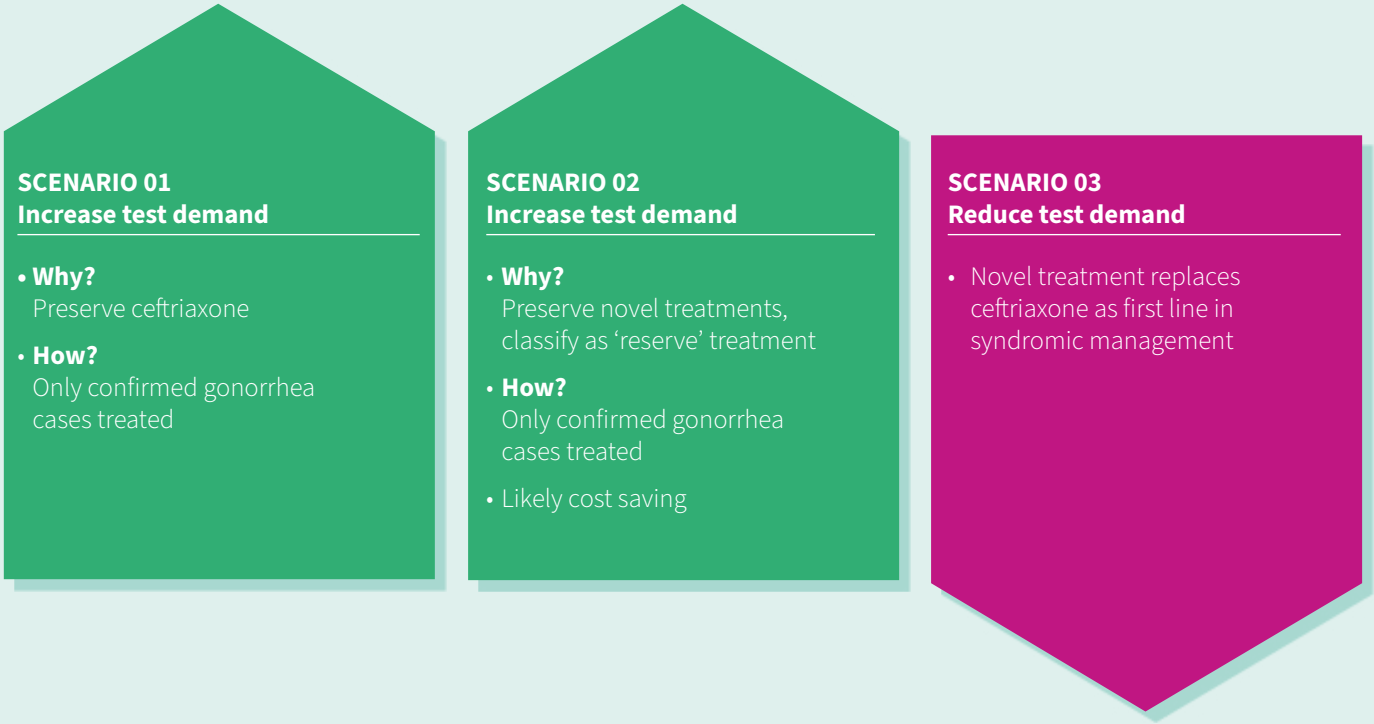
7.4 Demand and adoption

Following updated WHO recommendations (31), etiological testing policies have not been widely adopted in many LMICs. This may limit LMIC demand for gonorrhea tests.

Gonorrhea testing policy adoption is low for a variety of reasons. First, there are few affordable fit-for-purpose tests: on-market near-POC assays are unaffordable, and true POC tests are unaffordable and not commercialized in LIMCs. Second, LMIC policymakers find it hard to prioritize gonorrhea generally, as chronic underinvestment in surveillance has limited visibility of the burden, and morbidity data is difficult to attribute to gonorrhea directly. The investment case for testing is challenging to make without direct evidence of the harm from syndromic management and evidence of the effectiveness of testing across different use cases, including the opportunities to detect and treat asymptomatic infections. The complexities of the antibiotic pipeline, including high prices and limited alternatives in development, may not be widely understood, which could impact the perceived urgency of the situation. Lastly, when resources are limited, higher mortality diseases may take precedence over STI diagnostics.

For companies commercializing diagnostics, **both drug resistance and the potential different use cases for novel gonorrhea treatments have significant knock-on effects on gonorrhea test demand and deepen market uncertainty**. A few scenarios are possible (Figure 8): gonorrhea test demand may increase if concern about ceftriaxone-resistant gonorrhea grows, and policymakers prioritize testing to preserve the existing first-line therapy by ensuring only confirmed infections receive ceftriaxone. Similarly, gonorrhea test demand may increase if novel treatments are required, and policymakers want to ensure only gonorrhea-infected people receive the novel treatment. In this scenario, the test may even be cost-saving compared to syndromic management. However, gonorrhea test demand would reduce if novel treatments became the first line in syndromic management (i.e., effectively swapping new treatments for ceftriaxone). It will likely be a few years before there is additional clarity on the recommended policy for novel gonorrhea treatment use, as global stakeholders are only likely to consider their use when the new treatments have regulatory authorizations and additional evidence.Given the long-standing practice of syndromic management, when testing is adopted, **the transition to new approaches will likely take time for both health workers to implement and for patients to accept**. Additionally, in many settings, stigma around STIs and discrimination of affected populations continue to be barriers to dignified care and care-seeking more generally.

Figure 8. Effects of use cases for novel treatments on demand for tests



Countries may be reluctant to adopt testing for large populations due to concerns about the ability to sustain funding for testing if donor interest wanes.

Most test developers lack the resources to commercialize in high-, middle-, and low-income countries at the same time and will first focus on establishing their technology in high-return markets.

7.5 Supply and delivery

The near-term lack of gonorrhea POC test demand **disincentivizes suppliers from registering and commercializing tests in LMICs**. Most test developers lack the resources to commercialize in high-, middle-, and low-income countries at the same time and will first focus on establishing their technology in high-return markets. Moreover, given the limited established precedents and norms for testing STIs other than HIV and syphilis in LMICs, one can anticipate many costs associated with 'pioneering.' First movers in LMIC markets often need resources for educating policymakers, supporting local studies, registrations and policy adoption, and health worker training. These costs and timelines are a disincentive, even though in the long run, being first to market a novel test type has proven advantageous in many LMICs.

In some countries, existing test use is also a disincentive for new POC test suppliers. For example, inexpensive RDTs with suboptimal performance are available in some markets and may discourage quality-assured suppliers from engaging. Likewise, where Gram stain is available, use is likely to continue, given its low cost. Finally, a large installed base of a particular molecular platform may discourage new molecular platform developers from entering a market.

Pharmacies and drug shops also play a large role in STI care delivery in some settings, yet testing is not available in these outlets, resulting in inappropriate treatment (e.g. overtreatment, suboptimal prescribing). There are many barriers to testing in these settings. First, a suitable self-testing product is needed, as are regulations and policies that support OTC STI testing. Even when tests become available, there are several additional gaps. First, the tests are likely to cost more than treatments, diminishing the financial incentive for customers to test before treatment. Unless customers ask for tests, stores will have little incentive to stock tests, as proprietors generally prefer faster-moving products. Therefore, financial incentives may be required to ensure retailers have the incentive to stock and promote tests instead of simply selling a treatment. Additionally, on the customer side, there will be a need to create awareness of testing's benefits and a willingness to pay for testing.

8. Opportunities for intervention

This section provides an initial view of opportunities to address market shortcomings and to increase availability and access to gonorrhea POC diagnostics in LMICs. The opportunities are not specific to Unitaid's mandate and business model, and they are illustrative, representing a range of interventions that different global health actors could undertake.

Interventions directly focused on supporting POC gonorrhea testing are discussed first, followed by opportunities to integrate NG and STI testing more generally into other initiatives and programs.

8.1 Opportunities to directly support POC gonorrhea testing

Opportunities to support gonorrhea POC testing focus on developing LMIC markets for gonorrhea testing: supporting adoption and incentivizing suppliers to commercialize in LMICs (Figure 9). It is important to appreciate that even with support, the initial uptake of gonorrhea POC tests in LMICs will be limited compared to the need. Nevertheless, laying the groundwork for STI testing is an important global priority considering the burden disproportionately affecting women and vulnerable populations, as well as the threat of extensively drug-resistant gonorrhea and, with it, substantial treatment cost increases. There are both immediate opportunities (investing in product development, LMIC trials, and cultivating nascent market segments) as well as medium term opportunities focused on NG test adoption more broadly in LMICs. These are explained in more detail below.

Figure 9: Opportunities to support POC gonorrhea testing

8.1.1 Identify and cultivate nascent markets segments in LMICs

While demand is not expected to materialize at scale quickly, there are likely small customer segments interested in gonorrhea testing that may have the ability to pay. Identifying specific segments and supporting adoption and uptake in these segments would increase LMIC experience with gonorrhea POC testing, laying the foundation for testing to emerge more broadly with time. It's important to recognize that the number of patients reached may be limited and may include end users with the most likely ability to pay, i.e., private hospitals and clinics, programs targeting high-risk populations in countries where AMR is a major concern, or where HIV programs prioritize STI testing in key populations.

Without dedicated support, this nascent demand would be unserved because suppliers lack the visibility and know-how to reach these customers. Key activities may include:

- Identifying early adopter countries, their priority use cases, and market segments for gonorrhea testing.
- Understanding price elasticity in different market segments, identifying end users with the greatest willingness to pay, and acknowledging that this may not include the public sector initially.
- Articulating value propositions for testing that align with the local context and broader priorities (e.g., HIV, AMR).
- Ascertaining the evidence decision-makers need to include/advocate for gonorrhea testing and supporting efforts to generate missing evidence.
- Supporting test adoption and development of new policies for testing.
- Supporting suppliers with local registration, technology validations and assessments, and distribution. Suppliers with instrument-based platforms need a viable plan for maintaining instruments and supporting continuous functionality.
- Supporting programs with training and sensitization for health workers.

8.1.2 Refine LMIC demand forecasts, explore dual HIC/LMIC pricing strategies with suppliers

Work-to-date on demand suggests widespread scale-up of testing is unlikely at current prices. However, discussions with suppliers about LMIC markets could benefit from more refined estimates of LMIC demand, considering willingness to pay and potential volumes across several customer segments. Additionally, scenario modeling might explore the effect of AMR and different use cases for new gonorrhea treatment on gonorrhea test demand.

Overall, as POC STI tests are implemented in HICs, suppliers might be able to offer differential HIC and LMIC pricing, for example, leveraging volumes across both markets to offer COGS-plus pricing to LMICs. Whether this is a viable approach requires a better understanding of production costs at different volumes and LMIC demand and price elasticity. If analysis indicates that low-cost prices could be affordable for LMICs, time-limited market-shaping interventions (e.g., product subsidies, volume guarantees) could accelerate a transition to a high-volume, low-margin market in LMICs that offers sufficient scale to incentivize supply.

8.1.3 Fund product development that covers diverse user needs

A comprehensive POC STI approach requires additional product development, including a chlamydia LFA, extra genital sampling, and self-testing. High-performing chlamydia RDTs are challenging to develop, and while there are a few efforts to develop these RDTs, additional research and development funding may be needed to fill gaps or accelerate development. Tests accepting extra genital samples are also an urgent global priority. FIND's recent POC molecular NG/CT request for proposals includes funding for extragenital sample development and validation work. However, additional efforts may be needed to ensure multiple solutions come to market. Validated approaches for pooling samples from multiple sites in a single patient would also save time and cost. Finally, support for self-test product adaptation and usability studies may be considered, acknowledging the significant downstream investment required to support self-testing market development.

8.1.4 Support clinical trials in LMICs of fit-for-use POC products

Funding product validations and clinical trials in LMIC markets could incentivize suppliers to engage in these markets. Focusing on early adopter countries and linking trial participation for different developers to access terms such as registration, WHO PQ, and price, could accelerate LMIC commercialization. Depending on the timing of product availability, a multisite LMIC trial using a master protocol (i.e., a common reference standard, common protocol, and use of single-subject samples to evaluate multiple tests at a time) could increase the efficiency of funds.

8.1.5 Research studies to illustrate the value of POC gonorrhea testing

Creative approaches to demonstrating the benefits of testing are needed to build an investment case for gonorrhea testing for policymakers and funders. Although the 'optimal' POC tests are not on the market yet, studies using on-market tests can provide "proof of concept" for STI testing in different populations and contexts. Such studies could generate data on health outcomes, impacts, and the costs of testing. This data could inform cost-benefit studies and discussions

around optimal target prices for STI testing in LMICs.

8.1.6 Country-level enabling environment and implementation model development support

Providing time-limited support for STI focal points in MoHs may accelerate test adoption and rollout. New test introductions are resource-intensive, requiring piloting, policy development, procurement, and initial rollout. Supporting implementation could include local evidence reviews, health technology assessments and policy updates, pilots, development of resource mobilization strategies to ensure sustained funding, initial quantifications and procurement, and training for health care workers. MoH commitment or co-funding could be considered a requirement for support to ensure continued programming and test procurement after project implementation. Particularly for STIs, given the diversity of target populations, delivery channels, and use cases for gonorrhea tests, programs would benefit from support in developing implementation models for different priority populations. The nuances of testing in different populations and settings, as well as infrastructure and provider workloads are important considerations (73). Support could include developing and disseminating tools and models for engaging clients, health care workers and communities as well as sensitization, and behavior change work to reduce stigma and care-seeking barriers around STIs.

8.1.7 Pooled procurement for STI tests

A centralized procurement mechanism to consolidate demand across a fragmented market, including many low-volume buyers and private buyers, would reduce transaction costs and ease suppliers' ability to serve small and fragmented demand.

8.2 Opportunities to integrate gonorrhea testing

There are several opportunities to advance gonorrhea testing through other initiatives, among them:

8.2.1 Include gonorrhea and STI testing in integrated POC molecular testing initiatives

POC molecular test platforms are increasingly available in LMICs. Initiatives focused on introducing and scaling up POC NAAT could include supplier commitments for NG/CT test registration and access pricing in LMICs.

8.2.2 Strengthening POC diagnostics implementation in ANC settings

Comprehensive POC testing (e.g., malaria, anemia, HIV, syphilis, and increasingly hepatitis B, and possibly other STIs) alongside malaria prevention efforts can support healthy pregnancy and birth outcomes. In several LMIC settings, the burden of STIs in pregnant women is alarmingly high. While HIV testing rates in ANC are generally high, and syphilis testing rates are increasing, uptake of other tests is low. An initiative to strengthen use of POC testing in pregnancy, including gonorrhea testing, could have a significant impact, as pregnant women attending ANC are motivated patients coming for health-seeking and likely amenable to testing and, if infected, partner notification.

New test introductions are resource-intensive, requiring piloting, policy development, procurement, and initial rollout.

8.2.3 Intensify integrated delivery of STI and HIV testing and prevention

STI care can be an entry point for HIV care and has the potential to improve the engagement of hard-to-reach populations. STI testing can be a motivator to access care and can confirm risk in populations that may not otherwise test for HIV. STI testing can also increase PrEP uptake and retention. Similarly, incorporating STI testing into services for patients already in HIV care is an effective means of expanding access, to take advantage of frequent contact with health facilities. To expand beyond HIV and syphilis tests, support for integrated delivery of STI and HIV services could incorporate novel gonorrhea POC tests. Innovative models that integrate care, reduce stigma and discrimination, and strengthen engagement of partners and social contacts of people affected by HIV and STIs are also needed.

8.2.4 STI testing to strengthen engagement of key populations in HIV prevention and treatment

In many countries, stigma, social norms and laws discourage identification as a key population member. New care delivery models, such as STI clinics, that reach key populations without requiring individuals to identify as such are needed. POC tests as well as prevention and treatment services could be incorporated into these care delivery models. Developing and validating extra genital specimens on POC platforms, as described above, would complement this work.

9. Conclusion

With the looming threat of drug resistance and more costly next-generation antibiotics, the need for effective, affordable gonorrhea diagnostic tools is high. Additionally, the emergence of POC gonorrhea tests marks a potentially transformative advance in STI management, and several products are already available or nearing market readiness. Despite the need and the promise of new technologies, significant market challenges hinder test accessibility in LMICs. There is a high risk that products will become readily available in well-resourced settings while remaining largely inaccessible in LMICs.

Addressing this disparity requires concerted efforts to generate demand for testing, including heightening the perceived importance and value of testing among stakeholders at all levels, and improving the affordability and availability of fit-for-purpose tests.

Despite the many obstacles, it is imperative to advance POC gonorrhea testing markets in LMICs, even on a limited scale initially. Transitioning from syndromic to etiologic diagnosis will be a gradual process, heavily dependent on the availability of affordable and suitable diagnostics. Acting now, as tests become available, is an essential signal for a nascent market. Early work to implement testing will provide valuable evidence and experience and no doubt improve STI outcomes, especially for vulnerable populations that will benefit from diagnostics guided care, reduce transmission, and extend the lifespan of effective antibiotics.

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