COST-EFFECTIVENESS OF DIFFERENT SCREENING AND DIAGNOSTIC STRATEGIES FOR SEXUALLY TRANSMITTED INFECTIONS AND BACTERIAL VAGINOSIS IN WOMEN

by

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PREAMBLE

PLAGIARISM DECLARATION

I, *Elise van der Walt*, hereby declare that the work on this dissertation is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION

I dedicate my thesis to my family, especially my parents, and my fiancé.

I am forever grateful for your endless patience and support throughout my academic career and this last year especially. I could never have done this without you – I am forever grateful.

ABSTRACT

Genital inflammation associated with sexually transmitted infections (STIs) and Bacterial Vaginosis (BV) is considered a key driver in the HIV/AIDS epidemic. A new rapid point-of-care (POC) test that detects genital inflammation in women was recently developed by researchers at the University of Cape Town. The objective of this study was to establish the cost-effectiveness of this novel intervention in comparison to other relevant screening and diagnostic strategies for the management of STIs and BV in women. It follows prior research on the cost and affordability of national implementation of screening with this technology. This research indicated that it might not affordable policy option given current health budget constraints.

A decision analysis model was developed to estimate the cost and health outcomes associated with five different screening and diagnostic strategies for women seeking care in the South African public health sector. A decision tree was constructed, and all cost and effectiveness parameters were obtained from published and unpublished literature. The model incorporated all clinic-level and treatment costs associated with diagnosing and treating a single episode of disease. The main outcome measure was the effectiveness of each approach in correctly diagnosing an STI or BV in women, proxied by its sensitivity measure. One-way sensitivity analyses and threshold analysis were conducted to test key uncertainties and assumptions in the model.

In the base-case scenario, screening with GIFT and treating GIFT-positive cases based on syndromic management guidelines, was the most cost-effective strategy with an ICER of $2.60 per women diagnosed with an STI(s) and/or BV. This strategy remained the most cost-effective even when a variety of parameters were varied in one-way sensitivity analyses. A threshold analyses on GIFT's sensitivity revealed that the strategy would remain the most cost-effective unless the sensitivity of the test assay decreased below 14.83%.

From the perspective of the South African government, screening with GIFT and treating positive cases according to syndromic management guidelines is a highly cost-effective strategy for the management of STIs and BV in women in the reproductive age, but affordability considerations cannot be ignored. The newly developed rapid POC can significantly improve the management of STIs and BV in women through identifying asymptomatic women and at the same time, reducing their risk of HIV infection, but further research is required to inform decision-making.

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1. INTRODUCTION

1.1. Background

Globally, sexually transmitted infections (STIs) and Bacterial Vaginosis (BV) pose a massive, and often overlooked, challenge to public health and development. The annual incidence of STIs is exceeded only by that of malaria, lower respiratory infections and diarrheal diseases and places substantial pressure on health care expenditure and health system at large (Kamb et al., 2008; Torrone et al., 2018). In 2012, the World Health Organization (WHO) reported that annually, around 499 million new cases of the four most common curable STIs, *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and Syphilis infections*, occurred globally (World Health Organization, 2012). Global estimates of BV incidence and prevalence remains extremely limited (Torrone et al., 2018). However, reported STIs typically only represent around 50% of all infections. Many infections, especially in women, present asymptomatic, regardless of viral or bacterial aetiology (Kamb et al., 2008). Kaida et al. (2018) report that this estimated as high as 75%. BV is not classified as an STI but is associated with various STIs and is characterized by abnormal vaginal discharge in women in their reproductive age (Morris, Rogers and Kinghorn, 2001).

South Africa houses one of the largest burdens of STIs in the world (Johnson et al., 2007). The high prevalence of STIs in developing countries result in significant losses for individual and community productivity. Most of these infections are preventable or curable with relatively inexpensive and simple interventions. If left untreated, however, it can lead to various serious sexual and reproductive complications and increase the risk of HIV acquisition (Kamb et al., 2008; Masson et al., 2016). STIs are considered one of the leading causes of disability adjusted life years lost for women in the reproductive age in developing countries (Kamb et al., 2008).

There is an urgent need for the improvement of STI management in women in resource-constrained settings (Masson et al., 2016). The development of rapid point-of-care (POC) tests for STIs has been a priority on the global agenda since the 1990s, while syndromic management was originally only intended as a temporary solution (Romøren, 2008). The WHO has also developed the ASSURED criteria under the Sexually Transmitted Diseases Diagnostics Initiative. This acronym specifies 7 criteria for any newly developed diagnostic test in order to ensure that it meets disease control requirements. Affordability is one of the key requirements (Peeling et al., 2006).

Researchers at the Division of Medical Virology at the University of Cape recently developed an inexpensive, rapid POC test; the Genital Inflammation Test (GIFT). GIFT detects STIs and BV and inflammatory bacteria in the female genital tract with a sensitivity of 77% and a specificity of 71%. The device has been validated in a biomarker validation study and is to be rolled out in a cross-sectional

validation study to evaluate and optimize its performance. The validation study will be conducted at healthcare facilities in Cape Town.

The purpose of this proposed study is to conduct a cost-effectiveness analysis of different screening strategies, for STIs and BV among women in Cape Town and ultimately, the prevention of HIV.

1.2. Problem Statement

The persistent public health burden of STIs is the result of various complex and interlinked factors, but the delay in treatment resulting from existing diagnostic and treatment protocols is considered a major contributor. (Gaydos and Hardick, 2014). STIs and BV that are left untreated or that are treated inappropriately, can lead to reproductive complications in women such as infertility and adverse pregnancy outcomes (Kamb et al., 2008). STIs and BV, which causes inflammation in the female genital tract, are also recognized as key drivers of the HIV/AIDS (Johnson et al., 2012; Mlisana, 2014).

Inflammation in the female genital tract caused by STIs and BV, increase the risk of acquiring HIV by reducing the effectiveness of the mucosal barrier, recruiting HIV target cells and promoting HIV replication (Passmore, Jaspan and Masson, 2016; Masson et al., 2014). BV infection increases a woman's risk of acquiring HIV and the risk of transferring HIV to her partner or to her child during childbirth (Brotman et al., 2010). Furthermore, studies suggest that bacteria associated with BV can potentially reduce the efficacy of topical anti-retroviral therapy (ARV) pre-exposure prophylaxis (PrEP); a crucial strategy for the prevention of HIV. In general, women are already more vulnerable to acquiring HIV; up to eight times more than their male counterparts (Masson et al., 2016; UNAIDS, 2010). Johnson et al. (2012) estimated that roughly half of the new HIV infections in South African women in 2010 were due to other STIs. The management of these infections are thus crucial in preventing HIV in settings with a high burden of HIV, STIs and BV, such as South Africa (Mlisana et al., 2012). Various studies that evaluated interventions for the prevention of HIV in South Africa also show that improvements in STI treatment can have a significant impact on the epidemic and can potentially be cost-effective (Mayaud and Mccormick, 2001; Vickerman, Terris-Prestholt, et al., 2006).

Southern Africa has the largest burden of HIV in the world despite increases in resources earmarked for the epidemic which have allowed management and treatment to be improved in the region (UNAIDS, 2018). A large part of this burden is accounted for in South Africa, with 33% of new HIV infections and 29% of AIDS-related deaths in Eastern and Southern Africa in 2017 occurring in the country. These is the largest portions held by a single country in this region (UNAIDS, 2018).

In South Africa the majority of STIs are managed syndromically, rather than through costlier laboratory diagnosis (Mlisana et al., 2012). This approach is recommended by the World Health Organization

(WHO) in resource-limited settings and was introduced to the South African public health sector in 1994 (World Health Organization, 2003; Johnson et al., 2011). Syndromic management is based on the identification of signs or symptoms (syndromes) of a specific STI or BV according to pre-identified groups. Patients are provided with treatment that will address the majority, or the most serious of organisms typically associated with the identified sign or symptom (World Health Organization, 2003). Laboratory testing, such as nucleic acid amplification tests (NAATs) and Nugent scoring (the gold standards for STI and BV diagnosis respectively), is expensive and requires specialised equipment and trained personnel. Furthermore, it does not allow for immediate results. This is problematic in low- and middle-income settings where the rate of return to clinics, and consequent opportunity for uptake of treatment, is typically very low (reported as low as 37% in some studies). In high-burdened settings this would also provide a window for more transmission while the patients status remains unknown. (Brotman et al., 2010; Masson et al., 2016). Syndromic management has thus provided a relatively inexpensive and seemingly more applicable alternative as it allows for patients to receive treatment immediately (World Health Organization, 2003).

Various issues have, however, been raised with regards to syndromic management as a screening strategy for STIs since its institutionalisation in the early 2000s (World Health Organization, 2003). Research, however, reveals the occurrence of a large number of false positives, resulting in over-treatment and thus excessive use of antibiotics. This phenomenon is becoming an increasingly alarming worldwide, as it has significant implications for the formation of drug-resistant strains of various bacteria. Furthermore, it results in excessive economic burden by means of wastage of scarce resources. Another concern is the large portion of BV and STI cases that present asymptomatically. Syndromic management does not allow for the detection infection recognisable signs or symptoms of infection. Lastly, it relies solely on women to seek care for self-identified infections (Wajid, 2015; Passmore, Jaspan and Masson, 2016).

GIFT is a POC test (a cytokine rapid test) that was developed to detect genital inflammation in order to identify asymptomatic infections in the female genital tract as an indication of STIs or BV. The test allows for the detection of inflammation caused by bacteria that also increases women's risk of being infected with HIV but that is not identifiable by gold standard STI or BV laboratory tests (South African Medical Research Council, 2018). This test ultimately aims to identify cases that would normally be overlooked by syndromic management, thereby reducing the prevalence of STIs and BV as well as the HIV risk of women in South Africa (South African Medical Research Council, 2018).

In order to inform on whether or not this POC test provides the South African government with a feasible and good value for money option for care, a cost-effectiveness study is required. The

estimation of the cost-effectiveness and health outcomes of the device is a primary aim of the GIFT project. It stipulates the development of a cost-effectiveness model from the provider's perspective (South African government, Department of Health), incorporating screening and treatment costs incurred as well as medical costs averted through the accurate diagnosis of STIs or BV with GIFT.

1.3. Rationale

STIs and BV represent a massive public health issue. The WHO has set the ambitious goal of achieving a 90% reduction in the incidence of STIs and zero new infections by 2030. The improved detection and treatment of asymptomatic STI and BV cases can potentially make a significant contribution to this goal and forms a key part of the organization's STI prevention and control strategies. The WHO also prioritizes the development of point-of-care-tests (World Health Organization, 2012b, 2016b). Nationally, and as part of the Western Cape's Provincial Strategy Plan, zero new HIV and STI infections are a key part of the long-term vision for health of all South Africans (Western Cape Government Health, 2016). Literature and practical experience suggest that there is a need to move away from syndromic management and towards more effective strategies for screening and diagnosis of STIs and BV. POC testing or screening might be more suitable in developing country settings where expensive laboratory testing is not feasible and where return rates to health facilities are low. GIFT provides the health system with such a rapid POC screening device that can potentially improve management of STIs and BV in low- and middle income setting such as South Africa.

Currently, the cost-effectiveness of POC testing as a screening strategy for STIs has not been well established either globally or in South Africa. The cost-effectiveness of the newly developed GIFT device as a screening strategy is also yet to be established. The economic costs associated with providing universal screening for genital tract inflammation screening in the public sector has been estimated as part of the larger GIFT study. The original GIFT study protocol sets out for a CEA to be conducted and the availability of much of the cost estimates makes a CEA study of GIFT and other screening and diagnostic strategies more feasible in the short run.

The findings produced by this study can potentially inform the important policy issue of resource allocation to STI management in South Africa. Improved management in this area of public health can possibly contribute to ensuring universal access to POC screening for STIs and BV for all women utilising the public sector.

2. BRIEF LITERATURE REVIEW

2.1. Economic and Health Burden of STIs and BV

Kamb *et al.* (2008) report that STIs pose high costs on individuals in developing countries, with the average direct medical costs per single bacterial STI episode reaching up to three times that of the average daily income in low income countries. Associated indirect costs include productivity losses due to mortality and morbidity and other related adverse health outcomes. Globally, STIs also disproportionally affect the economically active population, which aggravates the economic impact of this public health issue. Young adults in particular, are more exposed to curable STIs, for various behavioural and biological reasons (Kamb *et al.*, 2008).

2.2. Economic Evaluation

According to Drummond *et al.* (2005), economic evaluation is the "comparative analysis of alternative courses of action in terms of both their costs and consequences". It encompasses the identification, measurement, valuation and comparison of the costs and consequences of each considered alternative (Drummond *et al.*, 2005). Within the methodological field of economic evaluation, various approaches exist.

One of four types are typically used; cost-minimisation analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). For all four approaches, economic costs of alternatives are measured in monetary terms. CMA is typically used where the alternatives broadly have equivalent consequences and therefore, outcomes are not measured or valued. The costs of the alternative courses of action are merely weighed up against each other. It is not considered a full economic evaluation and can be considered a subset of CEA. CBA is used when consequences, not necessarily common to all alternatives, are also measured in monetary terms (Drummond *et al.*, 2005; Fox-Rushby *et al.*, 2005). CUA, on the other hand, presents outcome measures in either quality-adjusted life years (QALYs) gained or disability-adjusted life years (DALYs) averted. Both these are utility measures that allows for single or multiple, dissimilar consequences to be compared. According to Drummond *et al.* (2005), CEA is suitable for scenarios where the decision-maker is operating within a given budget and considering a range of option within a given field. In this type of economic evaluation, outcomes are presented in natural units, such as years of life gained, or number of cases detected associated with a specific strategy. According to Fox-Rushby *et al.* (2005), CEA is the most commonly used form of economic evaluation in healthcare.

CMA and CEA provide insight on technical efficiency only, while CUA can inform on allocative efficiency within the entire health sector, for example. Technical efficiency refers to a situation where available resources are utilised so that output is maximised, and costs are minimised. Allocative efficiency on

the other hand, refers to where no person can be made better off without making another worse off (Fox-Rushby *et al.*, 2005). CBA is unique in that it can provide insight on allocative efficiency in general and can thus be used to argue for increased resource allocation to the health sector itself (Drummond *et al.*, 2005).

2.3. Cost-effectiveness Analyses of Screening and Diagnosis of STIs and BV

A brief review of the available literature on the cost-effectiveness of different screening and diagnostic strategies for STIs and BV is given here. Two systematic reviews of literature on the cost-effectiveness of Chlamydia interventions and screening were included. Studies included in these reviews were not individually reviewed.

Honey *et al.* (2002) conducted a systematic review of 10 studies comparing the cost-effectiveness of screening for *Chlamydia* with various laboratory tests, to testing and treating only symptomatic women in European populations. The authors concluded that overall, screening is a cost-effective alternative in terms of cases of pelvic inflammatory disease (PID) or *Chlamydia* prevented. NAAT laboratory testing was more cost-effective method of screening than the three other tests included. Rours *et al.* (2016) found similar results in a cohort of Dutch pregnant women based on cases of PID, preterm delivery and neonatal complications prevented. Honey *et al.* (2002), however, also note that many models lacked strong evidence to support the assumptions they made as well as sound effectiveness data.

Roberts *et al.* (2006), another systematic review on the cost-effectiveness of screening for *Chlamydia,* critique Honey *et al.* (2002) on being potentially misleading with their conclusion as many of their studies used restricted outcome measures such as "cost per case detected" and static models and that the relevant limitations were not fully discussed. Roberts *et al.* (2006) reviewed 59 studies, mainly from developed countries and report that the majority of studies found the combinations of screening with laboratory testing and treatment to be cost-effective, but that most studies had similar weaknesses to those identified in Honey *et al.* (2002). This prevented them from making concrete conclusions. Two other reviews judged sound by them, however, showed that screening is cost-effective and would even become cost-saving over a period of 4-5 years if to be implemented (Honey *et al.*, 2002).

Homan *et al.* (2002) assessed the cost-effectiveness of syndromic management, risk assessment and laboratory testing (as well as combinations of these) for various STIs among sex workers in Madagascar. The study found that the combination of syndromic management and regular risk assessment was more cost-effective than laboratory testing and risk assessment for reducing the prevalence of Gonorrhoea and Chlamydia (both cervical infections). The authors, however, note that

different results were obtained for vaginal infections and syphilis and emphasises the importance of disaggregate analysis across diseases *(could not access full paper).* Romøren (2008) investigated the cost-effectiveness of POC testing and syndromic management, with both the standard of care drug and a new one, of *Chlamydia* in Sub-Saharan Africa. The author finds that in the teenage study population, syndromic management with the new drug is the most cost-effective strategy, although screening with the POC test is also cost-effective. Among all age groups, only syndromic management with the new drug is cost-effective. This study does not, however, include additional benefits associated with the POC tests, such as reduced overtreatment, in their estimates (Romøren, 2008) This means that the POC outcomes are likely underestimated.

Hislop *et al.* (2010) include cohorts from various studies across Europe, USA, China and Egypt in their cost-effectiveness study of six rapid POC tests compared to NAAT for the detection of *Chlamydia.* They find that NAATs is still the most accurate and cost-effective approach to diagnosing this infection, measured as number of true cases detected and partners notified. It is, however, noted that one of the POC tests would become cost-effective if the acceptance of the test by patients would increase. Authors also note here, the "rapid test paradox", which refers to the lower sensitivity and specificity of POC tests being overshadowed by the increased treatments it ensures in comparison to laboratory tests which require patients returning to facilities for test results and the initiation of treatment. The rate of return was, however, not factored in to this evaluation. It is also noted that limited evidence on the effectiveness of these tests limit the comparison to NAATs (Hislop *et al.*, 2010).

In a Finish study, Kekki *et al.*, (2004) found screening, with Gram-stain, and treatment of BV in pregnant women to be cost-effective in terms of preterm deliveries prevented, compared to the no screening alternative. Kuznik *et al.* (2012) conducted a cost-effectiveness study of rapid POC tests as a screening strategy for syphilis in pregnant women in Sub-Saharan Africa. These authors also found that screening and treatment was more cost-effective than no testing and also a cost-saving approach in terms of stillbirths, congenital syphilis, neonatal deaths and DALYs averted. Huntington *et al.*, (2017) also conducted a study on the cost-effectiveness of three hypothetical POC NAATs in comparison to standard laboratory testing, based on UK data. The POC test testing for four STIs simultaneously was found to be the most cost-effective in terms of reduced inappropriate treatment of STIs, STI transmissions and PID. All three POC test were, however, costlier, but more cost-effective than standard care laboratory testing. A key limitation of this study is that given the hypothetical nature of the POC tests, the test pathways were mainly informed through expert opinion (Huntington *et al.*, 2017).

In order to account for differential timing of costs and outcomes, these are discounted in CEAs (Drummond *et al.*, 2005). In the literature, it was found that a discounting rate of 3-5% is commonly used in CEA on STIs and higher rates (up to 10%) were only used when modelling secondary outcomes such as fertility (Honey *et al.*, 2002). All of the studies only included direct costs as it was conducted from the viewpoint of the various health care providers, which were mostly national departments of health.

From this brief literature review it is clear that literature on the cost-effectiveness of screening strategies for various STIs and BV is mixed and quite muddled in terms of study design (especially outcome measures) and results and conclusions. The studies are difficult to compare due the different STIs, screening tests and approaches and populations included in each of the models. However, there is clearly a gap in the literature when it comes to the cost-effectiveness of different screening strategies of STIs and BV in low- and middle-income countries. Furthermore, there is a need for good quality CEAs to inform policymaking on the issue of STI and BV management and POC screening and testing.

3. AIMS AND OBJECTIVES

3.1. Aim

The main aim of this study is to establish the cost-effectiveness of GIFT for the screening and diagnosis of STIs and BV, in comparison to other relevant screening and diagnostic approaches. Economic evaluations, such as cost-effectiveness analyses, aim to inform decisions on resource allocation where limited resources are available (Mori *et al.*, 2017). The study will thus aim to inform on the relative cost-effectiveness, or value for money, of the GIFT device in the South African public health sector context.

3.2. Study Objectives

The objective of the study is to identify, quantify and value all resources associated with the identified screening strategies for STIs and BV in women at the primary care level to:

1. Estimate the unit costs associated with screening and treatment of STIs and BV using each identified approach. This will be conducted from the perspective of the provider; the Department of Health.
2. To estimate the effectiveness of each identified screening comparator.
3. To establish the incremental cost-effectiveness ratio associated with each comparator in terms of women diagnosed and treated.
4. To determine the relative cost-effectiveness of each comparator.

5. To make policy recommendations based on the findings.

4. METHODOLOGY

4.1. Study Design

The study will take the form of a cost-effectiveness analysis (CEA). This involves measuring and valuing costs and health outcomes (effectiveness) associated with different paths of care to compare these strategies in terms of its value for money (Mori *et al.*, 2017). According to the WHO the majority of STIs are caused by eight infections: *C. trachomatis, N. gonorrhoeae, T. vaginalis infections*, syphilis, genital herpes, human papillomavirus, human immunodeficiency virus (HIV) and hepatitis B virus (Kamb *et al.*, 2008). The STIs that will be included in this analysis were identified from Masson *et al.* (2016) and Passmore, Jaspan and Masson (2016) and include *C. trachomatis, N. gonorrhoeae and T. vaginalis;* the three highly prevalent curable STIs among women in South Africa. These infections, along with BV, will be included in the study due to both their high prevalence in South Africa and association to increased risk of HIV acquisition and transmission (Passmore, Jaspan and Masson, 2016).

The model will be constructed and parameterised from the perspective of the South African government as the healthcare provider. The study will be conducted prospectively as part of the GIFT study, given that the device validation pilot study has not yet commenced. The GIFT study's protocol sets out that the incremental cost-effectiveness ratio (ICER) of the newly developed rapid POC test be compared to the current standard of care; syndromic management. For this study, however, standard laboratory testing and GeneXpert and microscopy will also be compared in order to gather valuable insight on a wider range of screening and diagnosis alternatives for STIs and BV available in South Africa.

4.2. Cost-effectiveness Analysis

A decision-analytic model will be used to determine (a) the cost per woman correctly diagnosed per screening strategy and (b) the cost per woman treated per screening strategy. A simple decision tree model will be constructed using Microsoft Excel. All costs will be valued and presented in 2019 South African Rand (ZAR) and where necessary, costs will be adjusted for differential timing based on the relevant inflation rates. The model will be set-up to describe each alternative course of action, linking it to its relevant cost and outcome parameters. Ultimately the ICER of each strategy will be calculated based on the formula presented below in figure 1. In order to establish the incremental cost-

effectiveness ratio of each comparator, the incremental costs are divided by the incremental effectiveness.

Figure 1: Incremental cost-effectiveness ratio calculation

$$ICER = \frac{Cost(x) - Cost(y)}{Effectiveness(x) - Effectiveness(y)}$$

(Y represents the next least costly strategy)

Source: adapted from (Drummond *et al.*, 2005)

4.2.1. Screening Strategies

The alternatives included in the analysis is based on the GIFT study protocol with the addition of alternatives available in the South African setting. The primary study protocol stipulates a cost-effectiveness analysis to be conducted on the newly developed rapid POC test (GIFT) in comparison to syndromic management. However, to give a more accurate and holistic description of the available options in the South African setting, GeneXpert (for Chlamydia, Gonorrhoea and Trichomonas) and microscopy (for BV) and standard laboratory testing will be included in the analysis (Masson, 2018).

The comparators that will be included in the analysis are thus:

1. GIFT followed by Syndromic Management
2. GIFT followed by GeneXpert and Microscopy
3. GeneXpert and Microscopy
4. Standard Laboratory Testing
5. Syndromic Management

4.2.2. Description of strategies

4.2.2.1. GIFT followed by Syndromic Management

Symptomatic and asymptomatic women presenting at a primary health clinic are screened for genital inflammation using the GIFT POC test. This involves a nurse taking a lateral vaginal swab and applying it to the GIFT device in the clinic. In the case of a positive GIFT test result, the woman is and treated according to the Syndromic Management algorithm (see 4.2.2.5) (Masson, 2018). This screening process was estimated to take roughly 20 minutes per patients (Kairu, 2017)

4.2.2.2. GIFT followed by GeneXpert and Microscopy

Symptomatic and asymptomatic women presenting at a primary health clinic are screened for STIs and BV using the GIFT POC test. In the case of a positive GIFT test result, the woman is further tested

with GeneXpert and microscopy and treated accordingly (Masson, 2018). The GeneXpert TV and NG/CT assays (see 4.2.2.3.) can be run simultaneously and takes up to 90minutes to provide results (Gwen Stephens, Ceipheid, personal communication 2019, June 3).

4.2.2.3. GeneXpert and Microscopy

Women presenting at the clinic with signs or syndromes of STIs would be tested for Chlamydia (CT), Gonorrhoea (NG) or Trichomonas (TV) using the GeneXpert (CT/NG/TV assay) of for BV using microscopy. The microscopy test involves the nurse taking a vaginal swab (Peeling et al., 2006; Masson et al., 2014). For GeneXpert, a vaginal swab is taken from the patient and applied to the GeneXpert assays (Gaydos et al., 2013). Microscopy and GeneXpert are conducted at the clinic (Masson, 2018).

4.2.2.4. Standard Laboratory Testing

In the case of laboratory testing, a vaginal or cervical swab is typically taken by a nurse from a patient displaying symptoms and sent to the laboratory. Specific tests are requested testing either for a specific STI or a range of infections. Patients are then informed on their results and are required, in the case of a positive test result, to return to the clinic for the initiation of treatment (Masson, 2018).

4.2.2.5. Syndromic Management

Syndromic management is based on the identification of signs or syndromes of a specific STI or BV according to pre-identified groups. Patients presenting at the clinic with symptoms of STIs would be examined by the nurse and provided with treatment that will address the majority, or the most serious of organisms typically associated with the identified sign or symptom (World Health Organization, 2003).

4.2.3. Research procedures and data collection

The economic cost associated with each comparator will be obtained from the provider's perspective. For comparators 1-3 this is will include all clinic-level costs associated with examining a patient, taking a specimen, analysing a specimen and providing patients with treatment. The latter will include the cost of drugs for treatment. Clinic-level costs refers to and includes staff time, capital, recurrent and overhead costs. The cost estimates for comparators 1 and 2 will be obtained from the GIFT costing study (Kairu, 2017) and published literature, while the cost of Standard Laboratory Testing will be obtained from the National Health Laboratory Services (NHLS) and all clinic level costs will be based on the GIFT costing study.

For syndromic management, all clinic-level costs associated with the examination of a patient and providing her with treatment, inclusive of drug costs, will be obtained from GIFT study. The target

population will be women in the reproductive age (between the ages of 15 and 49) attending Spencer Road Clinic as costed in Kairu (2017).

The effectiveness of each comparator will be modelled based on the sensitivity and specificity of each test or approach. These parameters will be obtained from published literature. The sensitivity and specificity of the biomarkers used in GIFT device will be used as a proxy for the effectiveness of the test itself, as the device validation study has not yet commenced. To estimate the effectiveness of Standard Laboratory Testing, lost-to-follow up data will also be extracted from the literature. Disease prevalence will be used as a proxy for the probability that a woman entering the model has an STI and/or BV. These estimates will also be obtained from relevant published literature.

4.3. Sensitivity Analysis

At conclusion of the base case model, one-waty sensitivity analyses and a threshold analysis will be conducted to investigate the robustness of the evaluation and the generalisability of the findings. Key parameters will be varied within plausible ranges. The most relevant uncertainties are expected to occur with regards to the GIFT test price, staff costs as well as the sensitivity and specificity of the screening strategies. Furthermore, lost-to-follow up rates might significantly differ between settings, especially urban and rural. The rates are expected to be much higher in remote, rural areas due to geographical location and related travel time and costs. Other parameters to be varied in the sensitivity analysis will be decided upon the conducting of the base-case analysis.

5. DATA ANALYSIS AND MANAGEMENT

Cost and effectiveness data will be estimated and presented as per section 3.2 and as described in section 4.2. Primary data will be captured as per the data collection tool in Appendix A and entered into a Microsoft Excel document. All primary collected data will be kept on a password-protected folder on a personal computer which will be backed up on a regular basis. The primary data will be accessible to the research team only. The decision analytic model will be constructed in Microsoft Excel and analysed accordingly.

6. ETHICAL CONSIDERATIONS

6.1. Ethical Approval

This protocol will be submitted to the University of Cape Town's Human Research and Ethics Committee (HREC). Ethical approval for the primary (GIFT) study has been sought and granted from HREC (HREC REF: 365/2017) as well as the Western Cape Department of Health. No additional provincial approval is thus required to conduct the observation arm of the study at Spencer Road Clinic.

6.2. Potential Risks and Benefits

It is not foreseen that the study poses any potential risk or harm to any individual. There are no direct risks associated with collecting the relevant cost and outcome data from secondary sources. Potential risks in regard to the observation arm of the study will be minimised by conducting the observations from outside the consultation room and by the researchers having no direct contact with any of the patients. Furthermore, no personal identifiable information will be linked to any single observation.

No individuals will be required to enrol in the study and the study will thus have no direct benefits nor pose any direct risks to anyone. The study is likely to hold indirect benefits for the society and public health regarding the management (including testing, diagnosis and treatment) of STIs and BV. It can possibly also have implications for disease prevalence and the HIV epidemic. It will inform on whether GIFT is good value for money and evidently, whether it is worth for the South African government to invest resources in this intervention. This could ultimately contribute to improved sexual and reproductive health among women by decreasing the prevalence of HIV, STIs and BV in communities.

6.3. Autonomy and Informed Consent

Since no individuals will be recruited or enrolled for the purpose of this study. Cost and effectiveness data, with the exclusion of the clinic observation arm of the study for comparator 4, will be obtained from the GIFT costing study and published literature. Primary data, collected through observation will not involve any interaction with patients nor will any personal information be collected, so no informed consent will thus be required. Access to the GIFT study and facility data is already granted through the GIFT study protocol.

6.4. Confidentiality and Privacy

Confidentiality and privacy will be assured at all times, since the study will not use or capture any data containing personal identifiers. Electronically stored information and data will be password-protected and only accessible to members of the study team. Where relevant, hard copy documents will be stored in a locked filing cabinet to which only the study team will have access to as well.

7. PUBLICATION AND DISSEMINATION POLICY

Upon completion of this study, the dissertation will be submitted for the fulfilment of the requirements of the Master's in Public Health, Health Economics Degree. A policy brief aimed at the Western Cape Department of Health will also be constructed. Furthermore, an article will be prepared for submission to a peer-reviewed journal still to be specified.

8. LOGISTICS

The study will be carried out over 9 months.

Table 1: Study activities and timeline

Activity	**2018**		**2019**						
	Nov	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**
Finalise Protocol	x	x							
Full Literature Review			x	x					
Obtain Ethics Approval				x					
Secondary Data collection (Literature, procurement lists)					x				
Primary Data Collection (observations, facility records etc.)					x				
Capture data on electronic database					x				
Clean and analyse data					x	x			
Write-up						x			
Draft Dissertation						x			
Finalize Dissertation							x	x	
Submission									x

9. **BUDGET**

The primary study (GIFT) is funded by the Medical Research Council. A student bursary has been awarded to Elise van der Walt by the GIFT project for the conducting of this research as part of obtaining her MPH degree.

No financial costs are anticipated to be incurred for the data collection arm of this study.

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PART B: LITERATURE REVIEW

1. INTRODUCTION

Sexually transmitted infections (STIs) have a massive impact on sexual and reproductive health, globally (World Health Organization, 2016b). The burden caused by its widespread prevalence is not purely due to high associated morbidity and mortality but also associated treatment and management costs (Gaydos and Hardick, 2014). At a global level, the annual incidence of STIs is exceeded only by that of malaria, lower respiratory infections and diarrheal diseases and consequently places substantial pressure on health systems (Kamb *et al.*, 2008; Torrone *et al.*, 2018). Roughly 35 pathogens have been established as sexually transmissible (Chesson, Mayaud and Aral, 2017). Along with Bacterial Vaginosis (BV), one of the most common causes of vaginal discharge syndrome in women, this poses a vast, and often overlooked, challenge to public health and development worldwide; especially in low- and middle-income countries (LMICs) (Workowski and Bolan, 2015).

The purpose of this study is to conduct a cost-effectiveness analysis of different screening strategies, including the newly developed GIFT device, for STIs and BV among women in Cape Town and ultimately, for the prevention of HIV. It follows a cost estimation and budget impact analysis of the device conducted by Kairu in 2017. The GIFT device can potentially improve the management of STIs and BV in low- and middle-income settings such as South Africa.

Given the aims of this study, the objectives of this literature review were to:

1. Develop an understanding and provide an overview of the epidemiology and economic burden of STIs and BV as well as the strategies for screening and diagnosis among women.
2. To review the methodology of economic evaluation in healthcare and identify the most appropriate methods with which to conduct the required analysis.
3. To provide an overview and appraisal of the published literature on the cost-effectiveness of different screening and diagnostic strategies for STIs and BV to identify the gaps in the literature and areas for future research.
4. To consider the affordability of GIFT in the South African context.

The literature was sourced mainly through EBSCO HOST, PUBMED and Google Scholar. I was further explored through manual search for literature cited in identified articles and identifying studies from relevant systematic reviews. Supplementary and grey literature, such

as relevant reports and guidelines were sourced through Google and from the GIFT study protocol.

2.1. THE EPIDEMIOLOGY AND BURDEN OF DISEASE OF STIs AND BV

Despite steady developments and improvements in the diagnosis, management and treatment of STIs, it continues to constitute a massive public health issue. Furthermore, STIs and BV disproportionately affect the developing world and women in their reproductive age (Francis *et al.*, 2014; Van der Eem *et al.*, 2016). In LMICS, STIs and their sequelae rank under the top five reasons for adults seeking healthcare (World Health Organization, 2012b).

Most STIs are caused by one of eight pathogens: herpes simplex virus (HSV-2), hepatitis B virus (HBV), human papillomavirus (HPV), *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis, Treponema pallidum* and the human immunodeficiency virus (HIV) (Kamb *et al.*, 2008; Torrone *et al.*, 2018). In 2012, the WHO reported that annually, around 499 million new cases of the four most common curable, bacterial STIs (chlamydia, gonorrhoea, trichomoniasis and syphilis) occur globally (World Health Organization, 2012b). Global estimates of BV incidence and prevalence remain extremely limited (Torrone *et al.*, 2018). However, reported STIs and BV typically only represent 25-50% of all infections. This is partly because many cases, especially in women, present without any clinical signs or symptoms and thus remain undiagnosed (Kamb *et al.*, 2008; Kaida *et al.*, 2018). According to Woodman (2016), BV is the vaginal disorder that most affects women in the reproductive age. BV is characterised by the depletion of hydrogen peroxide producing lactobacilli in the vaginal tract and is caused by an imbalance in the ecology of normal vaginal flora (Mcdonald, Brocklehurst and Gordon, 2011). It is not considered a sexually transmitted infection itself but is associated with various other STIs and related sequelae, such as PID and adverse pregnancy outcomes. Although BV is related to sexual activity, its association to other STI-related infections of the genital tract is ascribed to biological interactions in the vaginal flora as opposed to common risk factors for acquisition (Morris, Rogers and Kinghorn, 2001; Woodman, 2016).

Generally, LMICs are estimated to have higher STI disease burdens than high-income countries (Chesson, Mayaud and Aral, 2017). Recent WHO estimates confirm that the majority of curable STIs occur in the developing world and that an annual incidence of 92

million new infections is accounted for by the African region alone (Van der Eem *et al.*, 2016). The prevalence of BV is also much higher in LMICs, and Sub-Saharan Africa in particular, compared to the developed world. Some studies have estimated that up to 55% of women in these populations are infected with BV. (Cohen *et al.*, 2012). This has significant health, economic and social implications.

Most of these infections are preventable or curable with relatively inexpensive and simple interventions. If left untreated, however, they result in various serious sexual and reproductive complications in both men and women, including pelvic inflammatory disease, cervical and other genital tract cancers, ectopic pregnancy, adverse pregnancy outcomes such as stillbirths and premature delivery, urethral strictures and epididymitis. Recent studies indicate that STIs and BV also increase the risk of HIV acquisition and transmission (Kamb *et al.*, 2008; Masson, Arnold, *et al.*, 2015; Chesson, Mayaud and Aral, 2017).

Poor health can pose significant costs on individuals and a society at large ad STIs place significant strain on both households and national health systems, especially in LMICs (World Health Organization, 2016a). Although the direct epidemiological and clinical aspects of a disease, such as mortality and morbidity, are necessary in determining its burden on a population, it is also important to understand its economic consequences (World Health Organization, 2009). The high prevalence of STIs in LMICs result in significant losses for individual and community productivity in these countries (Kamb *et al.*, 2008). Kamb *et al.* (2008) further reports that STIs pose high costs on individuals in developing countries, with the average direct medical costs per single bacterial STI episode reaching up to three times that of the average daily income in LMICs. Productivity losses occur as an indirect effect due to mortality and morbidity related to STIs and its sequelae (Kamb *et al.*, 2008).

STIs disproportionally affects the economically active population, which aggravates the economic impact of this public health issue. Young adults in particular, are more exposed to curable STIs, for various behavioural and biological reasons (Kamb *et al.*, 2008). The age distribution observed in many LMICs (relatively large youth populations) thus contributes to the high burden of STIs in these settings (Chesson, Mayaud and Aral, 2017). In 2012, 18% of the world's youth population, aged 12-24 years, lived in Africa and this number is projected

to increase with 60% by 2040, to reach 466 million (Department of Economic and Social Affairs, 2012).

Women and children are also more exposed to the burden of STIs (Aledort *et al.*, 2006; Chesson, Mayaud and Aral, 2017). Van der Eem *et al.* (2016) states that globally, STIs are the second largest cause of quality of life lost among women (after pregnancy-related adverse events) and considered one of the leading causes of disability adjusted life years (DALYs) lost for women in their reproductive age in developing countries (Kamb *et al.*, 2008; Naidoo *et al.*, 2014). Healthcare seeking for STIs among women in LMIC settings is often avoided, inadequate or delayed for various reasons. These include the asymptomatic nature of many STIs, limited sexual health awareness and access to health and the tendency to rely on home remedies or care seeking from traditional healers (Chesson, Mayaud and Aral, 2017; Wood *et al.*, 2018).

Various cultural values and behavioural norms, especially in the African context, can also further explain this phenomenon. According to Adeyemi (2011), in Africa, gender-based norms and power dynamics play a large role in the observed phenomenon of higher prevalence and incidence of STIs among women than among their male counterparts. Women are reported to have less power to say no to sex and especially unprotected sex, are frequently subjected to intimate partner violence and often stigmatised by communities regarding associated genital symptoms (Adeyemi, 2011; Wood *et al.*, 2018). The misdiagnosis and consequent unnecessary treatment for STIs (as is common under standard of care practices in resource-constrained settings) can lead to violence against women, as partner violence can be ignited when women inform their sexual partner on their STI diagnosis and the need for partner treatment (Kettler, White and Hawkes, 2004; Wajid, 2015). These factors affect both their risk exposure to STIs as well as their health care seeking behaviour (Adeyemi, 2011; Wood *et al.*, 2018).

STIS AND BV IN SOUTH AFRICA

South Africa, an upper-middle income country, houses one of the largest burdens of STIs in the world and a significantly high prevalence of bacterial STIs (Johnson *et al.*, 2007; Van der Eem *et al.*, 2016; The World Bank, 2019). Furthermore, unprotected sex is identified as the largest risk factor for morbidity and mortality in South Africa; a trend observed over at least

the past 10 years. Although this trend is most likely largely attributable to the HIV/Acquired immunodeficiency syndrome(AIDS) epidemic, this also includes morbidity and mortality resulting from other STIs (Institute for Health Metrics and Evaluation, 2018).

The South African public health sector serves 84% of the population (Mahlati and Dlamini, 2015). The vast majority of the STI burden thus falls on this sector and mainly surfaces at primary care level by women seeking family planning, child health or antenatal health services. Studies suggest, however, that the STIs treated in primary care only present a very small percentage of the actual burden of disease in the population, due to reasons explored in the previous section (Frohlich *et al.*, 2007). *C. trachomatis, N. gonorrhoeae and T. vaginalis infections* are included in this study. These infections, along with BV, are considered for the analysis due to both their high prevalence among women in South Africa and their association with the increased risk of HIV acquisition and transmission (Passmore, Jaspan and Masson, 2016). Of the common curable STIs, Chlamydia is associated with the highest genital cytokine levels, followed by gonorrhoea, trichomoniasis and BV; indicating high associating with HIV (Masson *et al.*, 2014).

Southern Africa has the largest burden of HIV in the world, despite increases in resources made available for HIV over the past decade that have allowed for improved management and treatment of this epidemic in the region (UNAIDS, 2018b). The latest available data reveals that in 2017, around 36,1 million people living with HIV, globally (UNAIDS, 2018a). South Africa accounts for a large part of this burden with 33% of new HIV infections and 29% of AIDS-related deaths in Eastern and Southern Africa in 2017 incurred in the country. This is the largest portions held by a single country in this region (UNAIDS, 2018b). According to Frohlich *et al.* (2007), the high burden of STIs and its interaction with HIV remains a major concern in the whole of Sub-Saharan Africa and South Africa in particular. This phenomenon especially affects young women as STIs and BV are highly prevalent among women in South Africa who are at high risk of HIV infection (Masson *et al.*, 2014; UNAIDS, 2018a). In general, women are also more vulnerable to acquiring HIV; up to eight times that of their male counterparts (UNAIDS, 2010; Masson, Arnold, *et al.*, 2015). Johnson *et al.* (2012) estimated that roughly half of the new HIV infections in South African women in 2010 were due to other STIs. The management of STIs and BV is thus crucial in preventing HIV in settings with a high co-burden of HIV, STIs and BV, such as South Africa (Mlisana *et al.*, 2012).

THE INTERACTION BETWEEN STIs, BV AND THE HIV EPIDEMIC

According to Woodman (2016), the extremely high prevalence of STIs and BV in sub-Saharan Africa possibly represents a crucial contributing factor to the high prevalence of HIV infection in the region. The relationship between STIs, BV and the transmission of HIV has been studied widely and a positive association is strongly suggested in the literature (Johnson, Coetzee and Dorrington, 2005; Cohen *et al.*, 2012; Mlisana *et al.*, 2012; Masson, Passmore, *et al.*, 2015).

Inflammation in the female genital tract typically caused by STIs and BV increases the risk of an individual to acquire HIV by reducing the effectiveness of the mucosal barrier, recruiting HIV target cells and promoting HIV replication (Passmore, Jaspan and Masson, 2016; Masson *et al.,* 2014). According to Brotman *et al.* (2010), BV infection increases a woman's risk of acquiring HIV, the risk of transferring HIV to her sexual partner and the risk of transferring it to her child during childbirth. Studies have also recently shown that bacteria associated with BV might reduce the efficacy of topical antiretroviral pre-exposure prophylaxis (PrEP) used for the prevention of HIV (Masson and Passmore, Personal Communication, 2018, November 18).

BV and STIs present asymptomatic in many cases. According to Mlisana *et al.* (2012), the vast majority of BV cases are asymptomatic and Kamb *et al.*, (2008) report that more than 50% of all STI cases are asymptomatic. It has been estimated as high as 75% for some STIs, chlamydia, gonorrhoea, trichomoniasis and syphilis, in South Africa and is especially true for the female population (Mlisana, 2014; Francis *et al.*, 2018). The level of inflammation in symptomatic and asymptomatic women who are infected with various STIs and BV is, however, very similar (Masson *et al.*, 2014). This suggests that because a vast amount of infections are left untreated under the current standard of care in South Africa, the management of BV and STIs in women, and ultimately the control of HIV remains problematic (Van der Eem *et al.*, 2016). Considering the above evidence, it becomes clear that the detection and treatment of STIs constitutes a crucial component of HIV control, especially in the presence of substantial STI incidence and prevalence.

MANAGEMENT OF STIs AND BV

It is clear from the review the literature that the management of STIs and BV essentially exists of three components; prevention, detection and treatment.

Prevention is a crucial aspect of disease management. It involves strategies to avoid transmissions, and thus new infections of a disease. Various STI prevention strategies exist, including condom promotion, health promotion and education, social and behavioural change interventions and vaccination programmes (World Health Organization, 2003; Kularatne *et al.*, 2018). According to Land *et al.* (2010), the implementation of evidence-based primary prevention strategies aimed at STIs is emphasized by the WHO.

Detection can further be divided into screening strategies and diagnostic approaches. Globally, various STI detection guidelines have been developed which consists of several screening and diagnostic approaches. These approaches are often complementary to one another (World Health Organization, 2016). Screening is defined as testing for a specified infection or infections in the absence of symptoms, often in an entire population or sub-population, while diagnostic approaches focus on the establishment of infection in the presence of symptoms (Land *et al.*, 2010; World Health Organization, 2012a).

Finally, treatment can either be diagnosis-based (following the confirmation of an infection through testing), presumptive (once-off or periodical administering of treatment for an STI in a high-risk sub-population without confirming that the infection is present) or done on a large scale through mass treatment (treating an entire general population for an STI) (Sahin-Hodoglugil *et al.*, 2003; World Health Organization, 2012a; Mlisana, 2014; Zwart *et al.*, 2018). The latter is controversial despite having clear advantages such as treating asymptomatic patients and eliminating the need for screening tests. It raises concerns including adverse effects of treatment, drug resistance, resource wastage and ethical concerns regarding the unnecessary treatment of healthy individuals. It can also potentially instil a false sense of security in a population, leading to riskier behaviour. Consequently, this treatment strategy is neither widely accepted nor recommended in many settings (Mayaud and Mccormick, 2001). According to Chesson, Mayaud and Aral (2017), data from the World Bank suggests that the adequate treatment of curable STIs in LMICs represents one of the most cost-effective ways to improve global health. Failing to treat these infections, delaying treatment or providing inadequate treatment can result in serious health complications.

According to the World Health Organization (2016), discretion is given to each country to establish the most suitable combination of prevention, detection and treatment in their setting, given the state of the local STI epidemic, the health system and available evidence. In

the following sections, the available approaches and tools for diagnosis and screening of curable STIs and BV will be further discussed.

Screening approaches

Screening refers to testing for an infection in individuals who have no clinical signs or symptoms and thus do not actively seek care for the disease or infection being tested for. This allows for early diagnosis of infections otherwise left untreated (World Health Organization, 2016a). Considering the high levels of asymptomatic STI and BV infections, screening could play a crucial role in the management of these infections. Two different approaches to screening exist. It can be opportunistic (case-finding) or register-based (Kraut-Becher *et al.*, 2004; Land *et al.*, 2010).

Opportunistic screening involves annual or more frequent periodic screening provided during non-STI related healthcare visits, whereas register-based screening involves individuals being contacted and invited for testing based on identified risk factors (Mayaud and Mccormick, 2001; Land *et al.*, 2010). In some situations, opportunistic screening would be targeted at high-risk populations only, whereas it could otherwise be implemented for an entire population. High-risk populations generally include pregnant women, young adults and HIV-positive persons (World Health Organization, 2016a). Antenatal screening for chlamydia is, for example, recommended by the WHO and by the Centre for Disease Control and Prevention (CDC) in the USA and EU, but is it rarely fully implemented (Rours *et al.*, 2016). According to the World Health Organization (2016), screening remains rare in most LMICs because affordable point-of-care (POC) tests for this strategy remain scarce.

Diagnostic approaches

The diagnosis of STIs and BV involve establishing the existence of an infection in the presence of symptoms, using diagnostic tests. These same tests are also used in screening approaches. Diagnostic approaches include both aetiological diagnosis through laboratory or POC testing and clinical diagnosis which includes the WHO syndromic management approach (Kettler, White and Hawkes, 2004). This section provides an overview of the available diagnostic tools for the detection of BV and the STIs included in the cost-effectiveness study.

Clinical diagnosis

Clinical diagnosis involves the identification of infections by healthcare professionals only based on signs and syndromes presented by a patient. Identified infections are then treated accordingly (Kettler, White and Hawkes, 2004). Bosu (1999) defines a syndrome as a "set of symptoms and signs that characterize a clinical condition". Given that resource constraints in many countries prohibit the routine use of expensive laboratory testing, the WHO developed a structured syndromic management approach in the late 1990s that exists of simple clinical diagnosis algorithms in the form of flowcharts. These algorithms guide healthcare providers to identify and manage STIs. This approach is recommended in resource-limited settings and is the standard of care in the South African public health sector (World Health Organization, 2003; Johnson *et al.*, 2011).

Under syndromic management syndromes of a specific STI or BV is identified according to pre-identified groups. Patients are provided with treatment that will address the majority, or the most serious, of organisms typically associated with the identified syndrome (World Health Organization, 2003; Kettler, White and Hawkes, 2004). Appendix A provides a simplified version of the flowchart provided by the South African Department of Health to identify sexually transmitted infection when patients present with abnormal vaginal discharge. The WHO approach distinguishes between seven syndromes, namely vaginal discharge, urethral discharge, lower abdominal pain, genital ulcer, inguinal bubo, scrotal swelling and neonatal conjunctivitis (Kettler, White and Hawkes, 2004; Department of Health, 2015).

Syndromic management is a relatively inexpensive alternative for the detection of STIs and allows patients to receive treatment immediately (World Health Organization, 2003). Various issues have, however, been raised with the approach since its institutionalisation in the early 2000s. The accuracy of syndromic management is undermined by the various overlapping syndromes and signs between different STIs as well as three large amount of asymptomatic infections. Many studies report a large number of false positives resulting in over-treatment and thus excessive use of antibiotics. This is becoming a pressing problem worldwide, as it has significant implications for the development of drug-resistant strains of various bacteria. Overtreatment also causes excessive economic burden through the wastage of scarce resources (Kettler, White and Hawkes, 2004; Wajid, 2015).

Abnormal discharge from the reproductive tract can have different origins, such as the cervix or the vagina and can also be caused by different pathogens. These are not easily distinguishable, however. Due to common symptoms patients are then often treated for two infections, such as chlamydia and gonorrhoea, while clinically only one of the infections are present (Kettler, White and Hawkes, 2004; Wajid, 2015). It is also not always possible to differentiate abnormal discharges, as a result of infection, from "normal" discharge. Consequently, these infections are not necessarily treated correctly when following the syndromic management algorithms, such as the vaginal discharge algorithm (World Health Organization, 2003). Syndromes in men, such as urethritis and genital ulcers are, however, more straightforward and easier identified than female genital discharge. Women also remain asymptomatic much more frequently than in men. This is problematic when following clinical diagnosis in the female population (Mlisana, 2014; Masson, Arnold, *et al.*, 2015). For these reasons, diagnosis through aetiological testing will always be considered the gold standard for STI detection (Kettler, White and Hawkes, 2004; Unemo *et al.*, 2013).

Aetiological diagnosis

Various laboratory tests have been developed for the detection of STIs and BV (Unemo *et al.*, 2013). The value of any diagnostic test is largely dependent on its accuracy, the ability to distinguish healthy cases from unhealthy cases, and can be measured in terms of sensitivity and specificity. Test sensitivity is the ability to correctly identify the true positives (those with the disease or infections), while test specificity is the ability to correctly identify the true negatives (those without disease or infection (Altman and Bland, 1994; Unemo *et al.*, 2013; Baratloo *et al.*, 2015).

Laboratory tests are commonly employed for diagnosis and screening in high-income countries (HICs). In LMICs, however, a lack of adequate infrastructure often excludes standard laboratory testing as the standard of care. Governments in these settings seldomly have the financial means to provide such services to the population, while the patients themselves frequently find these services inaccessible due to financial or geographical barriers (World Health Organization, 2012b).

Laboratory testing fulfils an important role in countries who can afford these technologies, in terms of diagnosis as well as the establishment of antimicrobial resistance (Unemo *et al.*,

2013). Generally, aetiological diagnosis for STIs can be divided into three broad categories. Firstly, methods exist for the detection of the microorganisms causing the infection. These methods include microscopy and suitable wet preparation or staining to allow the visualisation of pathogens (foreign microorganism causing the infection), antigen detection, culture and nucleic acid detection (Unemo *et al.*, 2013). Antigen testing involves the detection of proteins on the surface of the pathogen. Culture testing, on the other hand, requires a specimen to be placed in a suitable, controlled environment for bacteria to grow in. This allows the initially small number of microorganisms present in the clinical sample to multiply and consequently, be identified. Nucleic acid detection, which can be done using either non-amplified or amplified methods, involves the identification of nucleic acid; a complex organic substance present in all living cells such as DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). Amplification is a fairly new method that involves multiplying the nucleic acid present in the specimen to allow for the detection of very low initial amounts of these substances (Land *et al.*, 2010; Gaydos and Hardick, 2014). Each of these methods has its advantages and disadvantages.

Microscopy relies quite heavily on the expertise of the technician, involves complex staining procedures and often requires electricity. It does, however, provide more immediate results than some other approaches when it can be performed in the presence of patients and thus result in timelier treatment. Laboratory-based testing such as normal or amplified nucleic acid detection testing (NAAT), culture and antigen testing perform better in terms of sensitivity and specificity but require specialised personnel, advanced technical skills and specialised transport of specimens to ensure optimality. The waiting period between testing and results, often days or weeks, is also problematic in terms of lost-to-follow-up and delayed treatment initiation. Rapid POC tests based on these methods have overcome some of these challenges but dependable, high-performing tests are not yet widely available. (Land *et al.*, 2010; Unemo *et al.*, 2013)

The second type of aetiological testing is serological testing. This approach is based on the detection of antibodies; the host's response to infections. Many serological tests have been developed especially for the diagnosis of HIV and syphilis. One downfall of these tests is that antibodies can remain in the host long after successful treatment, but some have been

developed that can differentiate between previously treated or long-lasting infections and newly acquired ones (Unemo *et al.*, 2013).

Thirdly, aetiological tests that detect microbial metabolites in the host body, that occurs as a result of materials altering the pH levels in biogenic amines or genital secretions, have been developed. In some settings, these tests are useful when used alongside other diagnostic tools and is particularly important in the diagnosis of bacterial vaginosis through the whiff test and pH tests (Unemo *et al.*, 2013).

In recent years, major progress has been made in the development of POC tests for STIs. The development of rapid point-of-care (POC) tests for STIs has been a priority on the global agenda since the 1990s, while syndromic management was originally only intended as a temporary solution (Romøren, 2008). The WHO developed the ASSURED criteria under the Sexually Transmitted Diseases Diagnostics Initiative. This acronym specifies 7 criteria for any newly developed diagnostic test to ensure that it meets disease control requirements; affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free (or minimal equipment) and deliverable (Peeling *et al.*, 2006).

The following sections provide an overview of the gold standard and other available diagnostic tools, by infection type.

Chlamydia and Gonorrhoea

The gold standard for the diagnosis of *C. trichomatis* and *N. gonorrhoea* is laboratory-based NAATs. These tests are preferred over culture, the superior option up until the 1980s, due to their superior sensitivity, specificity and the various available specimen collection methods (vaginal swab, endocervical swab or urine sample) (Unemo *et al.*, 2013). According to Unemo *et al.* (2013) culture, however, remains an important aspect of gonorrhoea management as it allows the detection of antimicrobial resistance which is increasingly problematic in gonococci strains worldwide.

Other types of chlamydia diagnostic tests have also been developed, such as a laboratory-based and POC antigen tests such as enzyme-linked immunosorbent assays (ELISA) and Direct immunofluorescence assay (DFA). These tests, however, perform suboptimally in terms of sensitivity and specificity, even in comparison to culture, and are no longer recommended by

regulatory bodies such as the CDC in Europe and the USA for chlamydia diagnosis. (Unemo *et al.*, 2013; Workowski and Bolan, 2015).

Laboratory-based NAATs are widely used in HICs and more rapid and less expensive tests using the nucleic acid amplification method are also being developed. The GeneXpert CT/NG test is an example of a combined chlamydia and gonorrhoea polymerase chain reaction (PCR) NAA POC test that has been developed in the USA and is now commercially available. It is currently the only test of its kind that performs comparatively well to laboratory-based NAATs and can detect DNA of either pathogen from urine, endocervical or vaginal specimens. The test is ideally performed in on-site laboratories using the GeneXpert system and can present results in less than 2 hours. It still relatively expensive in an LMIC context and is thus not widely available on-site at healthcare facilities (Gaydos *et al.*, 2013; Gaydos and Hardick, 2014; Mlisana, 2014). Many other rapid POC tests for these two infections do not qualify for widespread use due to low sensitivity, despite acceptable specificity (Aledort *et al.*, 2006).

Trichomoniasis

Culture was the foundation of trichomoniasis diagnosis for several years, but laboratory-based NAATs have also become the gold standard for detection of this infection. Where NAATs with high sensitivity is not available, algorithms that include wet-mount microscopy is still recommended. For example, confirming a positive microscopy result with the NAAT POC test, like the OSOM Rapid Trichomonas Test, a rapid antigen detection test. A GeneXpert assay for detecting the trichomonas pathogen has also been developed. The OSOM rapid test is available in many developed world settings and has higher sensitivity than microscopy. It is less expensive than the Xpert assay and also has a shorter processing time (Unemo *et al.*, 2013; Workowski and Bolan, 2015; Garrett *et al.*, 2019).

Bacterial Vaginosis

BV can be diagnosed using one of two methods; clinical criteria (Amsel's diagnostic criteria consisting of four clinical requirements) or Gram stain using through wet-mount microscopy. The latter can be analysed using either Ison-Hay criteria or Nugent scoring methods. The latter is considered the gold standard (Unemo *et al.*, 2013; Workowski and Bolan, 2015).

STI management in South Africa

In the South African public health sector, which serves the vast majority of the population, STIs are managed based on the WHO clinical diagnosis approach, rather than through costlier laboratory diagnosis (Mlisana *et al.*, 2012). This service is primarily nurse-driven and is mainly provided at the primary care level. Syndromic management has made a considerable impact on the management of STIs in the country. It allows for the treatment of most pathogens at the initial health facility visit and is relatively easy and inexpensive to implement. However, many infections are left untreated or inappropriately treated (Frohlich *et al.*, 2007; Van der Eem *et al.*, 2016).

Global and local evidence suggests that there is a need to move away from syndromic management and towards more effective strategies for screening and diagnosis of STIs and BV. More specifically, there is an urgent need to improve STI management for women in resource-constrained settings (Masson, Arnold, *et al.*, 2015). Laboratory testing, such as NAATs and Nugent scoring with microscopy, the respective gold standards for STI and BV diagnosis, are expensive and require specialised equipment personnel. It also does not allow for immediate results and more transmissions may take place during the waiting period. This is unattractive in low- and middle-income settings, as in South Africa, as the rate of return to clinics, and consequently the opportunity for treatment uptake, is very low. Some studies report it to be as low as 37% (Obermeyer and Osborn, 2007; Brotman *et al.*, 2010). Accurate and affordable POC tests could be extremely valuable in LMICs where expensive laboratory testing is not feasible and return rates to health facilities are low. It could potentially reduce overtreatment and ensure adequate treatment for asymptomatic cases (Peeling *et al.*, 2006). According to Peeling *et al.* (2006), more infected patients can be correctly treated with a POC test of 65% sensitivity than with a NAAT with 90% sensitivity.

Researchers at the Division of Medical Virology at the University of Cape recently developed an inexpensive, rapid POC test. GIFT is cytokine rapid test that was developed to detect genital inflammation using inflammatory cytokines as biomarkers to identify asymptomatic infections in the female genital tract which then indicates the presence of an STI or BV. The test also allows for the detection of inflammation caused by bacteria other than those identifiable by STI or BV laboratory tests, but which also increase women's risk of being infected with HIV. This test ultimately aims to identify cases that would normally be

overlooked by syndromic management, thereby reducing the prevalence of STIs and BV and the risk of acquiring HIV among women in South Africa (South African Medical Research Council, 2018). A validation study of the biomarkers (cytokines IL-1B and IP-10) used in the GIFT device found a sensitivity of 77% and a specificity of 71% to establish the presence of an active STI. The researchers argue that, given the interaction with HIV, a test such as this that identifies genital inflammation, rather than aetiological testing that seeks to identify a specific pathogen (of which there are many) will be more useful for the prevention of HIV and simultaneously identifying asymptomatic infected women (Masson, Arnold, et al., 2015).

2.2. METHODOLOGICAL REVIEW: ECONOMIC EVALUATION

Economic evaluation is the "comparative analysis of alternative courses of action in terms of both their costs and consequences". It encompasses the identification, measurement, valuation and comparison of the costs and consequences of each considered alternative (Drummond *et al.*, 2015). This systematic comparison between two or more complementary and/or mutually exclusive alternatives can inform debate around efficient and equitable resource allocation and contribute to more transparent and rational priority-setting (Romøren, 2008; Hongoro, 2017). Technical and implementation issues such as the heterogeneity in outcome measures and methods and lack of willingness-to-pay thresholds within countries, however, inhibit the true impact and value of economic evaluations. This is especially true in developing countries where a lack of quality, routine data obstructs the development of high-quality and consistent studies (Romøren, 2008).

TYPES OF ECONOMIC EVALUATION

Within the methodological field of economic evaluation, various approaches to analysis exist. One of four types is typically used; cost-minimisation analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Drummond *et al.*, 2015). For all four approaches, the economic costs of alternatives are measured and presented in monetary terms.

CMA is typically used where the alternatives deliver broadly equivalent consequences. Therefore, it is not necessary to measure or value outcomes. For this reason, it is not considered a full economic evaluation and viewed only as a subset of CEA (Rudmik and Drummond, 2012; Drummond *et al.*, 2015). CBA involves measuring outcomes in monetary

terms as well. The outcomes of the alternatives are commonly monetized based on either the willingness-to-pay (WTP) or through the human capital (HCA) approach. The former measures how much individuals are willing to pay for an intervention, while the latter measures opportunity costs proxied by individual income (Fox-Rushby *et al.*, 2005; Drummond *et al.*, 2015).

CUA presents outcome measures in either quality-adjusted life years (QALYs) gained or DALYs averted. These are utility measures that allow for single or multiple, dissimilar outcomes to be compared (Drummond *et al.*, 2015). These effectiveness measures capture both the quantity and quality of outcomes resulting due to an intervention (Hongoro, 2017). With CEA, outcomes are presented in the natural units, such as years of life gained or the changes in blood pressure measured in millimetre of mercury (mm Hg) associated with a specific strategy (Drummond *et al.*, 2015). According to Drummond *et al.* (2015), this form of economic evaluation is suitable for scenarios where the decision maker is operating within a given budget and considering a range of options within a given field and mostly, with regards to a specific disease or group of diseases. Fox-Rushby *et al.* (2005) report that CEA is the most commonly used form of economic evaluation in healthcare. Economic evaluations published in medical literature, employing QALYs or DALYs as the outcome measure are often also labelled cost-effectiveness analyses, however (Romøren, 2008).

CMA and CEA provide insight on technical efficiency only, while CUA can inform on allocative efficiency within the health sector. Technical efficiency refers to a scenario where available resources are utilised so that output is maximised, and costs are minimised. Allocative efficiency, on the other hand, refers to a situation where no person can be made better off without making another worse off and is more concerned with the specific combination of resources than resources at large (Fox-Rushby *et al.*, 2005). Allocatively efficient levels of output are also technically efficient, but not the other way around. CBA is unique in that it can provide insight on allocative efficiency wider than one sector (such as health) and it can thus be used to argue for increased resource allocation to one sector from the general budget (Drummond *et al.*, 2015).

COST ANALYSIS

Cost analysis is an essential aspect of every economic evaluation. It encompasses the quantification and valuation of the resources utilised by each alternative in the analysis to establish the economic cost of each approach (Drummond *et al.*, 2015). In economic modelling, it is important to distinguish between the identification, measurement and valuation of cost inputs (Raftery, 2002; Fox-Rushby *et al.*, 2005).

Identification

Identification requires listing all resource inputs relevant to the programme or intervention to establish the scope of the analysis. Costs are included based on the perspective from which the analysis is conducted and the time horizon over which it is conducted. Broadly, a provider, patient (or household) or societal perspective can be adopted when conducting economic evaluations, depending on the objective of the study (Raftery, 2002; Fox-Rushby *et al.*, 2005; Riewpaiboon, 2008).

In the provider perspective, all costs incurred by a specific provider to deliver the intervention or programme of interest is included. This would typically consist of all direct capital, overhead and recurrent costs. The provider could be a public sector provider such as the Ministry of Health or a specific healthcare facility (e.g. provincial hospital), or it can be a provider situated in the private or NGO sectors. Depending on who the payer of the relevant healthcare services is and often, who the analysis is commissioned by, the analysis will be conducted based on relevant costs incurred in the sector of focus (Drummond *et al.*, 2015; Hongoro, 2017).

The patient, or household, perspective includes all direct and indirect costs incurred by healthcare users when consuming these services. Direct costs include all out-of-pocket expenditures related to a certain episode of illness such as transport costs, drug costs and user or hospital fees. Indirect costs include the value of time spent seeking healthcare and income lost due to illness and healthcare seeking behaviour. In the household perspective productivity losses and time costs of all relevant members, such as the legal guardian or other family members, would be added (Fox-Rushby *et al.*, 2005; Drummond *et al.*, 2015). Intangible costs, such as psychological harm caused to patients due to the disease or intervention under study can also be included in more comprehensive analyses. The societal

perspective is the broadest viewpoint and includes all costs incurred by the actors providing and utilising a health service or intervention, irrespective of who benefits or pays. In essence, it is the sum of both the provider and the patient perspectives (Drummond *et al.*, 2015).

A distinction is made between financial and economic costs. Financial or accounting cost refers to the actual expenditure on resources employed in a programme or technology and is often also referred to as explicit costs. The economic cost of an input includes both the explicit and implicit costs. The latter refers to the opportunity cost of consuming or utilising one resource rather than another and is defined as the value of the next best alternative foregone. In health economics, the economic costs of all resource inputs are ideally included in cost analyses (Simoens, 2009; Drummond *et al.*, 2015).

Measurement

Measurement involves estimating the quantity of each resource utilised in the relevant intervention or programme (Simoens, 2009). Resource quantities can be obtained from various sources such as administrative databases, direct observations, patient medical records, meta-analyses, clinical trials, interviews or through consensus development techniques such as expert opinion (Fox-Rushby *et al.*, 2005). The method by which resource quantities are obtained varies by the context in which the analysis is conducted. If the evaluation is conducted alongside a clinical trial, data will be obtained from the case report forms, whereas standalone evaluations will obtain data from sources such as case notes, routine facility data reports or through patient or staff interviews (Drummond *et al.*, 2015).

The broad categories of costs to include in an economic evaluation are capital costs (e.g. buildings, medical equipment, land, vehicles), recurrent costs (e.g. medical supplies, labour costs, training materials, medicines, laboratory supplies) and overheads (e.g. utilities, maintenance on capital goods, administration and other central services such as laundry or catering) (Drummond *et al.*, 2015). Since overhead costs are 'shared' between many departments or units within a facility or operation, it needs to be appropriately attributed to the relevant programme or intervention that is to be costed. There is no single, correct method when it comes to assigning such costs. Marginal analysis is, however, often preferred by economists. This involves adding or subtracting segments of an intervention to or from a given programme to see which costs change. This is appropriate when the choice is between

an incremental aspect of a programme. The choice is more often, however, between two programmes that will each employ the same resource(s). Another method is to establish the quantities of service consumed by the patient, such as the number of days in a specific ward, the number of laboratory tests run or the number of procedures performed, to ultimately determine the unit cost of the service (Angevine and Berven, 2014; Drummond *et al.*, 2015).

Valuation

Valuation refers to the methods used to establish the unit price or cost of each resource input. In health economics, it involves placing a monetary value on resources depleted due to the course of the disease, its diagnosis and treatment. The total cost of the intervention or programme is then calculated as the product of the unit cost and the quantity of the specific resource used (Simoens, 2009).

The principle of valuation of resources is grounded in the notion of opportunity costs. According to economic theory, in a perfectly competitive market, market prices will represent opportunity costs. Market prices do not always exist in the healthcare market, however, nor is it a perfectly competitive market. Consequently, list prices (e.g. for drug costs) are often used. This is not ideal since it does not necessarily reflect the true worth (cost) of the resource in economic terms from the perspective of the provider, for example (Simoens, 2009; Drummond *et al.*, 2015). Many resources are costed based on market prices, however, despite the theoretical economic cost for any resource being its opportunity cost. This is a commonly accepted pragmatic approach, however. It is inappropriate where resource prices are partly subsidised by a third party such as an international donor, for example, and needs to be adjusted accordingly in such cases.

Valuation of non-market inputs, such as patient or family leisure time and volunteer time, is also challenging. To mitigate the lack of market prices, these are often valued based on wage rates such as using the unskilled wage rate as a proxy for the value of volunteer time. Various other approaches exist, however, such as valuing leisure time at zero, average overtime earnings or average earnings (Drummond *et al.*, 2015). Shadow pricing can also be employed. This is the notion of assigning a monetary value to a resource not ordinarily quantifiable such as the productivity loss of a patient who is a housewife or the value of volunteer work. This is typically done on the willingness-to-pay principle and by using the value of a similar resource

such as the minimum wage as a proxy for the value of homemaker productivity. None of these methods is without controversy, however (Simoens, 2009).

Inputs can be costed based on one of two approaches; the ingredients approach (bottom-up) or gross-costing (top-down) (Xu *et al.*, 2014; Drummond *et al.*, 2015). The ingredients approach involves identifying, quantifying and summing every unit of a resource that is used in providing a health service or intervention. This is a time-consuming exercise, but yields a high level of precision in its estimates (Raftery, 2002; Simoens, 2009). In LMICS, this method is often not feasible due to the lack of available data (Hongoro, 2017). Conversely, gross-costing involves quantifying inputs at an aggregate level by allocating an entire budget to a specific service according to prespecified rules. This approach is much less complex than the former, but often less accurate, depending on the quality of routine data collected (Raftery, 2002; Simoens, 2009; Xu *et al.*, 2014). In practice, a combination of these methods is often used, especially in settings with more limited data availability (Hongoro, 2017).

The sources required for a costing study depend greatly on the costing approach used since micro-costing, for example, will require much more detailed cost data than gross-costing (Raftery, 2002). In the developed world, national and cross-country datasets containing cost data are often available. In LMICs, however, researchers must rely more heavily on individual costing studies in specific settings or on specific diseases. This tends to limit the generalisability of results (Fox-Rushby *et al.*, 2005; Simoens, 2009).

ESTIMATING EFFECTIVENESS

When considering the most appropriate measure of effectiveness or health outcomes, it is important to consider the objective of the intervention of interest. If there are multiple, it may be useful to consider a range of outcomes. The decision-maker is then presented with an array of options and make a judgement based on this (Simoens, 2009; Drummond *et al.*, 2015). This can, however, be problematic since it relies heavily on the judgement of the decision-maker, which is inherently value-laden, who then decides which outcome they value more.

Outcomes can be measured in various ways, including mortality measures (such as deaths averted or life years gained), morbidity measures (such as blood pressure, disease prevalence or incidence), disease-specific measures (such as disease profiles or indices) or generic

measures (such as health profiles or indices). The latter includes the WHO quality of life (QOL) profile and the EQ-5D health index upon which the QALY and DALY measures are based. These incorporate both aspects of mortality, or the length of life, and morbidity, and are constructed from standardized instruments that measure quality of life and generic health status (Fox-Rushby *et al.*, 2005; Drummond *et al.*, 2015). QALYs or DALYs are emerging as the preferred measures of health outcomes in economic evaluation (Drummond *et al.*, 2015).

(Drummond *et al.*, 2015) also differentiate between intermediate outcomes, such as 'cases of disease detected' or 'percentage reduction in blood pressure', and final outcomes, such as 'life years gained' or 'episode-free days'. Although the latter is generally preferred unless the intermediate outcome holds some unique value, the most important consideration is that the effectiveness measure is relevant to the objectives considered by the decision-maker. However, measures that relate to broader concepts such as health gain, are important for comparisons across spheres of the health and other sectors. Effectiveness data can be obtained from clinical trials, meta-analyses, expert opinion or pilot studies, given that the sources are judged to be relevant and of high quality (Drummond *et al.*, 2015).

DISCOUNTING AND ANNUITIZATION

Economic evaluation requires a time period to be specified over which the analysis will be conducted. The main consideration should be to accurately portray the decision problem to not mislead the user of the analysis; the decision-maker (Drummond *et al.*, 2015). It is generally accepted in economics that societies and individuals have a positive rate of time preference. Thus, all things being equal, additional consumption is preferred in the present or near future rather than in the future. Conversely, it is preferred to incur costs in the future rather than in the present or near future. Therefore, discounting is used to adjust costs and effects occurring in the future to the present time by expressing it as present values (Fox-Rushby *et al.*, 2005; Hongoro, 2017). This aims to remove temporal biases in decision-making such as the tendency to prefer investment in treatment, rather than prevention programs. It is considered appropriate to discount costs and outcomes that occur more than one year from the time point at which the analysis is conducted and to apply the same discount rate to both aspects (Angevine and Berven, 2014).

Some countries have guidelines that specify a discount rate, but this is not the case in many LMICs. The discount rate is ideally determined within the decision-making context and where no explicit guideline exists, it is considered acceptable to base it on the interest rate. The interest rate is considered to represent the opportunity cost of money spent in the present as opposed to in the future. Discount rates appropriate for health outcome measures are, however, more controversial. In practice, it is accepted to use any discount rate as long as it is thoroughly explored and varied through sensitivity analysis. In the literature, 3-5% is most often used as the discount rate for both costs and effectiveness (Fox-Rushby *et al.*, 2005; Hongoro, 2017).

Annuitization is a method used to account for costs occurring over more than one year. Capital costs should be annuitized over its useful lifetime, as it represent investments made at one point in time but used over time. Through annuitization, a once-off cost paid for a good is converted into equivalent annual costs (or payments) over its useful lifetime. This is typically done using depreciation rates or interest rates and replacement costs (Drummond *et al.*, 2015).

PRESENTATION OF RESULTS AND RECOMMENDATIONS

The results of CEAs and CUAs are typically presented in terms of incremental cost-effectiveness ratios (ICERs), calculated as the difference in the costs of two interventions, divided by the difference in the effectiveness of the interventions (see figure 1) (Drummond *et al.*, 2015).

Figure 1: Incremental cost-effectiveness ratio

$$ICER = \frac{Cost(x) - Cost(y)}{Effectiveness(x) - Effectiveness(y)}$$

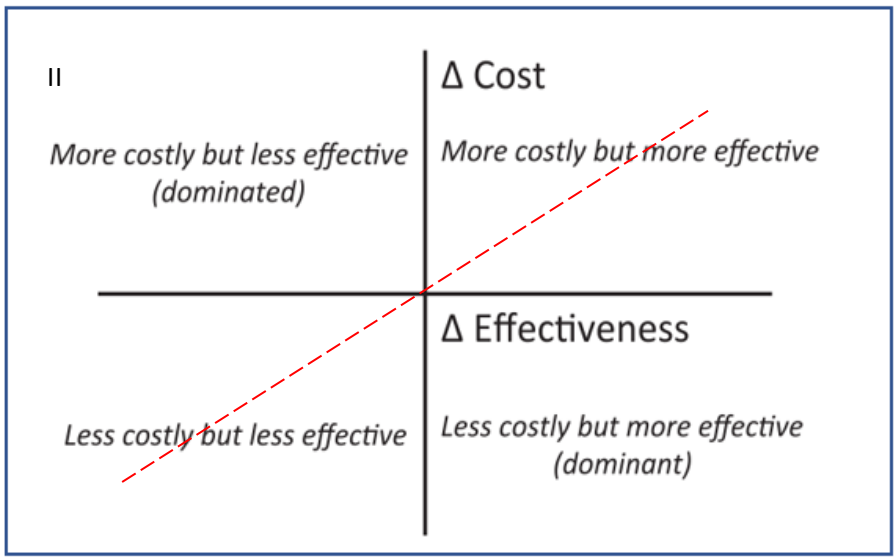
Where X represents the model comparator under consideration and Y represents the baseline strategy, which is either the least costly or the least effective.

Source: Adapted from (Drummond *et al.*, 2015)

These ratios can be presented on a cost-effectiveness plane, where the Y-axis represents changes in costs and the X-axis, changes in effectiveness (see figure 2). Each ICER obtained

from an economic evaluation can be visually represented as a point in one of these four quadrants. The point of intersection at the origin represents the baseline comparator, often the current standard practice, in the model. ICERs of interventions falling in the second quadrant are dominant and cost-saving, it both less costly and more effective than the baseline, while those in quadrant four are dominated and thus not cost-effective as it represents an option both costlier and less effective than the baseline. In theory, interventions with ICERs in the first and third quadrants are potentially cost-effective, but this will ultimately be determined relative to the other interventions presented on the plane and the relevant threshold value (Romøren, 2008; St John and Price, 2013; Drummond *et al.*, 2015).

Figure 2: Cost-effectiveness plane



Source: Adapted from (St John and Price, 2013)

The red, dashed line signifies the willingness-to-pay (WTP) or cost-effectiveness threshold which represents the maximum additional investment a specific society or decision-maker is willing to make for an additional unit of health. A strategy is deemed cost-effective if it has a positive ICER below this monetary threshold. The threshold is, however, not made explicit in many settings and where such thresholds have been specified, these are often criticised for being too arbitrary (Romøren, 2008; St John and Price, 2013; Drummond *et al.*, 2015). The WHO has attempted to make the threshold value more unambiguous and consistent across settings by establishing guidelines for a cost-effectiveness threshold based on a country's Gross Domestic Product (GDP) per capita. Interventions are deemed highly cost-effective if

the relevant ICER (per DALY averted) value is less than GDP per capita and cost-effective if it is between 1- and 3-times GDP per capita. This threshold faces much criticism and is widely regarded to be irrelevant for decision making, especially in LMIC settings, as it does not accurately reflect the opportunity cost of health (Kahn *et al.*, 2014; Bertram *et al.*, 2016; Woods *et al.*, 2016). The lack of evidence-based thresholds inhibits sound decision-making and ultimately undermines the value of economic evaluations for the health sector.

Thresholds in South Africa

As in most of the developing world, there is no standard WTP or cost-effectiveness threshold in South Africa to facilitate decision making in the health sector. However, two recent studies aim to provide a guide to contextualise cost-effectiveness findings in this setting.

Woods *et al.,* (2016) estimated cost-effectiveness thresholds for several countries, including South Africa, based on the opportunity cost of health and the statistical value of a life. It concludes that previously used thresholds, such as the WHO estimates, should be avoided as it is likely too high. Although based on several, it is suggested that the estimates may be used alongside country-specific information on the opportunity costs of health care funds to inform decisions on resource allocation. The estimated for South Africa was USD 2,221 – 8.909 (in 2013 PPP) and USD 1,175 – 4,714 (in 2013 prices) per DALY averted (Woods *et al.*, 2016).

Meyer-Rath *et al.*, (2017) produced estimates of a revealed WTP threshold for South Africa based on the South African HIV Investment Case. The threshold was derived by using the relationship between the budget for HIV from the three main funders and modelled estimates of life years saved by several HIV treatment and prevention intervention. This revealed a threshold, based on the budget under consideration, of USD 547–872 per life year saved (LYS); only a fraction of GDP per capita (2016) estimate of around USD 6000 (Meyer-Rath *et al.*, 2017). Although also based on various assumptions, this revealed WTP threshold can be useful to guide decision making on resource allocation in South Africa.

UNCERTAINTY

Uncertainty around the accuracy and validity of model parameters arises as data is collected and assumptions are made for economic evaluation purposes (Fox-Rushby *et al.*, 2005). In

any analysis it is important is to minimise uncertainty and to account for remaining uncertainty through statistical methods and sensitivity analyses (Rudmik and Drummond, 2012). One of two approaches to sensitivity analysis exist for model-based economic evaluation, deterministic or probabilistic, but researchers often employ both.

Deterministic sensitivity analysis involves varying either one input parameter (one-way) or multiple inputs simultaneously (multi-way), to explore the impact on the results (Simoens, 2009; Drummond *et al.*, 2015). Scenario analysis is a form of multi-way analysis that typically involves creating a "best-case" and "worst-case" scenario in which a range of variables is altered in their most optimistic and pessimistic ways, respectively. Another type is threshold analysis. It involves identifying the combination of variable estimates which ensures that the relevant cost-utility or cost-effectiveness ratio does not exceed the specified threshold (Fox-Rushby *et al.*, 2005; Simoens, 2009).

Probabilistic sensitivity analysis is carried out by running an analysis many times with a different set of estimate variables drawn from statistical distributions using Monte Carlo simulation. At completion, a cloud of points is presented on the cost-effectiveness plane that represents the joint statistical distribution for costs and effectiveness. Cost-effectiveness acceptability curves that represent the probability that each model comparator is efficient, applying various cost-effectiveness thresholds, can then be drawn (Simoens, 2009; Drummond *et al.*, 2015).

2.3. EMPIRICAL REVIEW: COST-EFFECTIVENESS ANALYSES OF SCREENING AND DIAGNOSTIC STRATEGIES OF CURABLE STIS AND BV.

SCOPE OF THE REVIEW

This review is centred around the cost-effectiveness of different screening and diagnostic strategies for curable STIs and BV. There exists a vast body of literature on this topic, and the scope consequently had to be demarcated. The scope of the review was limited to CEAs and CUAs published in English from the year 2000 to the present, and those related to the BV, chlamydia, gonorrhoea and trichomoniasis; according to those infections included in the CEA to follow this review. Studies on other curable STIs were included only where it was studied alongside one of the above-mentioned infections. Studies from HICs and studies conducted on men were included, although the CEA conducted this study will be conducted for women

in an LMIC setting. This was because of the limited amount of studies done in the latter populations. Cost-benefit analyses, studies conducted on age populations other than adults in their reproductive age and studies examining screening and diagnosis not based in healthcare facilities (such as home-based screening) were excluded from the review. Following a search of the published literature, 29 studies were identified and included, based on the above criteria.

OVERVIEW OF THE LITERATURE

Of the 29 studies, only six were conducted in LMICs, three of which in Sub-Saharan Africa. Two of these are South African studies (Sahin-Hodoglugil *et al.*, 2003; Colvin *et al.*, 2006). The literature is dominated by Chlamydia-related studies or studies evaluating interventions for a combination of chlamydia with other curable STIs. Fewer studies pertain to gonorrhoea alone, while only one was conducted on trichomoniasis alone. Two other studies, however, included this infection in their model. Only one study analysed a BV-related intervention. See appendix B for a summary of the included studies.

The review is divided into two sections; studies related to point-of-care tests and studies examining laboratory-based screening, clinical diagnosis culture or other diagnostic tools and screening strategies.

POINT-OF-CARE TESTING

Chlamydia

Ginocchio *et al.* (2003) investigated the cost-effectiveness of different screening and diagnostic strategies for chlamydia, based on a hypothetical cohort of young asymptomatic men in the USA. The model comparators included no screening, screening with a urine-based ligase chain reaction (LCR) test, a DNA amplification test (for of NAAT), and pre-screening with a urine-based leukocyte esterase (LE) strip test that detects white blood cells (an indication of infection) and an LCR test following a positive LE test to confirm the results (LE-LCR). The LE test is a rapid test with relatively low sensitivity (70%) and variable specificity for the detection of chlamydia. A dynamic decision-tree was employed in the analysis and the ICERs were presented as cost per additional case of PID prevented, since transmission to female partners and consequent complications of infection were included in the model. Ginocchio *et al.* (2003) report that the LE-LCR strategy was the most cost-effective. Although testing with

LCR alone prevented more PID cases than LE-LCR, it cost significantly more per male screened. LCR alone would become the most cost-effective strategy if the cost of the assay were to decline to less than US$ 18 (2000 US Dollars) or in settings with higher chlamydia prevalence (>5%).

Blake, Gaydos and Quinn (2004) conducted a CEA that assessed the cost-effectiveness of three screening approaches for the detection of chlamydia and gonorrhoea among male youth entering detention facilities. The comparators were similar to that of Ginocchio *et al.* (2003) and included urine-based NAAT screening of all youths entering the facility, pre-screening urine with a LE strip test followed by a NAAT for positive test cases and lastly, no screening. ICERs were reported as the incremental cost per additional PID case prevented and were based on a hypothetical cohort of 4000 men. Blake, Gaydos and Quinn (2004) found that universal screening for chlamydia and gonorrhoea with a urine-based laboratory NAAT in all male youths was cost-saving. Threshold sensitivity analysis revealed that it remained the case even at very low disease prevalence. Savings represented by this method was primarily due to its ability to reduce cases of PID in current and future female sexual partners.

The difference in findings between the two above-mentioned studies are likely the result of the great difference in NAA test cost; Ginocchio et al. (2003) estimated it at US$ 33 (2000 US Dollars) according to the maximum allowable Washington State Medicaid reimbursement, while Blake, Gaydos and Quinn (2004) derived its estimate, US$ 10. Neither of these two studies, however, made cost-effectiveness conclusions based on a WTP threshold.

Romøren (2008) employed a static decision-tree analysis to conduct a CEA on a pregnant population in Gabarone, Botswana. The model compared testing for chlamydia in antenatal clinics with a hypothetical POC test based on the effectiveness of various available POC tests (sensitivity ranging from 50% (baseline) to 85% and with 98.5% specificity) to syndromic management. Furthermore, these strategies were modelled for three approaches: management of all women, women under 30 only and women under 20 only, as well as for two different drug regimens; the existing drug and a new drug. Romøren (2008) presented the ICERs as the cost per additional cases of chlamydia cured. It is concluded that the most cost-effective strategy for the teenage population was syndromic management with the new, more effective single-dose drug compared to a week-long regimen with the existing drug, but that POC screening is also cost-effective in this population. When testing the model at

increased test sensitivity of 75%, the screening strategy became as effective but less costly than syndromic management. Only the syndromic management strategy with the new drug was cost-effective across all age groups. According to Romøren (2008), the introduction of POC tests is, however, crucial to reduce overtreatment, improve the effectiveness of STI management and to potentially enhance partner notification. The authors do not employ an explicit WTP threshold but employ an implicit one by stating that the ICERs of all the evaluated comparators were below that of the current cost of spending on a curable infection spent in Botswana. The suitability of this comparison is, however, dubious.

Hislop *et al.* (2010) compared three strategies for chlamydia screening a combined cohort from various studies across China, Egypt, USA and Europe. The comparators included screening with the Clearview POC test (80% sensitivity on vaginal swab specimens and 77% for urine specimens; 99% specificity for both), screening with the POC Chlamydia Rapid Test (CRT) (52% sensitivity for vaginal, cervical and urethral specimens combined and 64% for cervical specimens only; 97% specificity for all) and screening with PCR laboratory tests. The latter, the gold standard for diagnosis of chlamydia, was most frequently used in practice in these settings. ICERs were presented as the cost per additional true-positive case identified, treated and partners notified. Hislop *et al.* (2010) concluded that screening with NAATs remained the least costly and most cost-effective approach for the management of chlamydia, but that the POC CRT test might become cost-effective in a scenario where the acceptance of this test by patients was higher (in terms of waiting for test results and the location of testing) or if the test price was to be reduced. No WTP threshold is used in this analysis, but it was strictly not required since the strategies were all dominated by the baseline comparator.

Huang *et al.* (2013) had a similar objective and estimated the cost-effectiveness of a promising new POC test for chlamydia (92.9% sensitivity; 98.5% specificity) in comparison to NAA laboratory testing. The CEA was conducted for a hypothetical cohort of sexually active women in the USA and the ICERs were presented as the cost per additional PID case averted. Incremental to testing for chlamydia with the NAAT, testing with the highly sensitive POC was found to be cost-saving in the base case scenario. Upon conclusion, Huang *et al.* (2013) state that even moderately sensitive POC tests would be efficient in settings with low return rates to health facilities and that POC testing is favourable since it averts considerable amounts of

inappropriate treatment. None of these cost-effectiveness conclusions were based on a WTP threshold either.

Vickerman, Watts, *et al.* (2006) employed a dynamic mathematical model to establish the cost-effectiveness of joint screening for chlamydia and gonorrhoea in a female sex worker population in Cotonou, Benin. The screening comparators were syndromic management (standard of care) and screening with a POC test for both infections. At that time, different POC tests for chlamydia and gonorrhoea with high specify (>90%), but very inconstant sensitivity (25-85%) were available. Consequently, four different POC tests were modelled at different sensitivities (50, 60, 70 and 80%) but constant specificity (95%). ICERs were presented as the incremental cost per case of chlamydia or gonorrhoea averted and per HIV case averted. Vickerman, Watts, *et al.* (2006) reported that simultaneous screening for chlamydia and gonorrhoea with a POC test is a cost-effective strategy for preventing both infections and HIV, but that the results depend heavily on the sensitivity and costs of the test. However, even at a moderate sensitivity (>60%) and a test cost of US$4 (the most expensive test modelled in the study; 2004 US Dollars), the POC screening strategy remained cost-effective. Furthermore, it was concluded that the number of women inappropriately treated would dramatically decline when using POC tests. At a sensitivity of 70% and a test cost of US$ 2, the ICER would be US$ 152 per additional HIV infection averted. This presented one of the most cost-effective HIV prevention strategies in Sub-Saharan Africa and other populations at the time. The judgement of the cost-effectiveness of the model comparators was based on the upper bound for cost-effective interventions suggested by the World Development Report; $70 per DALY averted or $1300 per HIV infection averted.

Tsai *et al.* (2008) conducted a CEA on the management of chlamydia, gonorrhoea and syphilis among sexually active, symptomatic males in Taiwan. The model compared the standard of care (a clinical approach consisting of presumptive treatment while awaiting laboratory test results), syndromic management and a pure aetiological approach consisting of PCR testing for chlamydia and gonorrhoea. For syphilis, the latter included screening with the rapid POC plasma reagin (RPR) test or Venereal Disease Research Laboratory tests and confirming positive results with the *T pallidum* heamagglutination assay (TPHA). Tsai *et al.* (2008) did not present ICERs, but average cost-effectiveness ratios (ACERs) using the average cost per correctly treated case. It was found that syndromic management was more cost-effective for

treatment of chlamydia, syphilis and gonorrhoea than the presumptive treatment and aetiological testing approaches in terms of average cost-effectiveness ratios. These judgements are, however, not made based on a WTP threshold.

Tsai *et al.* (2008) concluded that overtreatment resulting from the syndromic management approach would not present any greater problem than with the standard of care approach. The results of the study are, however, represented as ACERs. This metric is not commonly accepted in health economics for basing cost-effectiveness conclusions on as it is considered to be misleading. ACERs do not consider any alternative courses of action nor does it maximise net health benefit associated with an alternative under consideration. Consequently, it does not indicate the relative value for money represented by an alternative and consequently, does not aid in decision-making between alternatives courses of action; the primary goal of economic evaluation (O'Day and Campbell, 2016).

Turner *et al.* (2014) conducted a CUA based on a dynamic transmission model in a cohort of simulated male and female patients attending genitourinary medicine (GUM) clinics in England. The model compared screening for chlamydia and gonorrhoea with an NAA POC test (performance was not specified, but it was stated that it is comparable to gold standard NAA laboratory tests) to testing with gold standard laboratory NAATs. ICERs were presented in terms of QALYs gained and secondarily, additional transmissions, PID cases and overtreatments prevented. The POC test under consideration was cost-saving for chlamydia and gonorrhoea management. It was found that this strategy averts considerable amounts of inappropriate treatment and would dominate even under very pessimistic assumptions. No WTP threshold was employed.

(Huntington *et al.*, 2018) conducted a CUA on the cost-effective of four different approaches for testing for chlamydia, gonorrhoea, trichomonas and *Mycoplasma genitalium* and was also modelled for a hypothetical cohort of patients attending a GUM clinic in England. The model compared three hypothetical POC NAATs to the standard of care, which included microscopy for trichomonas and *M. genitalium* and a laboratory-based NAAT for chlamydia and gonorrhoea. The performance of the POC tests was based on the accuracy of available POC tests at the time. The screening comparators included screening with a dual POC test for chlamydia and gonorrhoea (98% sensitivity), a triplex POC test (96% sensitivity) for chlamydia, gonorrhoea and *M. genitalium* and finally, a quadruplex POC (95% sensitivity) test for all four

infections. ICERS were presented in terms of QALYs gained and secondarily, in terms of PID cases averted, reduced inappropriate treatment and STI transmissions prevented. (Huntington *et al.*, 2018) found that incremental to the standard of care, each strategy became both costlier and more effective when considering the entire study population. The results differed between the subgroups considered (women, men-who-have-sex-with-men (MSM) and men-who-have-sex-with-women (MSW)) and depending on the WTP threshold under consideration. However, it was beyond the scope of the study to establish whether or not it would be feasible to implement different strategies on the subgroups. With an ICER of £36 585 per QALY gained (2015/2016 Pounds sterling), simultaneous screening for chlamydia, gonorrhoea, trichomoniasis and *M. genitalium* in the entire population with the quadruplex POC test was deemed the most cost-effective strategy. It was also the most cost-effective in terms of all three secondary outcomes. However, the highest WTP threshold under consideration was £30 000 per QALY gained (the upper threshold of the National Institute for Health and Care Excellence) which makes the conclusion seem counterintuitive since the cost-effectiveness ratio was above the threshold.

Gonorrhoea

Aledort *et al.* (2005) conducted a Markov model-based CUA to estimate the cost-utility of different screening strategies for gonorrhoea. The study was set in USA emergency departments and based on a sexually active cohort of 15-year-old women who were identified as at high risk for developing the infection during their lifetime. The model comparators included routine emergency department care (no screening), screening with on-site Gram stain microscopy of endocervical swabs (50% sensitivity; 94% specificity), screening with urine-based NAATs (95% sensitivity; 99% specificity), screening with endocervical swab-based NAATs (90% sensitivity; 99% specificity), screening with a vaginal swab-based rapid immunochromatographic strip (RIS) POC test(79% sensitivity; 91% specificity) and lastly, RIS test on patient-collected vaginal swabs (71% sensitivity; 94% specificity). Both NAATs are laboratory tests. The model was stratified along three age groups: 15-19, 20-24 and 25-29 years. ICERs were presented in terms of QALYs gained and secondarily, PID cases averted. Aledort *et al.* (2005) found that screening with the urine-based NAAT, with no screening as the baseline comparator, was cost-saving for women aged 15 to 29. It was concluded that this strategy would provide better targeted screening of asymptomatic gonorrhoea. However,

screening with the RIS POC test, using clinician-obtained specimens, would also become a cost-effective strategy if the test became less expensive than NAAT. The findings were not, however, based on a WTP threshold. Aledort *et al.* (2005) conclude that the potential of accurate rapid test technology holds great promise for improved management of gonorrhoea.

The objective of Bartelsman *et al.* (2014) was to estimate the cost-effectiveness of the alternative management approaches of gonorrhoea among a group of high-risk women and men in Amsterdam. The study was conducted retrospectively, examining two time periods when alternative standards of care existed. Consequently, the model compared the screening of high-risk patients using a POC microscopy to only testing symptomatic patients with the same diagnostic tool. In the first period (2008-2009), Gram stain had 96% sensitivity in men and 32% in women and in the second period (2010-2011), 95% and 23%, respectively. The overall specificity was nearly 100% in both periods. Screening high-risk patients only was a cost-saving strategy and proved cost-effective for both men and women. The Gram stain method, however, performs significantly poorer in the detection of the gonorrhoeal infection in women than in men. The average cost per correctly managed consultation decreased from €30.25 to €27.91 (price level not stated) from the first period to the second. Bartelsman *et al.* (2014) did not present ICERs, but ACERs (average cost per correctly managed consultation) and thus wrongly make cost-effectiveness conclusions based on this.

Zwart *et al.* (2018) conducted a CUA on different diagnostic approaches for the detection of anogenital gonorrhoea in men. The study population was MSM attending an STI clinic in Amsterdam. The first model comparator was for symptomatic MSM to receive Gram stain (on-site) followed by laboratory NAA testing. Presumptive treatment was then administered while awaiting NAAT results if Gram stain was positive. Asymptomatic MSM were only tested with NAAT. This strategy was the standard of care at the time. Secondly, all MSM receive NAA testing. The final model comparator was for all MSM to undergo both NAAT and Gram stain examination. Zwart *et al.* (2018) calculated the ICERs (in 2016 Euros) in terms of QALYs gained and secondarily, cases of epididymitis averted. The research revealed that extending Gram staining to all MSM would not be cost-effective with the ICER (€135 371/QALY gained) exceeding the relevant WTP thresholds and that discarding Gram staining would result in health losses. Both the WHO-recommended willingness-to-pay threshold of one- and three-times per capita GDP (€41 258 and €123,774/QALY gained in 2016) and the Dutch threshold

of €20 000/QALY gained were employed to reach their cost-effectiveness conclusions. The standard of care was the most cost-effective approach for the management of gonorrhoea in this population.

Kourbatova *et al.* (2008) conducted a static CEA to establish the cost-effectiveness of occupation-based for gonorrhoea and syphilis in a hypothetical cohort of 1000 people from different occupational groups in Moscow, Russia. These groups included workers from the food industry (e.g. food handlers), market salespersons, healthcare and education providers and public utility workers (e.g. hotel staff). The model compared were no screening, screening for gonorrhoea, screening for syphilis and screening for both infections. On-site Gram staining was used to test for gonorrhoea and the Wasserman reaction and microprecipitation reaction tests (two antigen tests used routinely in the study setting) were respectively used to test for and confirm syphilis infection. The ICERs (in 2003 US Dollars) were calculated as the cost per STI correctly treated against the common base of no-screening. They found that for both sexes, screening for syphilis only, and not for gonorrhoea, was the most cost-effective strategy with an ICER of $252 per STI correctly treated. This conclusion, is, however, not compared to any WTP threshold which makes it difficult to truly know if this intervention provides a good value for money option in this setting and the intermediate outcome denominator makes it difficult to compare the ICER to other studies.

Bacterial Vaginosis

Kekki *et al.* (2004) is the only study fulfilling the inclusion criteria for this review that investigated the cost-effectiveness of interventions related to BV. Decision tree analysis was employed in a population of low-risk, asymptomatic pregnant women in Finland. The screening approaches that were compared to the no-screening strategy were, screening with Gram stain (sensitivity 97.1%; specificity 99.7%) and consequent treatment with either topical clindamycin or with metronidazole. ICERs were presented as the cost per postpartum complication prevented and secondarily, per preterm delivery prevented. Kekki *et al.* (2004) found that although screening for and treatment of BV in early pregnancy might not be cost-saving, it would produce more health benefits at the same costs, making it a cost-effective strategy in terms of the primary effectiveness measure. When considering the alternative, incremental costs per preterm deliveries prevented, no-screening was the more cost-effective approach. There appeared to be no statistical difference between the two treatment

regimens. In settings where the rate of pre-term deliveries was higher than in the study setting, the screening strategy might have become cost-saving. No cost-effectiveness threshold was employed in the study.

DISCUSSION

Despite the POC tests examined in the studies discussed above were highly variable in terms of performance and the infections they detect, and the studies varied greatly in terms of model comparators, study methods and outcome measures, there seems to be a consensus that there lies great potential in POC testing for STIs. Many researchers argue that it holds great potential for reducing overtreatment, improving the effectiveness of STI management, improving HIV prevention and enhancing partner notification. There is also a consensus in the more recent literature that the development of rapid, accurate POC tests should be made a priority and this is endorsed by the WHO.

A shortfall of the results is that some of the examined POCs that were found cost-effective were only hypothetical test assays at the time. Two studies also wrongly used ACERs instead of ICERs to arrive at cost-effectiveness conclusions. Furthermore, only two of the studies employed explicit WTP thresholds, while one study employed an implicit threshold. This is not entirely due to bad practice but a lack of reliable thresholds available to researchers and decision-makers in these settings.

OTHER SCREENING AND DIAGNOSTIC APPROACHES

Chlamydia

Postma *et al.* (2000) conducted a CEA based on a dynamic decision tree analysis in a cohort of 2403 sexually active women from a pilot study in general practitioner practices in Amsterdam, the Netherlands. It assessed the cost-effectiveness of five screening strategies for chlamydia in women. Four of the strategies involve testing for chlamydia in women aged 15-19 years, 15-24 years, 15-29 years or 15-34 years, using a laboratory-based LCR test on urine, all of which are compared to no screening. The results of the CEA were presented both as the incremental cost per women cured and per major outcome averted (MOA). MOA referred to the most significant sequelae of chlamydia infection, namely PID, infertility, chronic pelvic pain, ectopic pregnancy and neonatal pneumonia. The model incorporated reinfection rates and partner referral. Annual screening for chlamydia of all sexually active

women aged 15-29 was found to be cost-effective. Furthermore, at a test cost of $17 (the true cost at the time of analysis; 1996 US Dollars), the strategy of screening sexually active women aged 15-19 would be cost saving, but screening women aged 15-24 who are sexually active (the CDC recommendation) would become cost-saving only if the test cost were to decline to below $13. Despite no explicit cost-effectiveness threshold being stated, Postma et al. (2000) argued that all three the strategies representing screening for women below 30 have favourable ratios. It was also argued that the inclusion of partner referral and reinfection was extremely important in the model as the cost per outcome would respectively increase by almost 100% and 60% if the parameters were to be excluded from the model.

In another study published in 2000 (with various overlapping authors), Welte *et al.* (2000), analysed the cost-effectiveness of population-based screening for chlamydia in the Netherlands. The model stretched over the first 10 years of the programme. The study population was a simulated cohort of asymptomatic, sexually active, heterosexual individuals between the ages of 15 and 25. The model compared annual screening with a urine-based laboratory LCR test to no-screening. The cost-effectiveness results are presented as the incremental cost per MOA associated with each alternative. The authors found that society would bear net costs for population-wide chlamydia screening initially, but that it might become cost-saving after 3-5 years. This indicates the possible benefits from a dynamic versus a static modelling approach for arriving at more meaningful cost-effectiveness conclusions. The ICER (in 1997 US Dollars) of screening, when considered over a 10-year period, was US$ 492 per MOA and US$1086 when indirect costs were included, but it is unclear what these ratios were compared to render it cos-effective or not. Welte *et al.* (2000) stated that, depending on the budget restriction imposed, other strategies could also become cost-effective and that it would also differ with the inclusion of only direct costs or if total costs were included as well. In the scenario analysis, women were excluded from the programme but was found unfavourable due to a small number of major outcomes averted.

Nyari *et al.* (2001) conducted a CEA on different screening strategies for chlamydia in three regions of Hungary in a population of asymptomatic women aged 15-19 years. The authors employed decision-tree analysis and included no-screening, screening with a laboratory-based ELISA (antigen) test and thirdly, screening with an amplified Gen-Probe assay nucleic acid hybridization (NAH) method (the predecessor of NAA method) in the model. ICERs were

presented as the incremental cost per cases detected and per cases prevented. Nyari et al. (2001) concluded that screening with Gene-Probe was the preferred strategy for chlamydial screening in young Hungarian women. Although screening with ELISA presented a cost-saving of US$ 20 per case detected and Gen-Probe an incurred cost of US$221 (price level not stated). The latter prevented 10 000 more cases than the former. In the base-case analysis, screening with ELISA was the most cost-effective alternative, followed by no-screening. When disease prevalence was increased, or the Gene-Probe test cost decreased, screening with the screening with ELISA became the more cost-effective alternative. No WTP threshold was used in this analysis.

Goeree *et al.* (2001) employed a Markov model in their decision analysis to establish the cost-effectiveness of seven different screening and diagnostic strategies for chlamydia. The study was conducted among women aged 15-24 years in the province of Ontario in Canada. The study comparators included: NAH or antigen diagnostic testing using endocervical swabs, diagnostic testing with endocervical swab-based NAAT, diagnostic testing with urine-based NAAT, universal screening with endocervical swab-based NAAT, universal screening with urine-based NAAT, screening of high-risk women with endocervical swab-based NAAT and lastly, screening high-risk women with a urine-based NAAT. The denominator of the ICERs were presented as additional chlamydia cases averted. The results of Goeree et al. (2001), showed that diagnostic testing and screening with endocervical swab-based NAAT dominated NAH and urine-based NAA testing and screening. This remained even when various parameters were varied in the sensitivity analysis. Furthermore, moving from antigen or NAH testing to swab-based NAA diagnostic testing would be cost-saving for the healthcare system and avert more cases of chlamydia and related sequelae. It was concluded that endocervical swab-based NAAT screening of high-risk women only would result in an ICER of US$ 1873 per additional chlamydia case averted (with endocervical swab-based NAAT diagnostics as the baseline comparator), while screening of all women aged 15-24 years with the same method would result in an ICER of US$ 5590 (price level not stated). The former is thus more cost-effective than the latter, but no WTP threshold is used so no concrete conclusion is made with regards to the absolute cost-effective of these strategies.

Gift *et al.* (2001) conducted a decision-analytic model to establish the cost-effectiveness of different testing and screening strategies for chlamydia in asymptomatic women who also

have a gonorrhoeal infection, in a cohort of 1000 women attending family planning clinics in the USA. The model comparators included test for gonorrhoea and if positive, treat presumptively for chlamydia too (Co-treat); test for both infections and treat separately according to positive test results (Test); test for both infections and treat women who test positive for gonorrhoea for both infections, but treat those who only test positive for chlamydia, only for chlamydia (Test/Co-treat). Furthermore, they considered different tests in the model, namely PACE 2 Gen-Probe (NAH) and LCR (NAA) for chlamydia and culture and LCR for gonorrhoea. PACE 2C Gen-Probe, that allows simultaneous testing for both infections, was employed in the relevant strategies. ICERs were presented as the net cost per case of PID averted, incremental to the next-less effective comparator. Gift et al. (2001) found that 'Test/Co-treat' followed by the 'Test' algorithm averted the most PID cases, regardless of the diagnostic test used. However, the former, along with 'Co-treat', resulted in larger overtreatment while the latter minimized this issue. In this study setting, as opposed to more high-risk settings such as STD clinics, emergency rooms or prisons, the gonorrhoea prevalence is typically low and often lower than the chlamydia prevalence. The coinfection rate of gonorrhoea and chlamydia is often, however, within or above the range of 20-40% required for dual therapy as suggested by the CDC. In such settings, it is recommended that management strategies be based upon chlamydia prevalence and not the coinfection rate. Therefore, in this setting, the 'Test' strategy (test for both infections and treat separately according to positive test results) was more cost-effective than treating chlamydia presumptively (dual therapy). These cost-effectiveness findings were, however, not based on a WTP threshold.

Mehta *et al.* (2002) also conducted a CEA on screening strategies for chlamydia and gonorrhoea. The study was set in the hospital emergency department in the USA and conducted on a theoretical cohort of 20 000 male and female patients entering the facility over 6 months. The model comparators included the standard practice (clinical diagnosis by clinicians), screening patients aged 18-31 years with a urine LCR test, screening only patients aged 18-31 years who report any risk factors and following the standard practice with the remaining patients, standard practice combined with screening of all 18 to 31-year olds and lastly, mass treatment of all patients between the ages of 18 and 31 years. The cost-effectiveness ratios were presented as the incremental cost per additional case effectively

treated. Findings for women and men are reported separately. Mass treatment was the most cost-saving alternative for both sexes, but the acceptability of this approach had not been established at the time. It was further noted that no exorbitant costs associated drug resistance that could potentially arise with such an approach, was considered. They conclude that the standard of care was the only other cost-saving strategy for men. This was likely due to the higher rates of symptomatic infections and lower management and treatment costs in this sub-population. For women, screening all 18 to 31-year olds in combination with clinical diagnosis was the second most cost-saving strategy. Mehta *et al.* (2002) did not compare their results to a WTP threshold.

Sahin-Hodoglugil *et al.* (2003) conducted a CEA on the same two STIs, based on a hypothetical cohort of one million South African women using static decision-tree analysis. The authors compared syndromic management, mass treatment and gold standard laboratory testing for chlamydia and gonorrhoea detection and treatment among women in their reproductive age. The gold standard tests included culture, LCR and PCR and they modelled treatment with two different drugs (doxycycline and azithromycin) for all three strategies. The ICER is reported as the incremental cost per gonorrhoea or chlamydia case cured. The authors state that mass treatment with doxycycline is the most cost-effective strategy in the base case analysis, but this strategy remained precarious in terms of ethical considerations and antimicrobial resistance, as was shown in Mehta *et al.* (2002). Moreover, the authors did not employ any WTP threshold. They conclude with various advantages and disadvantages of each alternative but do not make clear conclusions or recommendations nor do they provide final ICERs in their paper.

Kraut-Becher *et al.* (2004) conducted a CEA in correctional service setting in the USA. Kraut-Becher *et al.* (2004) assessed the cost-effectiveness of different programmes for the management of chlamydia and gonorrhoea amongst new male and female inmates in US jails. The model comparators included universal NAAT screening for both infections, universal NAAT screening for chlamydia only and thirdly, presumptive treatment for both infections. The ICERs are presented as the incremental cost per additional case of infection averted. It was found that universal screening of the female study population for both infections was cost-effective (ICER of US$ 3,690 per additional case of infection averted; in 2002 US Dollars), while screening for chlamydia only was cost-saving under baseline assumptions. For men,

universal screening effective (ICER of US$ 650) was not cost saving but could be considered cost-effective. These judgements were, however, not made based on a WTP threshold. Screening for chlamydia only (ICER of US$ 4,856) was more expensive than presumptive treatment and not sufficiently effective to make it a cost-effective strategy. In settings with a high prevalence of both infections, universal screening of both sexes for chlamydia and gonorrhoea would become cost-effective. It is concluded, however, that universal screening for chlamydia of both sexes could possibly be considered due to the highly costly effects of chlamydia and its sequelae on the female population.

De Vries *et al.* (2006) conducted a dynamic CEA to establish the cost-effectiveness of once-off screening and subsequent treatment for chlamydia in the patient and their identified sexual partner(s) with a PCR test. This approach was compared to no screening in their model. The study population was young Dutch adults, male and female, aged 15-29 and ICERs (in 2002 Euros) were represented as the costs per MOA averted and per PID case averted. They argued that although screening for chlamydia would result in a net cost that the Dutch society would bear, the ICER of €373 per MOA presents a cost-effective intervention against the Dutch threshold of €20,000 per QALY gained. The authors illustrate this with a crude calculation of cost-utility of their analysis and estimate this intervention to be below €1000/QALY. The intervention would become cost-saving when restricted to women only.

In a second study conducted in South Africa, Colvin *et al.* (2006) assessed the cost-effectiveness of the standard of care syndromic management algorithm for a wide range of STIs, in comparison to an enhanced package of care with components such as condom provision and information leaflets in addition to standard syndromic management. The analysis thus included the full spectrum of STIs that is managed with the syndromic approach in this setting. ICERs were estimated as the incremental cost per case correctly managed and secondarily, per case correctly treated. The CEA was conducted on simulated female and male patients in primary care clinics in Durban, KwaZulu-Natal. Colvin et al. (2006) found that patients in the clinics receiving the intervention syndromic management packages were more likely to receive appropriate treatment and STI management than under standard syndromic management. The incremental cost of this enhanced approach was $1.51 (2003 US Dollars) per additional patient correctly managed, which was considered a reasonable cost for the health improvement it provides. No WTP threshold is used in this analysis.

Adams, Turner and Edmunds (2007) conducted a CUA in England on a male and female population of ages of 16 to 44 years. The dynamic model estimates the cost-effectiveness of three chlamydia strategies, namely annual screening of all women, annual screening for women who have changed sexual partner in the preceding 6 months and annual screening for both men and women. These were modelled separately for different age groups (<20, <25, <30, <35 and <40). This was compared to the standard of care of screening for all men and women under the age of 25. The authors estimated both average and incremental cost-effectiveness ratios. The ICERs are reported as the cost per MOA and per QALY gained. The authors conclude that none of the investigated strategies is cost-saving for chlamydia management. If PID progression rates are lower than 10%, the current standard of care appears to be cost-effective in comparison to no-screening, while in cases of significantly low PID none of the screening strategies is cost-effective. In conclusion, screening of all individuals below the age of 20 is the most cost-effective approach in terms of the relevant threshold of £20 000–£30 000 per QALY (2004 Pounds sterling) gained when considering a PID progression rate of equal or higher than 10%, with an ICER of £ 24,103 per QALY gained. The authors, however, do in some instances make cost-effectiveness conclusions based on ACERs.

In another study, Ong *et al.* (2016) conducted a CUA to estimate the cost-effectiveness of different chlamydia screening approaches for young pregnant women, aged 16-25, in Australia. The model comparators were no screening, selectively screening only women aged 16-19 and/or those reporting more than one sexual partner in the preceding year and screening all women in the study population. The ICERs were presented in terms of QALYs gained. They reported that screening all women aged 16-25 for chlamydia during an antenatal visit is cost-effective in comparison to the other two strategies under consideration. The ICER of AUD 34,931 (2014 Australian Dollars) is well below the common threshold of AUD 50,000 in the Australian context. This strategy only loses its cost-effective status in cases where disease prevalence is very low (<3%), test or clinician costs almost double.

Rours *et al.* (2016) employed a static decision tree analysis to estimate the cost-utility of screening for chlamydia compared to no screening. The study population was pregnant Dutch women and the diagnostic test employed was a urine-based laboratory NAAT. The authors reported the ICERs as the incremental cost per QALYs gained. The results from Rours et al. (2016) show that universal screening for chlamydia would be cost saving if the test price does

not exceed €22 (2009 Euros). This strategy, compared to the Dutch threshold of €20,000 per QALY, is cost-effective in this setting even when varying various parameters in the sensitivity analysis. According to the study, screening could become even more cost saving if pregnant women or women below the age of 30 years were targeted.

Gonorrhoea

Bernstein *et al.* (2006) conducted a static CEA on a theoretical cohort of 10,000 women seeking care in the private sector in the USA. The objective of the study was to estimate the cost-effectiveness of different screening algorithms, using urine-based NAATs, for the detection of gonorrhoea in this population. These algorithms included; screening women younger than 25, screening women younger than 30, screening women younger than 25 reporting any risk, screening women younger than 30 reporting any risk and lastly, screening women younger 30 or those reporting risk of any age. Risk factors included pregnancy, acquisition of a new sexual partner in the preceding month and drug use. The ICERs from this study were reported as the cost per additional case treated and each algorithm was compared incrementally to a no-screening alternative. The authors reported that the most cost-effective approach would be to screen all women below the age of 25 who report any risk factor, for gonorrhoea and that this could reduce untreated infections with up to 30%. This strategy would also become cost-saving when disease prevalence rises to above 4.75% (compared to 3% at baseline). However, this might be a more realistic scenario in cases of specific populations such as emergency department patients or at correctional facilities, and the authors conclude that in general, population-based screening is likely to pose a net cost. Furthermore, the introduction of POC testing in this model might further enhance the cost-effectiveness of these screening algorithms. No WTP threshold is used in this analysis.

Trichomoniasis

Lazenby *et al.* (2014) conducted a CEA to estimate the cost-effectiveness of screening, treatment and follow-up of trichomoniasis in HIV-positive women in the USA. This was the only study conducted on this infection alone that met the inclusion criteria for this review. The model comparators were no screening and screening using culture. 200 women were included in the study, 100 who were screened and 100 who were not. The ICERs are calculated as the incremental cost per HIV transmissions averted. Lazenby *et al.* (2014) found that the

screening of HIV-positive women dominated the no-screening approach. The former represented the CDC guidelines at the time. Screening for *Trichomonas vaginalis* in this population could prevent up to 350 new HIV infections per year, a substantial number of cases in the USA setting, as well as provide cost savings. The perspective from which the study was conducted in the analysis was not clearly stated but based on the costs included (direct medical costs associated with screening and treatment of STIs and HIV treatment) it appears to be that of the healthcare provider. These judgements were not made based on a WTP threshold.

DISCUSSION

Most studies comparing screening to no screening or diagnostic testing only found the former to be the more cost-effective alternative and even cost-saving in some instances. However, these results vary greatly in terms of age groups and sub-population. Two studies found mass treatment to be the most cost-effective approaches for managing chlamydia and gonorrhoea and a range of STIs, respectively. The acceptability of this method, from both an ethical and a health perspective, is highly questionable and has become increasingly so in recent years (Mayaud and Mccormick, 2001; Mehta *et al.*, 2002; Sahin-Hodoglugil *et al.*, 2003). A major limitation in this body of work, like in the previous section, is the absence of a cost-effectiveness (or WTP) thresholds when making cost-effectiveness conclusions.

SUMMARY

The literature on the cost-effectiveness of different screening and diagnostic strategies that have been reviewed varies greatly in terms of study design, setting and methods. Given that four different infections are included in the review makes it even more challenging to compare the findings.

However, some common trends are found in the literature. Firstly, there is a rationale for the development of rapid, accurate POC tests in and further investigating the cost-effectiveness thereof in LMIC settings. Many studies emphasise the need for the development of rapid and accurate POC tests and increasing pressure is placed on this issue in the policy environment. The disproportionate amount of HIC research studies in the literature further points to the need to investigate these issues in LMICs where the burden of disease is the largest. Secondly, given the high level of asymptomatic infections, screening with accurate and rapid POC tests

has great potential to be cost-effective in comparison to diagnostic testing approaches. Many studies showed that where adequate disease prevalence is present and return rates to health facilities are low, approaches that allow immediate diagnosis and treatment have the potential to be highly effective strategies at sufficiently low cost. Thirdly, strategies such as mass treatment and clinical diagnosis (syndromic management) need to be considered all the more carefully for various ethical and health reasons such as the rise in antimicrobial resistance globally. Mass treatment does, however, occur less in more recent work as an STI management approach.

Overall, there is a gap in the literature in LMICs and Africa, where the brunt of the diseases occurs. Furthermore, the literature is largely focused on chlamydia as well as chlamydia-gonorrhoea coinfection. While these two diseases are highly prevalent and remain a major concern, other curable STIs and BV cannot be neglected especially when considering the link to HIV acquisition and transmission. There remains a need to find cost-effective interventions to decrease the prevalence and incidence of these infections and large potential for it to play an important role in HIV prevention.

The advancement of a rapid test such as the GIFT device holds great promise for the management of STIs and BV amongst women in South Africa and potentially, other LMIC settings. The cost-effectiveness of this device has, however, not been established. This will be the primary objective of this research study.

2.4 AFFORDABILITY OF GIFT IN THE SOUTH AFRICAN CONTEXT

A previous sub-study of the GIFT project aimed to estimate the cost and budget impact of implementing GIFT in primary healthcare facilities in South Africa. Costs of genital inflammation screening were estimated from the provider's perspective for women aged 15-49 years using a micro-costing approach. Costs were estimated for two clinics, the Desmond Tutu HIV Foundation youth clinic (DTHF) and the University of Cape Town Student Wellness Service (UCT SWS), over one year. The unit estimates obtained were utilised in the budget impact analysis for countrywide implementation.

The cost per woman screened for genital inflammation was estimated to be $24.26 at DTHF and $14.32 at UCT SWS, based on 2016 cost and utilisation data. These estimates proved sensitive to clinic utilization rates, personnel costs and population coverage rates.

Scaling up, a total cost ranging between $107,183,655 (for a semi-private facility) and $183,062,066 (for an NGO-funded facility) was estimated at country level. This respectively represented 10% and 17% of the available budget for HIV/AIDS at the time; a share considered to significantly high when considering the array of other existing interventions and new ones competing for funding (Kairu, 2017). This was observed amidst a declining trend of national budget allocation to the health sector; going from 14.5% in 2011 to 14.2% in 2014. Kairu (2017), however, concludes that this intervention has the potential to have a significant impact on the sexual and reproductive health of women in South Africa.

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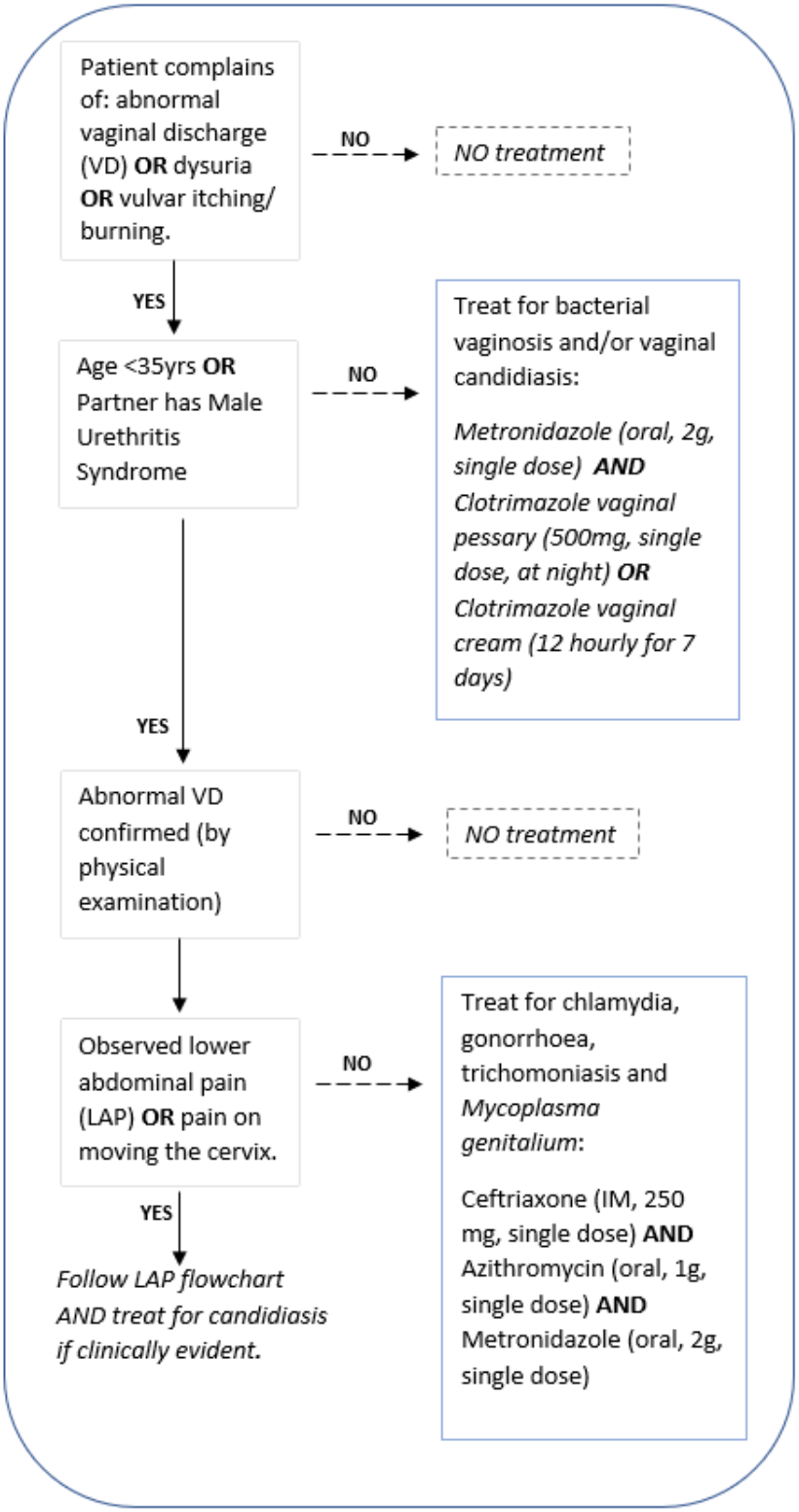
APPENDIX A: South African Department of Health syndromic management guidelines

Vaginal Discharge Syndrome



Source: adapted from (63)

APPENDIX B:

	Author/date	Type of study	Infection	Perspective	Population	Model comparators
1.	Postma *et al.* (2000)	Cost-effectiveness analysis	CT	Societal	Sexually active females; GP practices in Amsterdam	Four age-stratified screening strategies (with laboratory LCR) vs. no screening strategy.
2.	Welte *et al.* (2000)	Cost-effectiveness analysis	CT	Societal	Heterosexual females and males, 15-24 (simulated); Netherlands	Screening (with laboratory LCR) vs. no screening
3.	Goeree *et al.* (2001)	Cost-effectiveness analysis	CT	Provider (provincial ministry of health)	Women aged 15-24; Canada	Seven different strategies comparing diagnosis and screening as well as testing with urine- and swab-based NAH and NAA test assays.
4.	Gift *et al.* (2001)	Cost-effectiveness analysis	CT and NG	Provider (healthcare system)	Asymptomatic women; USA	Three different treatment and diagnostic algorithms with laboratory-based NAAT and NAH test assays.
5.	Nyari *et al.* (2001)	Cost-effectiveness analysis	CT	Not explicitly stated (costs included imply provider)	Asymptomatic women aged 15-19, Hungary	Screening with ELISA and Gen-Probe (both laboratory-based) and no screening.
6.	Mehta *et al.* (2002)	Cost-effectiveness analysis	CT and NG	Provider (Public healthcare provider)	Male and female emergency department patients (simulated), USA	Five different diagnostic, screening and treatment algorithms including variations of clinical diagnosis and testing with laboratory-based LCR assays; stratified by age groups.
7.	Ginocchio *et al.* (2003)	Cost-effectiveness analysis	CT	Provider	Young asymptomatic	No screening, screening with LCR (laboratory), and

					men (simulated), USA	pre-screening urine with LE test and confirming positives with LCR.
8.	Sahin-Hodoglugil *et al.* (2003)	Cost-effectiveness analysis	CT and NG	Provider (Healthcare system)	Women in reproductive age (simulated), South Africa	Syndromic management, mass treatment and laboratory testing (culture and NAATs).
9.	Kekki *et al.* (2004)	Cost-effectiveness analysis	BV	Provider (government)	Low-risk pregnant women, Finland	No screening compared to two screening approaches using gram staining and two different drug regimens.
10.	Kraut-Becher *et al.* (2004)	Cost-effectiveness analysis	CT and NG	Provider (healthcare system)	Male and female inmates, USA jails	Universal screening (using NAAT) for CT and NG, universal screening for CT only, and presumptive treatment both.
11.	Blake, Gaydos and Quinn (2004)	Cost-effectiveness analysis	CT	Provider (healthcare system)	Male youth entering juvenile detention (simulated), Massachusetts, USA	Universal chlamydia screening using(NAAT), selective NAAT screening of pre-screened LE-positive urines, and no screening.
12.	Aledort *et al.* (2005)	Cost-utility model	NG	Societal	Young female patients in emergency depts (simulated), USA	Five screening approaches including variants of screening using gram staining, RIS rapid and NAATs as well as no screening.
13.	Colvin *et al.* (2006)	Cost-effectiveness analysis	All STIs covered by syndromic management	Provider (provincial department of health)	Symptomatic female and male patients (simulated), Durban KZN	Enhanced syndromic management package vs. standard syndromic management
14.	Bernstein *et al.* 2006)	Cost-effectiveness analysis	NG	Not explicitly stated (unclear from representation)	Females utilising private sector care (simulated), USA	Six different screening algorithms using NAATs stratified by age groups and risk.
15.	De Vries *et al.* (2006)	Cost-effectiveness analysis	CT	Societal	Female and male adults aged 15 to 29, Netherlands	Screening using PCR vs no screening

16.	Vickerman *et al.* (2006)	Cost-effectiveness analysis	Ct and NG	Provider	Female sex workers, Benin	Screening using combined CT/NG POC test (at 3 different specificities) vs syndromic management
17.	Adams, Turner and Edmunds (2007)	Cost-utility model	CT	Provider (NHS)	Males and females aged 16 to 44, England	Three different screening strategies modelled for different age groups, sex and risk factors.
18.	Kourbatova *et al.* (2008)	Cost-effectiveness analysis	NG and syphilis	Limited societal perspective *(stated this way)*	Females and males from four different occupational groups (simulated), Russia, Moscow	No screening, screening for gonorrhoea only (using gram stain), screening for syphilis only (using MR and WR tests), and screening for gonorrhoea and syphilis.
19.	Romøren (2008)	Cost-effectiveness analysis	CT	Provider (government)	Teen age population antenatal care attendees (simulated), Gaborone, Botswana	POC testing and two syndromic management approaches (with standard of care drug and novel one)
20.	Tsai *et al.* (2008)	Cost-effectiveness analysis	CT, NG, syphilis	Not explicitly stated (costs included imply provider)	Sexually active symptomatic male patients, Taiwan	Syndromic management vs current clinical approach (presumptive treatment and laboratory testing) vs aetiological approaches (PCR test for CT and NG, RPR/Venereal Disease Research Laboratory test for syphilis and TPHA tests for TP)
21.	Hislop *et al.* (2010)	Cost-effectiveness analysis	CT	Provider/ government - NHS	Male and females ages 16–24 years, combined cohorts from various studies across Europe, USA, China and Egypt	Screening with the Clearview POCT, CRT POCT and laboratory-based PCR.

22.	Huang *et al.* (2013)	Cost-effectiveness analysis	CT	Provider (public healthcare provider)	Sexually active women (simulated), USA	Novel POC CT test vs. laboratory-based NAAT testing
23.	Bartelsman *et al.* (2014)	Cost-effectiveness analysis	NG	Provider	High risk men and women, Amsterdam	Screening of high-risk patients vs testing and treating symptomatic by POC Gram stain
24.	Lazenby *et al.* (2014)	Cost-effectiveness analysis	TV	Not explicitly stated (costs included imply provider)	HIV-positive women, USA	Screening using culture vs no screening
25.	Turner *et al.* (2014)	Cost-effectiveness analysis	CT and NG	Provider (NHS)	Male and female patients (simulated), England	Screening with POC NAAT vs standard off-site laboratory testing
26.	Ong *et al.* (2016)	Cost-utility model	CT	Provider (Government - primary third-party funder)	Pregnant females aged 16-25, Australia	Screening all pregnant women aged 16–25 years compared with no screening, selectively screening only stratified by subsets of age and risk factors.
27.	Rours *et al.* (2016)	Cost-utility model	CT	Societal	Dutch pregnant women	Screening (using laboratory-based NAATs) vs no-screening
28.	Huntington *et al.* (2017)	Cost-utility model	CT, NG, TV and MG	Provider (NHS (tariff-costing) and clinic NHS (micro costing))	Female and males (simulated), UK	Three hypothetical NAA POC tests (dual test for CT and NG; triplex test for CT, NG and MG; quadruplex test for CT, NG, MG and TV) in comparison to current practice of microscopy plus laboratory-based NAAT for CT and NG.
29.	Zwart *et al.* (2018)	Cost-effectiveness analysis	NG	Provider (healthcare payer)	Men-who-have-sex-with men, Netherlands	Three testing strategies: gram stain and confirmatory NAAT for symptomatic MSM only, NAA testing for all MSM and lastly, gram stain testing (and

						confirmatory NAAT) in symptomatic and asymptomatic MSM.

PART C: JOURNAL MANUSCRIPT

COST-EFFECTIVENESS ANALYSIS OF DIFFERENT SCREENING AND DIAGNOSTIC STRATEGIES FOR SEXUALLY TRANSMITTED INFECTIONS AND BACTERIAL VAGINOSIS IN WOMEN AGED 15-49 YEARS ATTENDING PRIMARY HEALTH CARE FACILITIES IN CAPE TOWN

ABSTRACT

Objective Genital inflammation associated with sexually transmitted infections (STIs) and Bacterial Vaginosis (BV) is considered a key driver in the HIV/AIDS epidemic. A new rapid point-of-care (POC) test that detects genital inflammation in women was recently developed by researchers at the University of Cape Town. The objective of this study was to establish the cost-effectiveness of this novel intervention relative to other relevant screening and diagnostic strategies for the management of STIs and BV in women.

Methods A decision analysis model was developed to estimate the cost and health outcomes associated with five different screening and diagnostic strategies for women seeking care in the South African public health sector. A decision tree was constructed, and all cost and effectiveness parameters were obtained from published and unpublished literature. The model incorporated all clinic-level and treatment costs associated with diagnosing and treating a single episode of disease. The main outcome measure was the effectiveness of each approach in correctly diagnosing an STI or BV in women, proxied by the sensitivity measure of diagnostic test or approach. One-way sensitivity analysis and threshold analysis was conducted to test key uncertainties and assumptions in the model.

Results In the base-case scenario, screening with GIFT and following with syndromic management for GIFT-positive cases, was the most cost-effective strategy with an ICER of $2.60 per women diagnosed with an STI(s) and/or BV. This strategy remained the most cost-effective even when a variety of parameters were varied in one-way sensitivity analyses. A threshold analysis on GIFT's sensitivity revealed that the strategy would remain the most cost-effective unless the sensitivity of the test assay decreased below 14.83%.

Conclusion From the perspective of the South African government, screening with GIFT and treating positive cases according to syndromic management guidelines is the most cost-effective strategy for the management of STIs and BV in women in the reproductive age, but implementation at national level would not be affordable. The newly developed rapid POC has the potential to significantly improve the management of STIs and BV in women through identifying asymptomatic women and at the same time reducing their risk of HIV infection. However, this analysis presents only a first step in establishing the cost-effectiveness of these interventions and paves the way for further research and consideration.

Keywords: Sexually transmitted infections, Bacterial Vaginosis, cost-effectiveness, point-of-care testing, genital inflammation screening, female reproductive health, HIV prevention

INTRODUCTION

Sexually transmitted infections (STIs) represent a significant challenge to global public health. In 2012 the World Health Organization (WHO) reported that annually, around 499 million new cases of the four most common curable STIs (*Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis* and Syphilis infections) occurred globally (World Health Organization, 2012). Recent WHO estimates confirm that the majority of these occur in the developing world and that an annual incidence of 92 million new infections is accounted for in the African region alone (1). Some studies have also estimated that up to 55% of women in Sub-Saharan Africa are infected with BV (2). STIs and BV are considered one of the leading causes of disability adjusted life years lost in women (3). If left untreated, STIs and BV can lead to various serious sexual and reproductive complications, and research indicates it increases the risk of HIV acquisition and transmission (3–6).

South Africa houses one of the largest burdens of curable STIs in the world, with high prevalence in women who are at high risk of HIV (7–9). Given that the public health sector serves around 84% of the population, the vast majority of this burden rests on the National Department of Health (10). In the public health system, most STIs are managed syndromically, rather than with resource-intensive etiological diagnosis (11). Under this approach developed by the WHO, syndromes of a specific STI or BV are identified according to pre-identified groups of signs and symptoms. Patients are then provided with treatment that will address the majority, or the most serious, of organisms typically associated with the identified syndrome (see Appendix A.1) (11,12).

Given that many cases, especially in the female population, are asymptomatic (estimated as high as 75% in some studies (13,14)) many cases are missed under the current standard of care since these women do not seek care (15,16). The accuracy of syndromic management is further undermined by the various overlapping syndromes and signs between different STIs (17). Research done in South Africa suggests limited knowledge of nurses in the public sector regarding appropriate treatment for the various STI syndromes (18,19). Some studies also report low specificity of this approach, resulting in overdiagnosis and -treatment and thus excessive use of antibiotics. The latter has implications for the development of drug-resistant

strains of various bacteria which is a growing concern, globally (12,17). Globally and locally, there is a need to move away from syndromic management and towards more effective strategies management of STIs and BV. More specifically, there is an urgent need to improve STI management for women in resource-constrained settings (5). Research also suggests that improvements in STI management can have a significant impact on HIV prevention, especially in settings where both HIV and curable STIs are highly prevalent (16,20,21)

The gold standard for diagnosing STIs are laboratory-based nucleic acid amplification tests (NAATs) and microscopic identification through Nugent scoring for BV (5,22,23). These methods are expensive and resource-intensive, making it unfeasible in resource-constrained settings (5). Furthermore, it does not allow for immediate results and requires that patients return to health care facilities to obtain results and receive treatment. More transmissions may take place during the waiting period and the rate of return to clinics, and consequently the opportunity for treatment uptake, is often very low in these settings. Some studies report it to be as low as 11% in the African context (24,25).

With the WHO's ambitious goal of a 90% reduction in the incidence of STIs and zero new infections by 2030, the improved detection and treatment of asymptomatic STI and BV cases form a key part of the organization's STI prevention and control strategies. In this context, the WHO has prioritized the development of relevant point-of-care (POC) tests (26,27). Nationally, under the new National Sexually Transmitted Infections Strategy, and as part of the Western Cape's Provincial Strategy Plan, zero new HIV and STI infections also form part of the long-term vision for public health in South Africa. This is within the context of the overarching framework for health which strives to universal coverage for all and vulnerable populations in specific. (28,29).

In reaction to growing concerns about the affordability of etiological diagnosis and the widespread concern with syndromic management, more rapid and less expensive NAATs have been developed. Cepheid's GeneXpert CT/NG test is an example of a combined chlamydia and gonorrhoea POC NAAT from the USA that is commercially available in South Africa. A similar assay has also been developed detecting trichomoniasis; GeneXpert TV. These tests perform comparatively well to laboratory-based NAATs and are ideally performed in on-site laboratories using the GeneXpert system. It can present results in roughly 90 minutes, but is

still relatively expensive in an LMIC context, however, and is thus not widely available on-site at health care facilities (6,30,31).

Recently, researchers at the Division of Medical Virology at the University of Cape developed GIFT (Genital Inflammation Test): a relatively inexpensive, cytokine POC rapid test that detects inflammatory bacteria in the female genital tract. STIs and BV cause genital inflammation, regardless of other symptoms such as vaginal discharge or genital ulcers being present. The measurement of key inflammatory cytokine biomarkers with a rapid POC test can thus potentially identify asymptomatic cases that are otherwise missed and consequently, women who are at an increased risk of acquiring and transmitting HIV. Identified women would then be treated immediately according to syndromic management guidelines (Masson and Passmore, Personal Communication, 2018, November 18). The device has already between validated in a biomarker validation study and is to be rolled out in a cross-sectional validation study in Cape Town clinics to evaluate and optimize its performance (Masson and Passmore, Personal Communication, 2018, November 18; 29).

Currently, limited research is available on the cost-effectiveness of screening with POC tests and STI management in general in LMICs and Africa. Furthermore, the cost-effectiveness of this novel test device has not yet been established. However, a cost estimation for this intervention at clinics in Cape Town for women aged 15-49 years, as well as a budget impact analysis of implementing it in all primary health facilities across South Africa, has been conducted by Kairu[33]. The cost per woman screened for genital inflammation was estimated to be $14.32 at a semi-private facility and $24.26 at an NGO-funded facility. Scaling up, a total cost ranging from $107,183,655 and $183,062,066 was estimated. This amounted to roughly 10%-17% of the total available budget for HIV and AIDS; suggesting that this would be highly costly in the South African setting.

A decision analysis model was developed using cost and probability estimates from existing literature to estimate the cost-effectiveness of five screening and diagnostic strategies for the three highly prevalent curable STIs in South Africa, *Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis infections,* and BV. These infections were considered for the analysis due to both their high prevalence in South Africa, but mainly their clear association with the increased risk of HIV acquisition and transmission (34).

METHODS

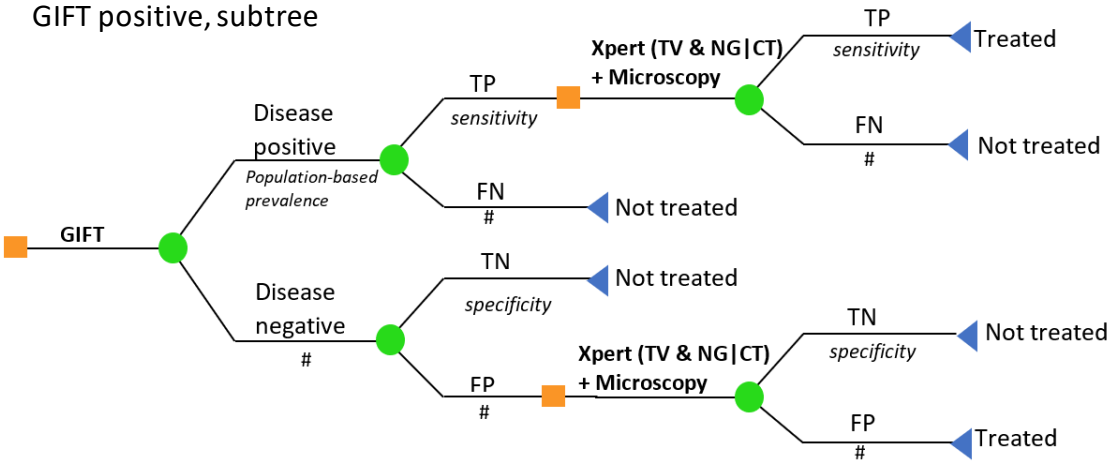
Decision Analysis Model

A decision tree (see Appendix A.2) was constructed in Microsoft Excel to estimate the cost-effectiveness of five different screening and diagnostic strategies for STIs and BV in women in the reproductive age (15-45 years) (35) entering the South African public health sector at primary care level. Economic costs and clinical effectiveness were estimated with the following screening and diagnostic strategies for *C. trachomatis, N. gonorrhoeae, T. vaginalis* and BV:

1. Syndromic management of symptomatic women seeking healthcare
2. Screening all women entering primary care facilities with GIFT followed by syndromic management for GIFT-positive cases (GIFT-SM)
3. Screening with GIFT followed by testing with GeneXpert NG/CT and GeneXpert TV assays and microscopy for GIFT-positive cases (GIFT-Xpert-Microscopy)
4. Screening with GeneXpert (NG/CT and TV) and microscopy alone (Xpert-Microscopy) in health facilities.
5. Screening with gold standard laboratory testing (PCR-Microscopy) at an off-site laboratory.

The model was populated with the probabilities of events based on estimates from published literature. These strategies were included based on the primary GIFT study protocol and expert opinion on the current circumstances and available technologies in the public health sector (Nigel Garret, email correspondence, 2018, August 29; Masson and Passmore, Personal Communication, 2018, November 18). Model outcomes were compared using incremental cost-effectiveness ratios (ICERs). In the model, the latter was measured as the additional cost per women diagnosed with an STI(s) and/or BV and put on treatment.

Figure 1: Extract from the full decision tree: GIFT, followed by GeneXpert and Microscopy for GIFT positive, subtree



TP= true positive; FN = false negative; TN = true negative; FP = false positive

Data

Effectiveness

The effectiveness of each approach was estimated based on the sensitivity and specificity of each approach, with the primary outcome being appropriate diagnosis and treatment administered. The latter was proxied by the sensitivity measure of each diagnostic test or approach. These parameters were obtained from published literature and are shown in table 1.

Where two or more tests are performed simultaneously in a branch of the decision tree, such as GeneXpert and microscopy, average effective measures were used.

Model probabilities

The probability of events in the model was obtained from published literature. The proportion of patients lost to follow-up (LTFU) in the laboratory testing arm was based on published literature related to HIV testing in Africa as no literature on LTFU rates for STI testing exists in these settings (25). The prevalence of BV and the three STIs was based on estimates from South African studies conducted on women in the reproductive age. The overall, average disease prevalence of the three STIs and BV was assumed in the model for simplification.

Table 1: Sensitivity and specificity of diagnostic tests and approaches and model strategies in detecting sexually transmitted infections and BV in women in their reproductive age in South Africa

Diagnostic test / Approach	**Sensitivity**	**Specificity**	**Missed cases*** ***(1-sensitivity)***	**Overtreatment** ***(1-specificity)***	**Reference**
Syndromic Management					
Any discharge causing STI	10.5%	96.0%	89.5%	4.0%	(16)
CT	13.9%	92.8%	86.1%	7.2%	(16)
NG	17.9%	92.8%	82.1%	7.2%	(16)
TV	13.8%	93.5%	86.2%	6.5%	(16)
BV	10.0%	94.4%	90.0%	5.6%	(16)
GIFT For detecting genital inflammation	77.0%	71.0%	23.0%	29.0%	(5)
GeneXpert for detecting CT	100.0%	97.6%	-	2.4%	(36)
GeneXpert for detecting NG	100.0%	100.0%	-	-	(36)
GeneXpert for detecting TV	96.4%	99.6%	3.6%	0.4%	(37)
GeneXpert (average)	99.4%	99.5%	0.6%	0.5%	
Laboratory PCR (CT,NG & TV)	100.0%	100.0%	-	-	(23)
Microscopy (BV) †	100.0%	100.0%	-	-	(23)
*Includes asymptomatic cases ** Including BV †Laboratory- and clinic-based, no difference between the two (Nigel Garret, personal communication, 2019, May 29)					

Table 2: Base, low and high estimates of the probability of events in the model

Variable	**Low**	**Base case**	**High**	**Reference**
Disease Prevalence*				
Chlamydia	4,2%	15.4%	32,8%	(1,7,13,14,16,38–44)
Gonorrhoea	1,8%	5.9%	10,9%	
Trichomoniasis	3,0%	10.8%	20,3%	
Bacterial Vaginosis	33,7%	44.5%	53,0%	
Clinic return rates	11.0%	20.0%	49%	(25)
*Based on the average prevalence from 11 studies done in South Africa from 2011-2018 **Of all three STIs and BV				

Costs

The cost of each subtree of the decision tree was based on estimates obtained from unpublished literature some external institutions such as the National Health Laboratory Service (NHLS) and Cepheid. The model incorporated all clinic-level capital and recurrent costs associated with each strategy for diagnosing and treating a single episode of disease. All screening strategies included the cost of a standard clinic visit, a physical and speculum examination (35) and treatment costs. In accordance with Kairu[33], no additional programme

start-up costs were included for GIFT strategies, expect training of personnel to administer the test. Where applicable, it also included the cost of taking a specimen, operating a test assay and obtaining results. Costing was done from the provider's perspective (Department of Health) and was inflated to 2019 Rand and converted to US$ based on the average exchange rate for 2019. All relevant cost data is presented in table 2.

Table 3: Cost of screening or diagnosis and treatment per patient

Variable	Cost (2019 ZAR)	Cost (US$)*	Reference
COMPONENT COSTS			
Clinic visit**	192.45	13.44	(33)
Medical consumables for taking specimen	13.00	0.91	(33)
Specimen transport¶	18.87	1.32	(45)
GIFT test (assay, consumables, equipment, training staff to use GIFT)	21.41	1.50	(33)
Testing with quadruplex PCR (NG,CT,TV) (outsourced service, quoted price)	473.39	33.07	NHLS state price list, 2018
Testing with laboratory-based microscopy (outsourced service, quoted price)	42.67	2.98	NHLS state price list, 2018
UNIT COSTS			
Syndromic Management	192.45	13.44	(33)
Screening with GIFT	213.09	14.89	(33)
Screening with GeneXpert (CT/NG and TV) & Microscopy	988.74	69.07	(33,46) Gwen Stephens, *Ceipheid,* personal communication 2019, June 3
Screening with laboratory (multiplex PCR-Microscopy) tests	706.92	49.38	(47)
CT treatment	8.71	0.61	(48)
NG treatment	13.58	0.95	(48)
TV treatment	1.57	0.11	(48)
BV treatment	1.57	0.11	(48)
Syndrome A treatment†	13.08	0.91	(48,49)
Syndrome B treatment‡	14.59	1.02	(48,49)

* R1 = US$ 14.32 (Average exchange rate 2019)
**Includes standard visit to family planning clinic and physical (vaginal) examination.
¶ For single specimen transported from clinic to NHLS.
†According to SM Vaginal Discharge algorithm: treat for BV and/or vaginal candidiasis.
‡According to SM Vaginal Discharge algorithm: treat for Treat CT, NG, TV and *Mycoplasma genitalium.*

The cost of a standard clinic visit and examination, as well as screening with GIFT, was based on estimates from Kairu[33]. This was included in the cost estimate, at least partly, of all the strategies, depending on the component costs included in the cost estimates obtained from the literature.

The cost associated with screening with GeneXpert NG/CT and TV assays was mainly based on an unpublished study by Stime *et al.*[42] Capital and overhead costs of a standard clinic visit was added to this estimate since this was not included by Stime *et al.* [42] The cost of laboratory testing was mainly obtained from the quoted NHLS price since service is outsourced from the Department of Health. The total unit cost, however, included a standard clinic visit, taking of specimens as well as the transport cost of two specimens.

Drug costs were obtained from the latest available Western Cape Department of Health's master procurement catalogue at the time of analysis (April 2019) and treatment regimens are based on the guidelines for STI treatment in South Africa. Given that syndromic management is mainly followed in the public health sector, guidelines do not specify treatment regimens for individual infections, but rather for groups of infections with similar symptoms (see guidelines in Appendix A.1). Costing of treatment for individual infections were based on regimens used in Garret *et al.*[35] Average treatment cost was assumed in the base case scenario for simplification.

Model Assumptions

Only women in their reproductive age, ages 15-49 years, were included following Kairu[33]. This age group typically carry the highest burden of social and psychological consequences of STIs and are typically most susceptible to STIs and BV (WHO 2013). For syndromic management, it was assumed that all women who have symptoms seek care and accepted consequent treatment. All screening strategies were based on opportunistic screening of any woman entering a primary healthcare facility. It was assumed that all women accept the screening tests and resulting treatment when administered.

In addition, certain assumptions were made when using and adapting relevant data from secondary sources. Firstly, the effectiveness of GIFT was based on the sensitivity and specificity found in the biomarker validation study, as this has not been established in the field. The prevalence of diseases for the study population was based on the average estimates

from 11 studies conducted in South Africa from 2011-2018. These studies were all based in different study settings and included different age groups, although within the bounds of 15-49 years, and they followed varying research methodologies. Furthermore, the probabilities of the four disease were averaged in order to create a simpler decision problem.

Cost parameters were also collected from varying sources. A standard clinic visit was included for all model comparators, for which the costs were extracted from Kairu[33]. Across non-GIFT strategies, this was then combined with cost estimates from other relevant sources. Cost sources for the different model comparators also differed in the extent to parameters were compounded. Laboratory testing, for example, was cost based on a single cost estimate received from the NHLS, while for Xpert and Microscope and GIFT unit costs were made available. Therefore, the costing of staff time and the inclusion of consumables were not standard across cost estimates. In accordance with Kairu[33], it was also assumed that screening with GIFT would have no additional personnel time implications, as it was regarded as insignificant.

Sensitivity Analysis

We performed one-way sensitivity analyses to establish the robustness of the results given the high variability of estimates found in literature, uncertainties in the data and the assumptions made in the model. Key parameters were varied across a reasonable range while holding all other parameters constant at their base case values. These parameters included GIFT test cost, personnel time, GeneXpert test costs, GIFT sensitivity, lost to follow-up rates, disease prevalence, test and treatment uptake and syndromic management sensitivity. Parameter values were varied based on relevant values from the literature.

We also performed a threshold analysis for GIFT sensitivity. Lastly, four alternative decision trees in which the decision analysis was modelled for each disease separately was constructed to test the average disease probability and treatment costs assumption made in the base case decision tree.

RESULTS

Base-case scenario

Screening with GIFT-SM was the most cost-effective strategy in the base case scenario with an ICER of R38.20 (US$ 2.60) per women diagnosed and put on treatment. GIFT-Xpert-Microscopy, with an ICER of R586.76, was dominated and thus eliminated from the decision-making problem. The remaining two strategies were also cost-effective, but with much higher ICERs than GIFT-SM of R740.61 and R902.37 respectively.

Table 4: Base case cost-effectiveness results

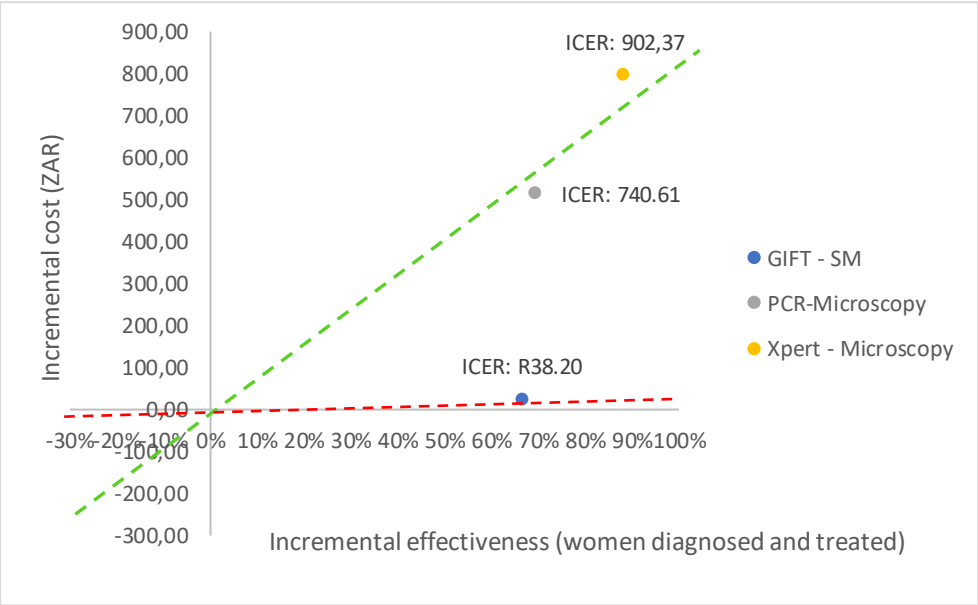
Approach	**Cost (ZAR)***	**Incremental cost (ZAR)**	**Effectiveness****	**Incremental effectiveness**	**Incremental cost-effectiveness ratio (ICER)ǂ**	**ICER (USD)**	**Missed cases*** ***(1-sensitivity)***	**Overtreatment** ***(1-specificity)***
Syndromic Management	193.17	-	0.11	-	-	-	89,5%	4,0%
GIFT-SM	218.57	25.40	0.77	0.67	38.20	2.60	23,0%	29,0%
GIFT-Xpert-Microscopy	580.66	387.49	0.77	0.66	586.76 ¥	-	23.0%	0.1%
PCR-Microscopy	707.90	514.73	0.80	0.70	740.61	50.36	20.0%	-
Xpert-Microscopy	989.97	796.80	0.99	0.88	902.37	61.36	1,2%	0.5%

*Cost per women to diagnose and treat a single episode of disease
**Combined sensitivity of approach
ǂ Incremental cost/Incremental effectiveness; Incremental to standard of care (SM)
¥Dominated

Figure 2 provides a graphical depiction of the relationship between the incremental cost and effectiveness of each alternative and three hypothetical thresholds. All the ICERs appear in the first quadrant, revealing that each comparator presents a cost-effective option; being more both more effective and costly than its predecessor. The figure graphically shows that GIFT-SM is the most cost-effective of the three, having the lowest ICER. To make inference about the absolute cost-effectiveness of alternatives in the decision-making context, a cost-effectiveness- or willingness-to-pay (WTP) threshold is required. For a threshold lower than R38,20 (USD 2.60), none of the options would be cost-effective. Similarly, for a threshold above R740.61 (USD 50.36), but below R902.37 (USD 61.36), both GIFT-SM and PCR-Microscopy would be cost-effective.

There exists no standard threshold in South African but there have recently been attempts to estimate such thresholds. Woods *et al.*[50] estimated a cost-effective threshold of USD 1,175 – 4,714 (in 2013 prices) per DALY averted, while Meyer-Rath *et al.*[51] estimated a revealed WTP threshold of USD 547–872 per life year saved. However, the results of this study cannot be directly compared to these thresholds due to the lack of a mutual ICER comparator, and no definite conclusion on the absolute cost-effectiveness can thus be made. Nonetheless, an ICER of R38.20 (USD 2.60) per additional woman diagnosed and treated seems low in the South African context.

Figure 2: Cost-effective plane depicting base case ICERs and hypothetical cost-effectiveness thresholds



Since screening with GIFT gives an indication of genital inflammation only, the exact infection would still not be identified, and treatment can thus not be made more specific to minimise overtreatment. The GIFT strategies, however, show improvement in terms of identifying cases that is typically missed under the current standard of care (23% compared to 89.5%), albeit not as effective as PCR, Xpert and Microscopy.

Sensitivity Analysis

The cost of the GIFT test assay was varied 50% both ways to account for possible fluctuations in the current quoted prices as manufacturing is still underway. This rendered similar ICERs than the base-case scenario with no changes in the relative cost-effectiveness observed.

The time cost of administering GIFT to a patient was not explicitly factored into the cost study by Kairu[33] since time spent on this additional aspect of the clinic visit was regarded negligible. However, it was estimated that this screening process would take up to 20 minutes per patient (33). To test the effect of this assumption on the results, the personnel cost related to the GIFT strategies was varied upward across a reasonable range. These variations revealed that GIFT-SM becomes less cost-effective with an increase in personnel cost but remained the most cost-effective strategy in the model.

The cost of GeneXpert test assays was also varied with 50% both ways to account for exchange rate variability (upward) and the possibility that the GeneXpert machines can in some cases be provided to state institutions at subsidised prices (downward) (Gwen Stephens, *Ceipheid,* personal communication 2019, June 3). In this analysis, the relative cost-effectiveness also remained unchanged with the upward variation, but Xpert-Microscopy dominating PCR-microscopy when the cost was varied downward.

Since GIFT has not been validated in a pilot study, the base-case sensitivity of the device is based on the findings from the biomarkers study. Consequently, there exists a possibility that the device might have different sensitivity in practice. GIFT sensitivity was consequently decreased with 50% and increased to 100% to test this limitation. These variations did not affect relative cost-effectiveness of the comparators, although the ICER of GIFT-SM did increase with a decrease in sensitivity and vice versa.

Disease probabilities and LTFU were varied according to the highest and lowest estimates found in the literature. At both 11% and 29% average disease probability, the ICERs of each model comparator did not change significantly from the base-case scenario and the cost-effectiveness conclusions remained the same. When the LTFU was varied to 49%, GIFT-Xpert-Microscopy continued to be eliminated due to extended dominance. In addition, PCR-Microscopy was eliminated through absolute dominance by Xpert-microscopy.

Table 5: The impact of one-way sensitivity analyses on the cost-effectiveness results

	Incremental cost-effectiveness in 2019 ZAR			
	GIFT-SM	GIFT-Xpert-Microscopy	PCR-Microscopy	Xpert-Microscopy
Base case	38.22	Dominated*	740.61	902.38
COST PARAMETERS				
GIFT test assay				
+50%	41.79	Dominated*	740.61	902.38
-50%	34.65	Dominated*	740.61	902.38
GIFT personnel time				
+50%	161.30	Dominated*	740,61	902,38
+30%	112,06	Dominated*	740.61	902.38
+10%	62.83	Dominated*	740.61	902.38
GeneXpert Test assays				
+50%	38.22	Dominated*	740.61	1 194.18
-50%	38.22	Dominated*	Dominated**	610.57
PROBABILITIES				
GIFT sensitivity				
+27%	29.11	Dominated*	740.61	902.38
-50%	86.98	Dominated*	740.61	902.38
LTFU				
11%	38.22	Dominated*	655.84	902.38
49%	38.22	Dominated*	Dominated*	902.38
Disease probabilities				
11%	37.45	Dominated*	740.10	901.86
29%	39.13	Dominated*	741.22	902.99
Syndromic management sensitivity				
15%	40.99	Dominated*	791.89	950.83
23%	47.07	Dominated*	903.03	1051.18
HEALTH-SEEKING BEHAVIOUR				
Symptomatic women seeking care				
58.8%***	157.90	Dominated*	855.13	992.51
70%	125.37	Dominated*	824.00	968.01
Acceptance of screening test				
18.9%	7.22	Dominated*	740,61	902,38
25%	9.56	Dominated*	740,61	902,38
50%	19.11	Dominated*	740.61	902.38
70%	142.95	Dominated*	740.61	902.38

*Eliminated through extended dominance
** Eliminated through absolute dominance
***Survey included both male and female school learners.

Our model assumed that all women who have symptoms seek care under syndromic management and that all women who are screened accept the test administered to them. These assumptions were tested based on other studies and estimates found in the literature. Health care-seeking behaviour among women in South Africa remains limited to an extent and is typically worse in rural compared to urban settings (35). Estimates from two sources were used to test the health care seeking assumptions with further one-way sensitivity analyses. Firstly, Sahin-Hodoglugil (2003)[34] produced a baseline estimate of 70% of women seeking care for STIs. Secondly, the National Survey on youth risk behaviour was utilised. This survey revealed that 58.8% of the study population received treatment for a known STI. These variations did not change the relative cost-effectiveness of any of the strategies and GIFT-Xpert-Microscopy remained dominated. It did produce higher ICERs for the remaining strategies than in the base-case analysis, due to a decrease is the cost of the baseline strategy, syndromic management.

The assumption on screening acceptability was tested by introducing this parameter to the model and varying it based on estimates used in two studies conducted in the United Kingdom, due to lack reliable local estimates available for this study setting. This analysis results in a paradox since lower acceptance rates increases the relative cost-effectiveness of, but in reality, fewer health outcomes would be realised if fewer women agree to be screened, as in these scenarios. This is due to the structure of the model and ICER calculations. Care should be judging these estimates. To optimise this screening strategy, acceptance rates should be established and considered. No changes were, however, observed in the relative cost-effectiveness conclusions.

A single threshold analysis was also conducted on GIFT test sensitivity. Threshold analysis revealed that the GIFT+SM strategy would remain the most cost-effective unless the sensitivity of GIFT were to decrease to below 14.83%. The individual decision tree analyses revealed that GIFT-SM was still the most cost-effective strategies when looking at the diseases individually. For bacterial vaginosis, GIFT-Xpert-Microscopy is dominated by PCR-Microscopy with absolute dominance. For trichomoniasis, GIFT-Xpert-Microscopy was dominated by PCR-Microscopy through extended dominance.

Table 6: Results from separated decision trees

BV	**Incremental Cost (2019 ZAR)**	**Incremental effectiveness**	**ICER**
Syndromic management	-	-	-
GIFT-SM	27,76	0,67	41,43
GIFT-Xpert-Microscopy	504,71	0,67	753,30*
PCR-Microscopy	514,92	0,70	735,60
Xpert-Microscopy	796,88	0,90	885,42
CT	**Incremental Cost**	**Incremental effectiveness**	**ICER**
Syndromic management	-	-	-
GIFT-SM	25,08	0,63	39,75
GIFT-Xpert-Microscopy	370,14	0,63	586,59
PCR-Microscopy	514,83	0,66	778,87
Xpert-Microscopy	797,09	0,86	925,78
NG	**Incremental Cost**	**Incremental effectiveness**	**ICER**
Syndromic management	-	-	-
GIFT-SM	24,21	0,59	40,96
GIFT-Xpert-Microscopy	325,70	0,59	551,11
PCR-Microscopy	514,05	0,62	827,79
Xpert-Microscopy	796,03	0,82	969,59
TV	**Incremental Cost**	**Incremental effectiveness**	**ICER**
Syndromic management	-	-	-
GIFT-SM	25,50	0,59	43,14
GIFT-Xpert-Microscopy	348,87	0,56	619,36**
PCR-Microscopy	514,50	0,62	828,50
Xpert-Microscopy	796,35	0,79	1014,46
*Eliminated through absolute dominance **Eliminated through extended dominance			

Discussion

A significant proportion of women with STIs and/or BV remain untreated under syndromic management due to the asymptomatic nature of their infections. In our model, we compared the cost and effectiveness of four alternative STI and BV management strategies to this standard of care. These strategies were modelled for women aged 15-49 years.

The results from the economic evaluation suggest that the introduction of screening with the rapid GIFT device into the South African public health sector would be the most cost-effective way to improve care in this population and reduce the burden of STIs and BV, relative to other model comparators. Given the interaction with HIV/AIDS, reducing this burden can

significantly reduce the amount of new HIV transmission and infections. Introducing this screening approach can also aid in the identification of high-risk women to be put on pre-exposure prophylaxis programs for the prevention of HIV (Masson and Passmore, Personal Communication, 2018, November 18). According to Sahin-Hodoglugil *et al.*[31], the early treatment and prevention of curable STIs such as chlamydia and gonorrhoea can lead to significant health gains in a population.

The robustness of the cost-effectiveness results was tested in various sensitivity analyses. The conclusion remained the same in all the analyses with the ICER of GIFT-SM only increasing or decreasing and PCR-Microscopy eliminated by dominance in two cases. From the sensitivity analysis, testing the acceptance of GIFT screening by women arises as an opportunity for further study during the GIFT pilot study or other research in order to truly establish whether the approach could improve STI management or not.

Given that GIFT-SM does not render desirable health outcome in terms of overtreatment, PCR-Microscopy might be considered in high-risk of high-burdened settings to enhance STI management in such settings. However, although GIFT-SM is the least desirable in terms of overtreatment (see table 5), Lennard *et al.*[47] and Passmore, Jaspan and Masson[30] note that the other infections present in women that typically lead to a false positive result with GIFT, such as *Atopobuim*, *Prevotella, Shuttleworthia* and *Aerococcus*, are not detected by gold standard STI and BV tests. These organisms would, however, also respond to the antibiotics administered. This would result in unintended health gains not measured in this analysis.

However, Kairu[33] found that from a budget impact perspective the national roll-out of an annual, opportunistic screening intervention might not be feasible. Such an approach would provide a single GIFT screening to every woman, between the ages of 15 to 45 years, at a primary care health care facility, annually. Requiring up to 17% of the available budget for HIV/AIDS intervention, it is not likely to be prioritised amidst the array of existing and other new interventions. Nevertheless, tailor-made implementation strategies could be considered, such as implementing screening only in high-burdened or high-risk populations, to optimise the introduction of screening amidst the resource constraints faced by the Department of Health. Such strategies should be further researched for sound policy recommendations to be made.

To limit start-up costs, GIFT screening could be introduced alongside annual HIV testing programmes. The latter is a key objective of South Africa's National Strategic Plan for HIV, TB and STIs 2017-2020 (28). Alternatively, key populations should be identified for whom the approach should be initiated. Such populations could include women at high risk for STIs such as sex workers, HIV-positive persons, young adults or women residing in settings with known high disease prevalence. In this case, register-based screening (target individuals are identified through existing databases) could be useful or key screening questions could be set up to identify these individuals as they enter healthcare (opportunistic screening). Information system challenges might arise, however, and additional costs might arise where systems would need to be created or improved to ensure adequate record-keeping of screening history or to identify high-risk individuals.

The study faced various challenges and limitations, with the simplicity of the model of choice due to data constraints and the use of secondary data from varying sources likely being the most significant. The model was designed as a static, decision tree analysis that did not include any sequelae or long-term complications typically associated with STIs nor did we factor in re-infections. This might likely have led to the cost of having an STI or BV being underestimated. Adverse drug events were also not included due to the short-term nature of the analysis and would likely have underestimated the cost of treatment. On the contrary, the model did not include the potential benefits of HIV/AIDS prevention through STI treatment or the effect of increased diagnosis and treatment on STI prevalence in the population over time. This may have led to an underestimation of effectiveness of the screening interventions. To establish a more sophisticated, dynamic model that would be able to inform decision-making more comprehensively, future research should focus on estimating these parameters.

Furthermore, the effectiveness of GIFT was assumed to be the sensitivity and specificity found in a biomarker validation study and is potentially thus not a true representation of the effectiveness that would be yielded when implemented in the field. Although this assumption was tested in the sensitivity analysis, implementation challenges that may arise in the field may influence the model outcomes more than captured in the analysis.

CONCLUSIONS

Although syndromic management remains the most affordable approach to care, it is not adequately dealing with the massive STI and disease burden faced women South African women. Screening with gold standard and more rapid tests such as GeneXpert and microscopy, on the other hand, provides more desirable health outcomes in terms of women diagnosed and treated and limiting overtreatment, but it remains relatively expensive in this resource-constrained setting. The results from the economic evaluation suggest that the introduction of screening with the rapid GIFT device in the South African public health sector would be the most cost-effective way to improve STIs and BV care in women while simultaneously having positive effects on the HIV-epidemic. However, previous research suggests that national implementation may not be affordable within the South African context. This analysis presents a first attempt to establishing the cost-effectiveness of the various screening. It reveals that further research should be done on the feasibility of different implementation options within this resource-constrained setting. Furthermore, to enable the establishment of a more comprehensive and dynamic model research should focus on quantifying the effect screening for STIs would have on prevented HIV cases and STI disease probability and its consequent impact on the outcomes of the decision model.

List of abbreviations used

BV – Bacterial Vaginosis

GIFT- Genital Inflammation Test

HIV/AIDS- Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome

LTFU - Lost to follow-up

POC- Point-of-care

WHO – World Health Organization

STIs - Sexually Transmitted infections

USD- United States Dollar

ZAR- South African Rand

DECLARATIONS

Ethics approval

The study was approved by University of Cape Town Human Research Ethics Committee (HREC)

Consent application

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

This study was commissioned by the GIFT project. Both EVDW and ES received remuneration for this work and worked as external consultants.

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Authors' contributions

EVDW analysed and interpreted the cost and effectiveness data for the model comparators and was the major contributor in writing the manuscript. ES contributed in study design, data analysis and interpretation of the findings. All authors read and approved the final manuscript.

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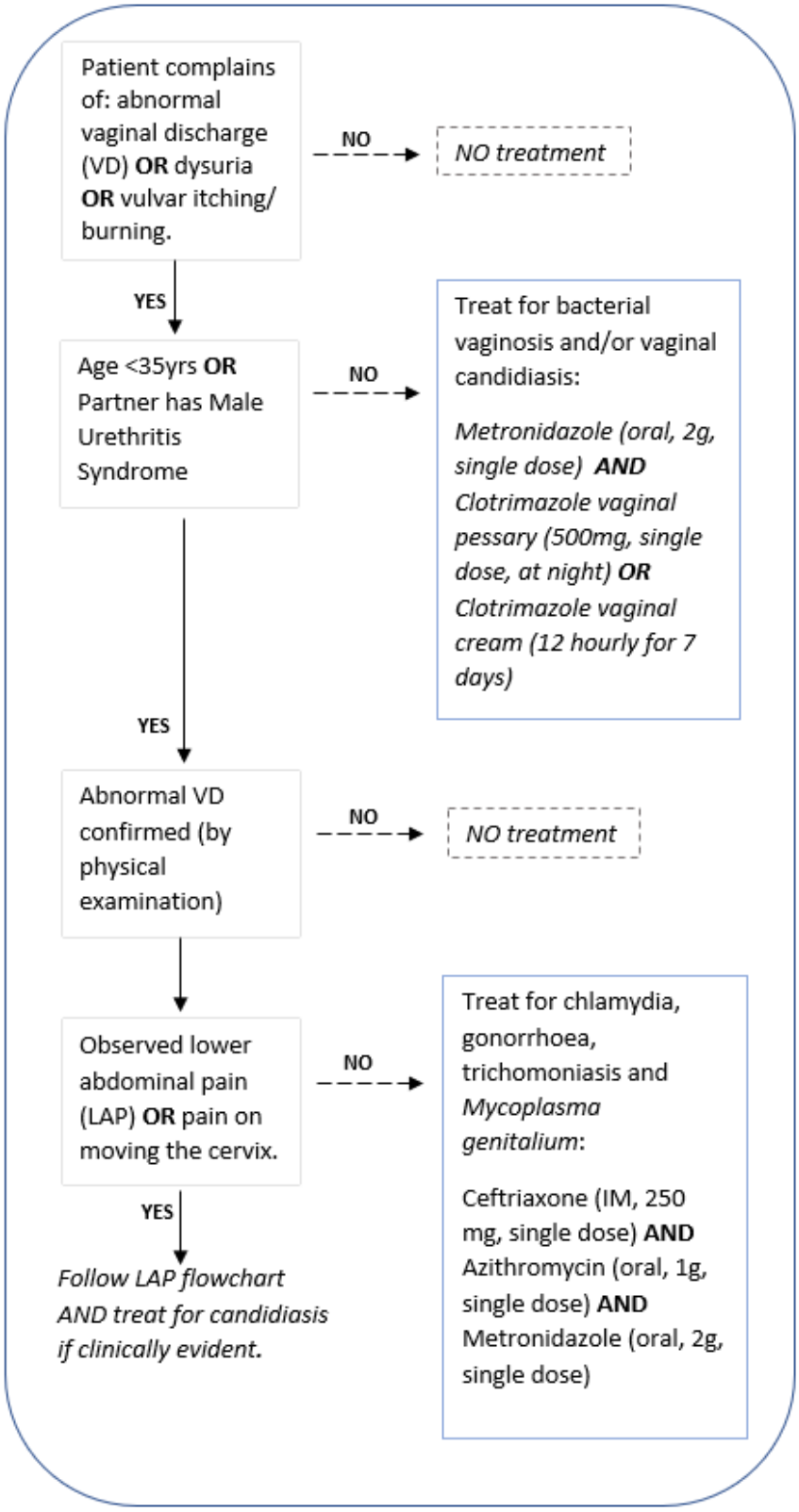
APPENDIX A

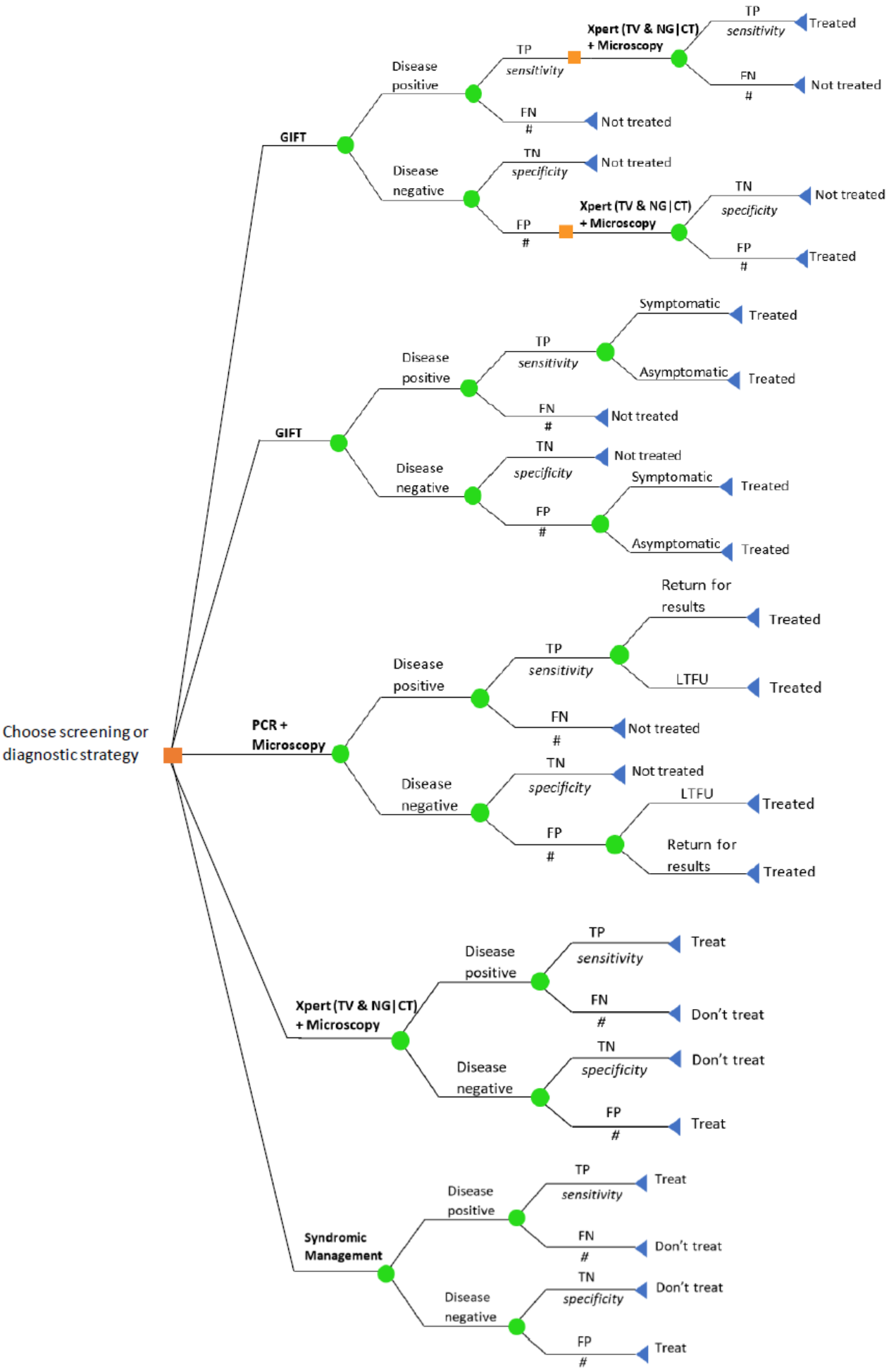
A.1. South African Vaginal Discharge Syndrome flowchart*



Source: Adapted from Department of Health[46]

*Based on WHO recommendations, but modified for country-specific use

A.2. Decision tree



PART D: POLICY BRIEF

HEALTH ECONOMICS UNIT

POLICY BRIEF

October 2019

THE COST-EFFECTIVENESS OF RAPID POINT OF CARE SCREENING FOR SEXUALLY TRANSMITTED INFECTIONS AND BACTERIAL VAGINOSIS IN SOUTH AFRICA

Is genital inflammation screening of women a cost-effective option for STI management in primary health?

KEY POINTS

- The co-burden of STIs and HIV remains a large burden on the South African public health system and women are disproportionately affected.
- Many STI and BV cases are missed under the current standard of care.
- Screening women at primary health care level can improve the management of female sexual and reproductive health.
- GIFT provides a possible solution to diagnose and treat significantly more women at a reasonable extra cost of R38.22 per additional diagnosed and treated women.
- Given that national rollout is unaffordable under the current health care budget, different implementation strategies should be further researched.

SEXUALLY TRANSMITTED INFECTIONS AND BACTERIAL VAGINOSIS IN SOUTH AFRICA

South Africa houses one of the largest burdens of sexually transmitted infections (STIs) and bacterial vaginosis (BV) in the world (1). Coupled with the widespread HIV epidemic, the country faces a significant public health challenge (2). This double burden of disease disproportionately affects the female population. It is estimated that at least 25% of South African women are infected with a bacterial STI and women are up to eight times more likely to acquire HIV than men (3,4). The majority of STI and BV cases in women do not, however, have any recognisable symptoms and consequently do not seek care (5). Failure to treat, or delaying treatment of STIs and BV can lead to various sexual and reproductive health complications and can facilitate the acquisition and transmission of HIV (6).

The public health system serves around 84% of the population, therefore the vast majority of this burden rests on Department of Health resources (7). In this system, most STIs are managed syndromically, rather than with resource-intensive etiological diagnosis. Under this approach developed and endorsed by the World Health Organization (WHO) for resource-constrained settings, syndromes of a specific STI or BV are identified according to pre-identified groups of signs and symptoms. Patients are then provided with treatment that will address the majority, or the most serious, of organisms typically associated with the identified syndrome (8).

Gold standard diagnostic tests for STIs and BV remain expensive in the South African context. Strides have, however, been made in the development of more rapid, point-of-care (POC) tests using the same technology as laboratory-based gold standard tests. Tests such as Cepheid's GeneXpert test assays for different STIs have been developed and are commercially available in South Africa. These tests are ideally performed in the health care facility and can present results in roughly 90 minutes (9,10). Researchers at the Division of Medical Virology at the University of Cape Town recently developed another rapid POC; GIFT (Genital Inflammation Test). GIFT is a relatively inexpensive, cytokine rapid test that detects inflammatory bacteria in the female genital tract. STIs and BV cause genital inflammation, regardless of other symptoms such as vaginal discharge or genital ulcers being present. The measurement of key inflammatory cytokine biomarkers with a rapid POC test can thus potentially identify asymptomatic cases that are otherwise missed and consequently, women who are at an increased risk of acquiring and transmitting HIV (Masson and Passmore, Personal Communication, 2018, November 18). This study follows a cost estimation and budget impact analysis conducted by Kairu[11] which found that national implementation of GIFT screening would require up to 17% of the available budget for HIV/AIDS, suggesting that it would be unaffordable under the current budget.

DESCRIPTION OF STUDY

The study was conducted to establish whether screening with the newly developed GIFT device would be a cost-effective approach to STI and BV management for women in the reproductive age from the viewpoint of the South African Department of Health. A cost-effectiveness study, in the form of a decision tree analysis, was conducted from the perspective of the Department of Health the provider of health services. Five different screening and diagnostic approaches were modelled for detecting BV, chlamydia, gonorrhoea and trichomoniasis women in the reproductive age (15-45 years).

Screening Strategies

6. Syndromic management of symptomatic women seeking healthcare
7. Screening all women entering primary care facilities with GIFT followed by syndromic management for GIFT-positive cases
8. Screening with GIFT followed by testing with GeneXpert NG/CT and GeneXpert TV assays and microscopy for GIFT-positive cases
9. Screening with GeneXpert (NG/CT and TV) and microscopy alone
10. Screening with gold standard laboratory testing

(NG = *Neisseria gonorrhoea*; CT = *Chlamydia trichomonas*)

To establish the relative cost-effectiveness of these five strategies, the incremental cost-effectiveness ratio (ICER) was obtained for each. This was measured as the additional cost incurred per women diagnosed and treated for BV, chlamydia, gonorrhoea and trichomoniasis.

Relevant cost and effectiveness data, as well as the probability of model events, were obtained from various published and unpublished sources. Cost estimates included all clinic-level capital and recurrent costs associated with each strategy for diagnosing and treating a single episode of disease. Effectiveness was based on the relative sensitivity and specificity measures of the diagnostic test(s) or clinical approach.

KEY FINDINGS

Although syndromic management remains the least expensive approach to STI management, it leaves many STI and BV cases (up to 89.5%) (12) undiagnosed due to the high number of asymptomatic infections in women. Nevertheless, expensive gold standard etiological diagnosis in off-site laboratories remains unfeasible in the South African context due to resource-constraints.

The results from the analysis revealed that screening with GIFT and following with syndromic management-based treatment for positive cases was the most cost-effective approach in the model. It rendered an ICER of R38.22 per women diagnosed and treated. GIFT followed by GeneXpert and microscopy was dominated by GeneXpert and microscopy alone. Strategies 4 and 5 rendered ICERs between of R740.61 and R902.38 respectively.

Screening women at primary health care level can thus improve the management of female sexual and reproductive health by identifying asymptomatic cases. At a relatively low additional cost per women, much greater health gains can be made in the management of STIs and BV in women, in comparison to the standard of care. It can also aid in the prevention of HIV, not just by diminishing opportunities for STI- or BV-associated transmission and acquisition, but also by identifying women to be placed on pre-exposure prophylactic drugs. Such screening can also assist with identifying index cases for partner-notification (Masson and Passmore, Personal Communication, 2018, November 18).

KEY CONCEPTS

Bacterial Vaginosis: Vaginal disorder characterised by the depletion of hydrogen peroxide producing lactobacilli in the vaginal tract caused by an imbalance in the ecology of normal vaginal flora.

Cytokines: Proteins secreted by cells of the immune system that affect communication and interaction between cells. To regulate the bodies response to trauma or disease. Inflammatory cytokines promote infection.

Cost-effectiveness: When the benefits of an intervention is worth at least what is paid for them.

ICER: The ratio of incremental cost to incremental effectiveness of interventions considered in the model. Commonly expressed as the additional cost per each additional effect derived from an intervention, in comparison to the standard of care.

Dominated strategy: an alternative which renders higher incremental cost but lower effectiveness than previous less costly strategy or which delivers an ICER higher than the next more costly strategy.

Opportunistic vs. register-based screening: Opportunistic screening refers to annual otherwise periodic screening provided during non-STI related healthcare visits. Register-based screening involves individuals being contacted and invited for testing based on identified risk factors.

POLICY IMPLICATIONS AND RECOMMENDATIONS

- Current syndromic management guidelines are not effective in handling the massive burden of disease faced women South African women.
- Introduction universal opportunistic annual screening for all women between the ages of 15 and 45 years entering primary health care clinics could improve health outcomes but is not affordable given current budget constraints.
- Focused implementation strategies could be considered, such as introducing the intervention in high-risk population. Such populations could include women at high risk for STIs such as sex workers, HIV-positive persons, young adults or women residing in settings with known high disease prevalence. This would require register-based screening to identify individuals based on medical history or presenting key screening questions to identify individuals as they enter healthcare (opportunistic).
- To ensure optimal coverage of the target population, sound information systems would need to be in place to ensure adequate record-keeping of screening history and to identify high-risk individuals in the case of register-based screening.
- Efforts should be taken to establish the acceptability of screening in the target population, before implementation. The GIFT pilot study could be an opportunity for such research.

CONCLUSION

The South African public sector succumbs to the combined burden of curable STIs, BV and HIV which disproportionately affects the female population. The newly developed rapid POC, GIFT, provides a promising tool with which to improve STI and BV management at primary care level. The results from this study indicate that implementing screening with GIFT could be a cost-effective option for the Department of Health to diagnose many cases which would typically be missed under the syndromic management due to their asymptomatic nature. Implementing a universal, annual GIFT screening for all women entering primary health care in the public sector would significantly improve detection and treatment of STIs and BV. However, the feasibility of this remains doubtful within the constrained health budget . Alternative strategies, such as screening high-risk women only, could be considered. Further research is required to supplement decision-making.

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APPENDIX 1: Author guidelines for journal article submission

BMC COST-EFFECTIVENESS AND RESOURCE ALLOCATION

Research article

Criteria

Research articles describe country-level or international primary research on the costs, effectiveness, or cost-effectiveness of (single or combined) interventions.

Cost Effectiveness and Resource Allocation strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories.

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The information below details the section headings that you should include in your manuscript and what information should be within each section.

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The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study

- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

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- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

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All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate

and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

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- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
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All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

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Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Medicine. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

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Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Figures, tables and additional files

See General formatting guidelines for information on how to format figures, tables and additional files.

APPENDIX 2: Human Research Ethics Council: Study approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
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Observatory 7925
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

26 February 2019

HREC REF: 086/2019

Prof Edina Sinanovic
Health Economics Unit
Public Health & Family Medicine
Falmouth Building

Dear Prof Sinanovic

PROJECT TITLE: COST-EFFECTIVE OF DIFFERENT SCREENING STRATEGIES FOR SEXUALLY TRANSMITTED INFECTIONS AND BACTERIAL VAGINOSIS AMONG WOMEN IN CAPE TOWN. (MASTERS CANDIDATE: MS ELISE VAN DER WALT)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Elise van der Walt will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637

HREC 086/2019