Improving the management of sexually transmitted infections among pregnant women in sub-Saharan Africa

An evaluation of the syndromic management of sexually transmitted infections

and

An economic evaluation of costs and health consequences of the existing versus new chlamydia management strategies

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Dissertation for the degree Philosophiae Doctor (PhD)

2008

Faculty of Medicine, University of Oslo, Norway

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 784

ISBN 978-82-8072-319-2

Cover: Inger Sandved Anfinsen.
Printed in Norway: AiT e-dit AS, Oslo, 2009.

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Acknowledgements

"Improving public health control of sexually transmitted diseases in Botswana" was one of several institutional collaboration projects within the Health Sector Agreement between Norway and Botswana. I want to express my gratitude to the institutions involved in planning and conducting this study: The Health Research Unit, the AIDS/STD Unit and the National Health Laboratory in the Ministry of Health in Botswana and the University of Oslo, Norway. I am indebted to the Health Sector Agreement which covered the cost of the field work, and to the Norwegian Research Council for funding a doctoral fellowship.

This story started more than a decade ago, and there are many people who have been important to me or to the project in this period. First, Johanne Sundby picked me up back in 1996, when I was a student and wanted to "do something" in Africa. She sent me to Botswana to participate in the field work of a planned study on STIs, which later led me to conduct the current study. Johanne has been, and still is, an inspiring co-supervisor who has given me a lot more than she formally needed to. Per Hjortdahl has been my main supervisor and guided me through the project with his long research experience. He has been present when I have needed him and at the same time allowed me independence and opportunity to make this my own research. Professor Ivar Sønbø Kristiansen has been an informal, though committed supervisor of the economic evaluation in this thesis. He has without exception generously shared his time as if it was an unlimited resource.

In Botswana, Mr. Khulumani in the Health Research Unit and Dr. Rahman in the AIDS/STD Unit provided valuable contributions to formal and organizational aspects of the study. Dr. Rahman has been a key person, being the head of the STD Unit and in charge of the national STD program. Mrs. Velauthapillai, head of the Microbiology

Department at the National Health Laboratory, has been enthusiastic to this project from the start, aspiring to improve the diagnostic aspects of STI management. She has been a hard working study partner, and she still is a good friend. The laboratory performed all analyses on top of their routine work, and I want to thank the staff explicitly for their assistance. I also want to thank the staff at the Government Clinics for their cooperation, and not least: the pregnant women who volunteered to participate in the study.

I'm forever in debt to my father, Tor Inge Romøren, for being an informal, though ideal co-supervisor; with his never-ending, enthusiastic support and his always useful, always pedagogic feedback. Thanks to both my parents for practical, emotional *and* financial support; in fact I was granted an "m&d fellowship" the first half year in Botswana when I was hoping to get funds from the Research Council. Elise Klouman came in rather late in the project, but with her PhD on STIs in Tanzania, she is the person to whom I have felt closest when it comes to field of interest. I have sincerely enjoyed being on the same wavelength as her during discussions and manuscript revisions. Bjarne Robberstad and the Health Economics Bergen (HEB) at the University of Bergen introduced me to economics in health care. Robberstad has impressed me by his capability and competence, and by choosing to spend his resources on the health challenges in sub-Saharan Africa. His PhD thesis has been very inspiring.

I am indebted to the Faculty of Medicine who admitted me to the PhD program. I have been provided office facilities at the Section for General Practice, in a milieu of academic general practitioners whom I sincerely respect. This has been very inspiring when looking for the road ahead, thanks to all of you! Then a thank to Magne Thoresen for statistical assistance, to Torbjørn Fosen Wisløff for assistance with the technical

modelling, and to Morten Ariansen for always providing valuable data support when more or less desperately needed. Tore Steen and Fatima Hussein have been valuable “persons on site” when I have been in Oslo and needed information from Botswana. I also want to mention Eelco and Nelly Boonstra who stayed in Maun in 1997. I’ll never forget how they welcomed me and served “brunost” when I had had my very first experience alone in rural Africa...

I met my husband to be, Jon Mordal, when I came back after my first year in Botswana. He joined me on my second stay, and played tennis and worked as a car mechanic while I was doing my fieldwork. Thank you for sharing my ups and downs throughout the PhD process! Obviously more important is my gratitude for your willingness to share your life with me, but that’s another story. Last, I have enjoyed the flexibility of being PhD student, which in the first years meant the possibility to pack for a trip to Jotunheimen whenever the weather forecast was good. I have been even more happy to have this position during the last four years - while having small children. It has allowed me to spend a lot more time with Elias and Kristin than I would as an average doctor, which currently feels more important than anything.

Oslo, November 2008

Summary

Sexually transmitted infections (STIs) are a major health problem in many parts of the developing world. STIs cause substantial morbidity and mortality, which disproportionately affect women. Because many of the complications are pregnancy-related (1, 2), adequate diagnosis and effective treatment of STIs in pregnancy is critical. Additionally, there is substantial evidence that the presence of other STIs increases both HIV infectiousness and susceptibility (3, 4), and a long-term STI-control program is emphasized as one of the cornerstones of HIV prevention (5). Striving for optimal strategies and high performance in the STI program is essential; in countries where health care budgets are limited, the potential for improvement is often larger and can have a substantial effect on the overall burden of disease.

In countries without laboratory support, the diagnosis and treatment of STIs are based on the syndromic approach, in which simple flowcharts (usually called algorithms) are used to classify presenting symptoms and clinical signs into defined syndromes (6). Asymptomatic patients are not diagnosed with this strategy – thereby risking the development of complications and transmission of the infection. Low specificity results in high levels of overtreatment, which increases drug costs and the risk of drug resistance. Patients who are diagnosed and treated with an STI they don't have, unnecessarily experience anxiety, stigma, and side effects of drugs. The strategy relies heavily on the quality of care provided, and it is a recognized problem that health care providers frequently fail to follow the guidelines (7-10). Also, STI clients who actually are adequately assessed must overcome a series of hurdles before they can be considered cured: obtain prescribed drugs, comply with treatment, and ensure that their partners are treated to

avoid reinfection (11). There has long been a consensus that for chlamydia and gonorrhoea, simple, affordable and preferably on-site tests are needed to improve the management (12). Major progress has recently been made, and several tests are now on the market.

This study has two components. In a cross-sectional study, 703 antenatal care (ANC) attendees were interviewed and examined, and specimens were collected to identify the prevalence of *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis,* bacterial vaginosis, *Candida* species and syphilis. We evaluated the syndromic approach for the detection of vaginal and cervical infections in pregnancy, and determined if risk scores could improve the diagnostic accuracy. Subsequently, we used data from the epidemiological study to conduct an economic evaluation of the STI management. A decision analytic model was developed to compare the costs and health consequences of using point-of-care (POC) tests versus syndromic management to diagnose chlamydia among antenatal care attendees in sub-Saharan Africa, using Botswana as a case. In this analysis we also compared erythromycin with azithromycin treatment and universal with age-based chlamydia management. We chose to focus on chlamydia, which is more common than gonorrhoea in this population, but the model can be adapted to the economic evaluation of the management of other STIs such as gonorrhoea and trichomoniasis.

The aim of the first paper in this thesis is to draw attention to the effectiveness (or the lacking effectiveness) of the extensive prescription of antibiotics to STI patients in Botswana and to discuss possibilities for improving the cure rates. We found that many of the women had a history of STI symptoms in their current pregnancies and had been prescribed STI treatment. There was no significant difference in the prevalence of chlamydia among the women who had and the women who had not been prescribed

erythromycin four times daily for ten days. Contrarily, none of the women who had been prescribed a single dose of ceftriaxone had gonorrhoea. The different effectiveness between the two drugs may reflect low compliance with the complex erythromycin regimen. We conclude that interventions to increase compliance could improve cure rates, and the use of a simpler drug regimen should be considered when low compliance is likely. This is discussed in the economic evaluation.

In paper two and three, we evaluate the syndromic approach, and discuss that diagnosis and treatment of cervical and vaginal infections among pregnant women in sub-Saharan Africa presents major challenges. Chlamydia and gonorrhoea were found in one out of ten of the pregnant women in the cross-sectional study, whereas one of two had trichomoniasis or bacterial vaginosis. Although in extensive use, the syndromic management is not suited to detect these conditions among pregnant women. The high prevalences among women who had gone through routine antenatal care, as well as the evaluation of the syndromic approach for study purposes, indicate that management guidelines for trichomoniasis and bacterial vaginosis in antenatal care should be revised. For chlamydia and gonorrhoea, the conclusion is even clearer: Without diagnostic tests, there are no adequate management strategies for cervical infections in pregnant women in Botswana, a situation which also is likely to apply to other countries in sub-Saharan Africa.

The results of the economic evaluation of chlamydia management are presented in the last paper. Azithromycin was less costly and more effective than was erythromycin. The specific POC tests resulted in more cases cured than the syndromic approach, substantially reduced the overtreatment with antibiotics and improved partner management. The incremental costs of POC tests appeared acceptable, especially when testing was restricted

to younger women. Our findings indicate that changes in the management of chlamydia among pregnant women in sub-Saharan Africa have the potential to improve people's health, reduce unnecessary costs and improve the cost effectiveness of the current strategy.

List of abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
CBA	cost benefit analysis
CEA	cost effectiveness analysis
CER	cost effectiveness ratio
CUA	cost utility analysis
CI	confidence interval
HIV	human immunodeficiency virus
ICER	incremental cost effectiveness ratio
LCR	ligase chain reaction
CHOICE	*cho*osing *i*nterventions that are *c*ost *e*ffective
LR+	positive likelihood ratio
LR-	negative likelihood ratio
NHL	national health laboratory
NPV	negative predictive value
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
POC	point of care
PMTCT	preventing mother to child transmission (of HIV)
PPV	positive and negative predictive value
ROC	receiver operating characteristics
RTI	reproductive tract infection
SA	syndromic approach
SDI	Sexually Transmitted Diseases Diagnostics Initiative
STI	sexually transmitted infection
VDS	vaginal discharge syndrome
WHO	world health organization

List of papers

1. **Romoren** M. Rahman M. Sundby J. Hjortdahl P. **Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana.** *Sexually Transmitted Infections 2004, 80:395-400.*
2. **Romoren** M. Velauthapillai M. Rahman M. Sundby J. Klouman E. Hjortdahl P. **Trichomoniasis and bacterial vaginosis in pregnancy: inadequately managed with the syndromic approach.** *Bulletin of the World Health Organization 2007, 85:297-304.*
3. **Romoren** M. Sundby J. Velauthapillai M. Rahman M. Klouman E. Hjortdahl P. **Chlamydia and gonorrhoea in pregnant Batswana women: time to discard the syndromic approach?** *BMC Infectious Diseases 7:27, 2007.*
4. **Romoren** M. Hussein F. Steen TW. Velauthapillai M. Sundby J. Hjortdahl P. Kristiansen IS. **Costs and health consequences of chlamydia management strategies among pregnant women in sub-Saharan Africa.** *Sexually Transmitted Infections 2007, 83:558-566.*

Background

Global inequity in health care

The geographical distribution of financial resources for health is uneven. The 30 member countries of the OECD make up less than 20% of the world's population, and spend 90% of the world's resources on health (13). Poorer regions, such as Africa and South-East Asia, account for more than 50% of the global burden of disease, but spend about 2% of the global resources. In sub-Saharan Africa, the health challenges seem unmanageable in their number and degree of seriousness. The region has the highest child and adult mortality in the world, with the HIV/AIDS epidemic representing the highest burden of disease (14).

The Millennium Development Goals

In September 2000, 189 countries committed to accelerate development in poor countries by endorsing an interrelated set of development goals; the Millennium Declaration (15). Improving health received considerable prominence. Three of the eight goals focused on reducing key causes of mortality in poor countries: maternal and perinatal conditions, diseases affecting children and infants, and major communicable diseases including HIV/AIDS (16). When evaluating the status five years after the declaration, progress was disappointing, particularly in sub-Saharan Africa, where life expectancy has actually fallen in many countries (17). Wars, political instability and corruption have all contributed in different settings, but a common factor has been the lack of resources. Total health expenditures per capita from all sources did not reach $20 in 29 of the poorest countries in 2002, and an additional $13-25 per person a year is required immediately (16).

With regards to the lack of monetary resources, the need to increase the funding for health care is one of two major policy issues (16-18). Accurate costing is necessary, as well as active planning of practical actions that need to be undertaken, including raising the necessary funds (19). Making best use of available resources is equally important. If countries are to have any chance of achieving their goals, they need to re-evaluate the existing strategies to determine whether more could be achieved with the resources already available (16). It is likely that improvements in health could be achieved immediately by replacing less effective strategies with more effective ones. Further, the health worker crisis must be addressed. According to the World Health Report 2006, there are 57 countries with critical shortages equivalent to a global deficit of 2.4 million doctors, nurses and midwives (20). Again, the crisis is proportionally largest in sub-Saharan Africa. Inadequate skill mixes and distributional imbalances participate to the problem, and "the exodus of skilled professionals in the midst of so much unmet needs places Africa at the epicentre of the global health workforce crisis".

Priority setting in developing countries

In this first decade of the 21st century, immense advances in human well-being coexist with extreme deprivation (20). In all economies, budgets are insufficient to meet all health care needs - and demands (21). For decision makers in resource poor settings, making best use of the resources is a vital, yet extremely difficult task with serious consequences for people's health and public health. A basic criterion in priority setting in health is the societal wish to maximize general population health given the available resources (22). Many societies also want to distribute resources to reduce health inequalities, by giving

high priority to interventions that target poor, children, or severely or chronically ill people. Next, the society may have specific preferences such as providing acute care in life threatening situations.

Although societies may have explicit objectives and strategies for the health system, priority setting of health interventions is often ad-hoc, and resources are not used to an optimal extent (22). An underlying problem is that multiple criteria play a role and decisions are complex (23). Policy makers face not only budgetary, but also practical constraints, such as the availability of health personnel – a considerable challenge in developing countries (24). Interests groups exercise their influence on policy makers to prioritize interventions according to their preferences, and policy makers may act in order to maximize political support. Policy makers in developing countries may also follow funding preferences of international organizations or donor communities (22).

The role of economic evaluations

The systematic approach of economic evaluations has the potential to contribute to an informed debate and a more rational and transparent priority setting(22). The breakthrough for the use of economic evaluations in developing countries came with the 1993 World Development Report, Investing in Health (1, 18). The actual use and impact of cost-effectiveness analyses face numerous challenges, especially in developing countries. A number of technical and implementation problems have been experienced, such as the heterogeneity of methods and outcome measures, complicating the synthesis and interpretation of cost-effectiveness results (24).

Since 1998, the CHOICE project in the World Health Organization (WHO) has worked with assembling regional databases on the costs, impact on population health and cost-effectiveness of key health interventions (http://www.who.int/choice/en/). Their 'generalized cost-effectiveness analysis' uses a common set of tools and methods to allow comparability of strategies and interventions within maternal, neonatal and child health, HIV/AIDS, tuberculosis and malaria (25). The desired usefulness of this information for health policy and planning is in assessing if current intervention strategies represent an efficient use of the available resources, and which of the potential additional interventions that are not yet implemented, or not implemented fully, should be given priority on the grounds of cost-effectiveness (24). However, knowledge gaps are numerous and wide for health interventions and economical evidence still lacks for important disease groups, particularly for historically marginalized services and currently under-served populations (24). For the disease groups that happen to be covered, evidence is missing or inadequate for many of the relevant alternatives (18).

STI management in sub-Saharan Africa

The evaluation of the syndromic approach for the detection of vaginal and cervical infections in pregnancy is based on our epidemiological study from Botswana, whereas the economic analysis on costs and benefits of chlamydia management strategies is partly based on these data. It is our explicit wish that our results will be useful for other countries in sub-Saharan Africa. The antenatal care framework and the STI management are similar in these countries as well as in other developing countries (Box 1). In the WHO's epidemiological grouping of countries, Botswana is within the Afr-E region; sub-Saharan

African countries with very high adult and high child mortality rate. Botswana is simultaneously, along with Gabon, South Africa and three islands, classified as an "upper middle income" country, whereas the remaining countries in sub-Saharan Africa are classified as "lower middle income" or "low income" countries (26). Due to their relative wealth and a well functioning primary health care, Botswana may have the possibility to explore new health interventions and act as an example to more resource constrained settings.

Box 1 HIV/AIDS, STIs and antenatal care in sub-Saharan Africa

Sub-Saharan Africa: Since the end of the last Ice Age, the north and sub-Saharan regions of Africa have been separated by the extremely harsh climate of the sparsely populated Sahara. Today, sub-Saharan Africa (in red) is a term used to describe those countries of the African continent that are not considered part of the political North Africa (27). There are 42 countries in sub-Saharan Africa, located in Central, East, West and Southern Africa, and six islands. Generally, sub-Saharan Africa is the poorest region in the world, and home to 34 of the world's 49 least developed countries. The region will continue to need the highest per capita levels of technical and financial support of any region, along with sustained political commitment by all stakeholders, if it is to make major progress towards meeting the Millennium Development Goals by 2015 (28).

HIV/AIDS: Sub-Saharan Africa is the region in the world most seriously affected by HIV/AIDS, with AIDS remaining the leading cause of death. Examinations by UNAIDS and WHO of global and regional trends suggests the pandemic has formed two broad patterns: generalized epidemics sustained in the general populations of many sub-Saharan African countries, especially in the southern part of the continent; and epidemics in the rest of the world that are primarily concentrated among populations most at risk, such as men who have sex with men, injecting drug users, sex workers and their sexual partners.

STIs: The world's highest rates of new STI cases per 1 000 population occur in sub-Saharan Africa (29). The high prevalence and incidence of STIs can be explained by a variety of social, cultural, and economic factors, patterns of sexual activity, and lack of access to

appropriate treatment. As in other developing countries, the diagnosis and treatment of STIs in sub-Saharan Africa is mainly based on the syndromic approach guidelines.

ANC: In sub-Saharan Africa, fully 68% if women report at least one antenatal visit (30). The ANC coverage in Botswana, Cape Verde and Zambia is extremely high, above 95%, and ten additional countries are all above 90%. Of the women who receive antenatal care, 36% attend 2-3 times, 54% attend four or more times. A key objective of maternal health care programs has been to ensure that women present for antenatal care early in pregnancy in order to allow enough time for essential diagnosis and treatment regimens such as treatment of STIs and management of anaemia. Unfortunately, women in the region are most likely to wait until the second trimester, and a substantial proportion present only in the third trimester.

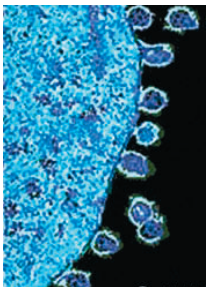
Introduction

Sexually transmitted infections in sub-Saharan Africa

Sexually transmitted infections (STIs) are highly prevalent in the developing world. WHO estimated that 340 million new cases of gonorrhoea, chlamydia, trichomoniasis and syphilis occurred throughout the world in 1999 in men and women aged 15-49 years (29). Sub-Saharan Africa has the highest worldwide prevalences of these infections, which are major causes of morbidity, particularly in women (31). STIs can cause acute symptoms, but a large number of infections are asymptomatic. Both symptomatic and asymptomatic infections can lead to the development of serious complications such as pelvic inflammatory disease, ectopic pregnancy and infertility. For pregnant women and their offspring, there is a risk of additional complications: intrauterine growth retardation, pre-term birth, perinatal morbidity and mortality, and postpartum upper genital tract infections (32).

The advent and increase of HIV infection has further highlighted the importance of STIs as a major problem. Epidemiological and biological studies have shown that other STIs and non-communicable reproductive tract infections (RTIs) can enhance HIV transmission (Box 2). Consequently, UNAIDS and WHO have recommended that high priority be given to the development of STI control program s, as one of the most important interventions for curbing the spread of HIV/AIDS (33, 34). To explore cost-effective alternatives or additions to existing STI strategies is therefore of high relevance to health policy at both national and international levels.

Box 2 The relationship between STIs/RTIs and HIV-transmission



HIV particles budding from a human cell

There is compelling biological and epidemiological evidence that both ulcerative and non-ulcerative STIs/RTIs are co-factors for HIV-transmission (35). Numerous studies have examined the biological plausibility of the association. Among HIV positive individuals, other STIs/RTIs increase HIV infectiousness by increasing HIV shedding in the genital tract, probably by recruiting HIV-infected inflammatory cells as part of the normal host response (36). Treatment of these infections reduces the HIV-concentrations in genital fluids to levels that are not significantly different from those among controls without the STI. In pregnancy, genital HIV shedding has an additional dimension, the potential for increased transmission from mother to child during delivery. Among HIV-negative individuals, STIs/RTIs appear to increase susceptibility to HIV by recruiting HIV target cells to the genital tract. Ulcerative STIs also increase the infectivity with HIV and susceptibility to HIV through disrupted mucosa and bleeding (36).

Cohort studies of HIV seroconversion have estimated the increase in the risk of HIV infection associated with specific STIs/RTIs or STI syndromes, and community level intervention studies have measured the effect that STI treatment can have on HIV incidence. However, estimating the proportion of HIV-infections attributable to STIs/RTIs, and further, preventable by treating STIs/RTIs, is methodologically challenging, and studies differ in their findings (37). The community based randomized trial in Mwanza, Tanzania found a 38% reduction in HIV incidence in communities where syndromic STI management was strengthened, and concluded that this intervention is highly cost-effective (an estimated cost of $10 per DALY saved) (38). A community based randomized trial in Rakai, Uganda, showed that mass treatment of STIs reduced the STI prevalence, but found no difference in HIV incidence between the study arms (39). Lack of agreement between studies may be explained by unobserved differences such as varying degrees of exposure bias and confounding (37). The importance of STIs/RTIs on new cases of HIV in a population will also be dependent of the phase of the HIV epidemic, the sexual networks, the RTI/STI under study and the STI management strategy (36, 40).

Management of STIs in developing countries

Most of the serious health problems caused by STIs and RTIs are preventable. Communities with good access to effective preventive community interventions and improved treatment services have lower rates of STIs/RTIs and their complications than communities where services are poor, disrupted or not used by people at risk. Reducing the burden of STIs requires a broad spectrum of activities, ranging from education and labour policies to good clinical management (Box 3).

Box 3 Components in STI/RTI control at the community level (41)

- Economic and social policies that reduce family separation may reduce risk and vulnerability.
- Education and employment opportunities for girls reduce the economic pull of sex work, empower women and reduce STI risk.
- Raise awareness of STI/RTI symptoms and complications, as well as how they can be prevented – especially among populations who may be at high risk.
- Promote safer sexual practices – including consistent condom use, fewer partners, and delaying sexual onset.
- Ensure easy access to condoms.
- Preventive and treatment interventions targeting vulnerable groups such as sex workers.
- Reducing barriers such as cost, distance, limited clinic hours and long waiting times means better access to care.
- Promotion of improved health care services will convince more people to use services.
- Screening and case finding of asymptomatic or less obvious infections when possible
- Manage symptomatic STI/RTIs effectively.
- Counsel patients on staying uninfected after treatment. Encourage them to comply with treatment, assist with partner notification and treatment, and reinforce prevention.

Diagnosis and treatment of STIs in the developing world is usually limited to the *syndromic approach*. As early as in the 1970s, public health physicians, especially those working in Africa, became interested in testing simple clinical tools for controlling and treating STIs (42). This resulted in the design and promotion of "syndromic management" guidelines by the World Health Organization in the beginning of the 1990s (6). The

syndromic approach is developed for the management of *symptomatic* STI patients, in countries where accurate laboratory diagnosis is out of reach. With the use of simple flowcharts, usually called algorithms, presenting symptoms and clinical signs are classified into defined STI syndromes such as genital ulcer and vaginal or urethral discharge syndrome. The patients are treated with standardized drug regimens including at least two antibiotics - to cover the possible causes of their syndrome. The advantages of syndromic management include prompt and standardized management and treatment at the first visit, as well as cost and resource savings by not having to use laboratory tests.

This thesis has its primary focus on the management of the five cervical and vaginal infections within the *vaginal discharge syndrome* (VDS) (Table 1). This is the most commonly used syndromic management algorithm, but its inappropriateness has been acknowledged for decades (43). First, the five conditions can all be cured, but their detection and treatment is complicated by their frequently asymptomatic nature. The entry point to the VDS algorithm is symptoms of abnormal vaginal discharge; and many people with an STI/RTI are not identified because they are asymptomatic or have mild symptoms. The *low sensitivity* is a major disadvantage of the syndromic approach, reducing the possibility of preventing reproductive complications and sequelae and of interrupting onward transmission (32, 42, 44, 45).

Second, abnormal vaginal discharge is common and has thus *low specificity* for the conditions in the vaginal discharge algorithm. This results in high levels of overtreatment, which increases drug costs and the risk of drug resistance, while patients unnecessarily experience side effects of drugs and changes in endogenous flora. Studies have consistently shown that for the cervical infections, treating patients with symptoms and signs of

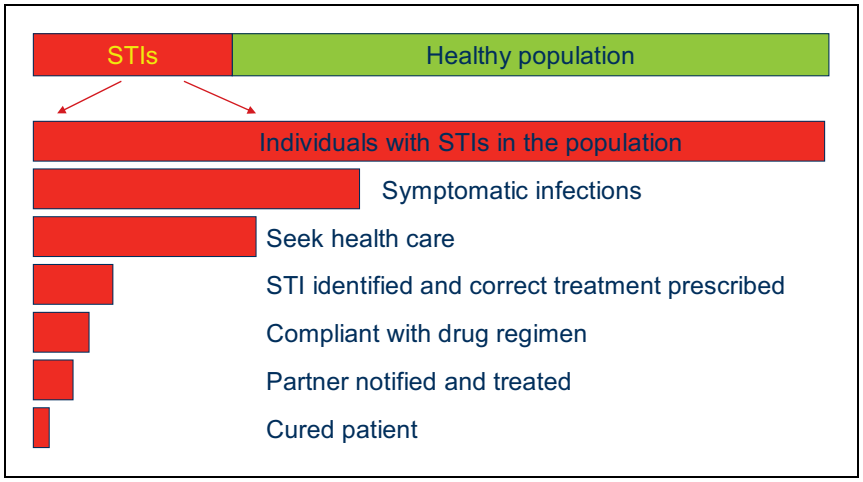
abnormal vaginal discharge is not, or only modestly, better than random treatment (43, 46-48). The high level of over-diagnosis also undermines partner notification. In most low-income countries, partner notification is patient based; patients are told to inform their partners and refer them for treatment. In the syndromic approach, all presenting partners are empirically treated. However, as most patients diagnosed with vaginal discharge syndrome do not have an STI, their partners should neither be notified nor treated (49). It is also problematic that both the complexity of multiple drug regimens and the diagnostic uncertainty may reduce patient compliance (50).

Table 1 The infections and conditions within the vaginal discharge syndrome

Cervical infections	
Chlamydia	A sexually transmissible infection caused by obligate intracellular bacteria which may cause cervicitis in women and urethritis in men.
Gonorrhoea	A sexually transmissible infection caused by bacteria which may cause cervicitis in women and urethritis in men.
Vaginal infections/conditions	
Trichomoniasis	A sexually transmissible infection with a single-celled protozoan parasite which may cause increased discharge, vulvovaginal soreness and itching and dyspareunia in women and urethritis in men.
Bacterial vaginosis	An endogenous syndrome marked by an increased vaginal pH, milky creamy discharge, and amine or fishy odour. Microbiologically, bacterial vaginosis is characterized by a shift in the vaginal flora from the dominant flora of *Lactobacillus* spp. to a mixed flora that includes *Gardnerella vaginalis*, *Bacteroides* spp., *Mobiluncus* spp., and *Mycoplasma hominis.*
Vulvovaginal candidiasis	An endogenous fungal infection of any of the *Candida* species (of which *Candida albicans* is most common) which may result in increased discharge, vulvovaginal soreness and itching and dyspareunia in women. The yeast may be transmitted to male partners and cause balanitis.

The syndromic approach relies heavily on the *quality of care* provided. It is a recognized problem in the routine care that STI patients quite often are assessed improperly and that the opportunity for counseling and health promotion is underutilized. In a national evaluation of the quality of the STI management in Botswana, only 17% of the patients were assessed and managed according to the guidelines (51). Another study showed that female STI patients in Botswana were managed in an average of 5.4 minutes (7). The lack of access to specific diagnostic tests and the uncertainties of the syndromic diagnoses may discourage health workers from following the guidelines, and partly explain inadequate history-taking, lacking or insufficient examination, insufficient or unnecessary prescriptions, and a lack of commitment to counseling on treatment compliance, safer sexual practices and partner notification (3).

Figure 1 Challenges with the management of STI patients (The Piot-Fransen model)



There are a number of challenges to providing effective STI/RTI services (Figure 1). Evidence from Rakai, Uganda has shown that relying on treatment of only those with

symptoms implies that less than 8% of the infected population receives effective treatment (52). Cure rates are even lower, as insufficient compliance and re-infection from untreated partners are effective obstacles to cure after the encounter with the health facility. Similar estimates from Mwanza, Tanzania are also pessimistic, indicating that cure rates among symptomatic patients visiting health centres are less than 10% (11).

Alternative approaches to STIs in developing countries, in particular to solve the challenges with the vaginal discharge syndrome, have been thoroughly discussed (32, 45, 53). However, strategies such as risk assessment and clinical screening do also have low sensitivity and specificity; whereas mass treatment is linked to development of antibiotic resistance and high drug wastage (54, 55). The development of simple POC tests for *C trachomatis* and *N gonorrhoeae* has been a high priority since the 1990s (54, 56, 57). The continued use of the syndromic approach in the management of cervicitis has been viewed as a temporary solution for health care providers awaiting the availability of such tests (57).

Diagnostic tests for STIs

The use of laboratory services has long been a natural and established routine in the management of STIs in high income countries. In sub-Saharan Africa, access to reliable diagnostic testing in general is severely limited (58), and advanced STI tests have been beyond reach for most laboratories. Simple, affordable diagnostic tests for STIs are needed in the developing world: to precisely diagnose symptomatic patients, reduce the over-treatment, and to screen for asymptomatic infections in selected populations. Point-of-care tests are particularly valuable. As they allow immediate diagnosis and treatment, lower sensitivity than advanced, laboratory-based tests can be accepted. A POC test with a

sensitivity of 65% can lead to a greater proportion of infected patients treated compared to a nucleic acid amplification test with sensitivity of 90% when the return rate for test results and treatment is low (59).

Major progress in the development of POC tests has recently been made. A range of tests are now on the market for several STIs, including all microbes targeted with the vaginal discharge algorithm (Table 2) (42, 60). The Sexually Transmitted Diseases Diagnostics Initiative (SDI) at the WHO was founded in 1999 - in response to the widely perceived need to improve care for patients with STIs in resource-poor settings through improved diagnostics. Evaluation and field-testing of existing POC tests for chlamydia, gonorrhoea and syphilis are important priorities for SDI (60, 61).

Table 2 Simple diagnostic tests for the microbes targeted with the VDS algorithm[a]

Infection	Test	Sensitivity	Specificity	Ref.
Chlamydia	Immunoassay	25-85%	≥ 90%	(60, 62-66)
Gonorrhoea	Immunoassay	25-85%	≥ 90%	(60, 62, 66, 67)
	Microscopy	♂ 84-95%	≥ 95%	(62)
		♀ 50%	≥ 95%	(62)
Trichomoniasis	Microscopy	45-70%	92-100%	(60, 68-70)
	Latex agglutination test	>95%	> 90%	(71)
Bacterial vaginosis	Nugent's criteria[b]	?/100%	?/100%	(60, 72)
	Amsel's criteria[b]	50-90%	80-95%	(60)
Vulvovaginal candidiasis	Microscopy	30-85%	≥ 95%[c]	(69, 73, 74)

[a]The sensitivity and specificity of the tests are only for guidance, as it will depend on the prevalence of the condition in the population, the reference standard used etc.
[b]Bacterial vaginosis is a clinical syndrome, and the sensitivity and specificity of Nugent's criteria is uncertain in the absence of a reference standard. The performance of Amsel's criteria is compared with Nugent's criteria.
[c]Colonization with candida species is common, and the detection of candida by microscopy (or culture) is highly specific, but does not necessarily confirm *infection*.

POC tests for the diagnosis of chlamydia and gonorrhoea currently include microscopy of cervical or urethral smears for gonorrhoea and immunoassays for both

infections (62). The immunoassay detects antigen using high-affinity antibodies fixed onto nitrocellulose strips, does not require additional equipment and can give a visual result within 30 minutes. So far, evaluations of POC tests for chlamydia and gonorrhoea have shown variable sensitivities (25-85%), but high specificity (>90%) (62, 66). A recent study found that a commercially available chlamydia test which is widely used in China had a sensitivity of 50% and a specificity of 98-99% (63). A study of a rapid test to diagnose gonorrhoea in high risk Brazilian women found a sensitivity of 60% and a specificity of 90% (67). More tests are in development, and most likely, more sensitive tests will be available within a few years. Encouraging data on an improved rapid test for ocular chlamydial infection have recently been published (75). The evaluated test had a sensitivity of 84% and a specificity of 99% using a polymerase chain reaction (PCR) test as the reference standard.

Point-of-care tests for chlamydia in the antenatal care in Botswana

One of the aims of this thesis was to conduct an economic evaluation of using POC tests for chlamydia in the antenatal care in sub-Saharan Africa, using Botswana (Box 4) as a case. We chose to focus on pregnant women because of the additional advantage of preventing adverse obstetric outcomes and neonatal infections. We focused on chlamydia because it was the most common cervical infection in this population and because of the described severe weaknesses of the existing diagnostic strategy. Although POC tests for chlamydia can prove to be cost saving in a broader perspective, health authorities in resource poor settings may be discouraged by the direct cost of purchasing and using such tests. In Botswana, the prevalences of HIV and other STIs are very high. In 2005, 33% of the

antenatal care attendees were HIV infected (76). STIs are a major public health problem: during the last decade, there have been registered between 100 000 and 200 000 STI-related outpatient consultations each year (77, 78). To explore POC tests as an alternative or addition to the current STI management is consistent with the health policy in Botswana (79, 80), and the economic possibility to introduce this intervention should be present.

Currently, pregnant women in Botswana complaining of vaginal discharge or lower abdominal pain are managed with the vaginal discharge algorithm according to national syndromic approach guidelines (Figure 2) (81). Based on a risk assessment and the signs found on clinical examination, the women receive treatment for chlamydia and gonorrhoea and/or trichomoniasis and bacterial vaginosis and/or candidiasis. In addition, all antenatal care attendees are clinically screened for STIs/RTIs. The antenatal care guidelines recommend a routine speculum examination at the first antenatal visit, to "exclude genital infections, abnormalities and pelvic tumors" (82).

There is a logistic advantage of introducing an extra service to a relatively well-functioning antenatal care program. The attendees meet at the clinic routinely; a good framework for diagnosis, treatment and follow-up. Screening for syphilis and HIV is incorporated into the antenatal routine, and at the first visit, blood is drawn for Hb, blood group, rhesus-factor, syphilis and HIV tests (82). Specimens for a POC test can be taken at the genital examination at the first visit, the test can be analysed on-site and treatment provided if necessary. Thus, POC testing for chlamydia will not lead to any change in the number or overall content of the routine antenatal care visits.

In the process of implementing the prevention of mother-to-child-transmission (PMTCT) program, and subsequently the antiretroviral treatment program, the laboratory

capacity in Botswana has been extensively upgraded to manage routine and clinical HIV testing, monitor the epidemic and perform research. In addition, all health posts and clinics have a lay counselor who performs point-of-care tests for HIV. This experience shows that utilizing clinicians or lay counselors to perform simple rapid tests in the primary health care is feasible.

Box 4 The health system and health situation in Botswana (79)

Botswana is located in southern Africa, landlocked between South Africa, Namibia, Zambia and Zimbabwe. The country is flat, at about 1 000 metres above the sea, with an arid or semi-arid climate. More than two-thirds of the land area consists of the Kalahari Desert. In North-West, the Okavango River drains inland to form the Okavango Delta, while the majority of the population lives in the eastern region. After 80 years as a British Protectorate, it attained self government in 1965 and became the independent Republic of Botswana. The Botswana Constitution established a non-racial multiparty democracy, which maintains freedom of speech and affords all citizens equal rights. From being one of the poorest countries in Africa, it experienced a remarkable economic transformation due to the emergence of the minerals sector shortly after the independence.

Botswana has one of the best health care systems in Africa, based on a primary health care ideology with access for all citizens to essential health care, and an equitable distribution of resources and utilization of health services. Almost 90% of the residents live within 15 km of a clinic or health post, while mobile stops cover small communities. The government health services are affordable, with either small user fees or free services. Drugs are provided free of charge. Experienced nurses lead the clinics, and nurses are responsible for the outpatient consultations and the antenatal care. 'Family welfare educators' work in the villages and play an important role in the primary health care, representing a tradition of successfully utilizing personnel with little training or education as health workers.

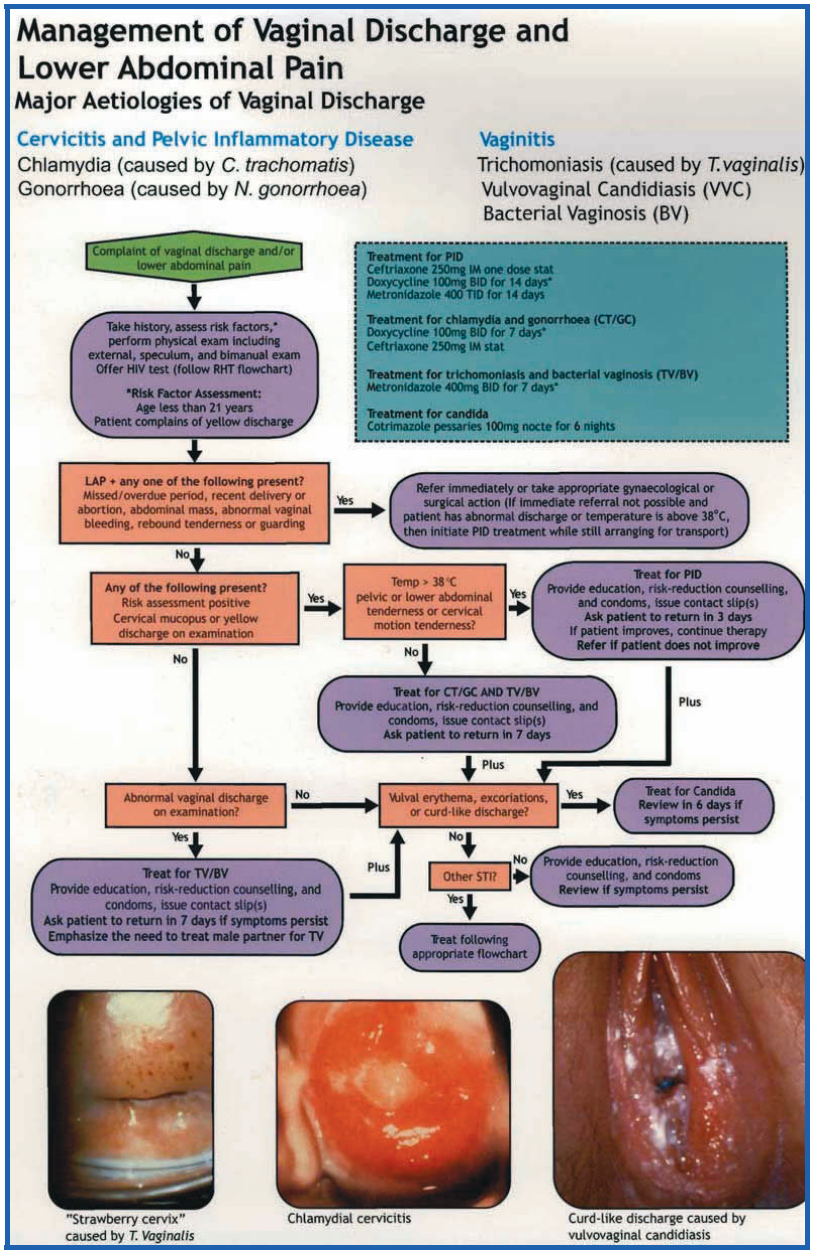
As many other developing countries, Botswana is undergoing a health transition, where changes in lifestyle and economy has resulted in a decline in communicable diseases and an increase in cardiovascular diseases and diabetes. However, the transition is incomplete: the fertility as well as the occurrence of infectious diseases are still high, and AIDS has emerged as a major cause of morbidity and mortality. Improvements in core health indicators (Table 3) have stagnated or been reversed: infant and child mortality rates have dramatically increased, and the life expectancy has fallen from nearly 65 years in 1985-1990 to 40 years in 2000-2005 (83). The morbidity related to HIV comprises an enormous challenge for the health care system, which itself is struggling with the loss of manpower.

The recently retired president Mogae described the HIV/AIDS epidemic as a national emergency, and the response to the crisis has been more comprehensive than anywhere else in the region (84). The Prevention of Mother to Child Transmission program (PMTCT) started in 1999, and Botswana has now lowered the rate of mother-to-child transmission of HIV from 40 to less than four percent. Since 2002, an antiretroviral treatment program has been expanded with the intention to reach all infected people with symptoms or a CD4-count less than 200. Shortage of skilled personnel was one of the largest challenges to treatment scale-up, partly solved by in-service training of health professionals and the use of lay workers. Today the program is seen as a successful model for other African countries.

Table 3 Core demographic, economic and health indicators in Botswana (85, 86)

Country statistics	Estimate	Year
Demographic indicators		
Total population	1 858 000	2006
Annual population growth rate (%)	1.9	1990-2006
Economic indicators		
Per capita GNI in US$	5 900	2006
% of government budget spent on health care	5	1995-2005
Health indicators		
Total fertility rate	3	2006
Maternal mortality rate	380 per 100 000 live births	2005
Life expectancy at birth	49	2006
Infant mortality rate	90 per 1 000 live births	2006
Under 5 mortality rate	124 per 1 000	2006

Figure 2 The vaginal discharge algorithm in Botswana, 2005



Economic evaluations in health care

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences (87). It encompasses identifying, measuring, valuing and comparing the costs and the health consequences of the alternatives being considered, which means that the difference in costs is compared with the difference in health outcomes (87). The process is a systematic approach to decision making under uncertainty, designed to help decision makers think clearly about the many elements of complex decisions (88).

The use of economics in health care is concerned with increasing efficiency of current and new health interventions. *Technical efficiency* exists when no greater output can be achieved with a given set of resource inputs. *Allocative efficiency* is used in a broader perspective, and exists when the available resources are allocated to maximize the objectives of the health care system. If an intervention can achieve the same or better results more cheaply relative to the existing care, or if greater effectiveness is achieved to the same costs, it will be judged better (more technically efficient) (89). Commonly, new interventions imply greater health benefits, but also greater costs compared to the current management. Implementation of such strategies raises allocative efficiency questions, as the benefits of improved care (unless the health care budget is increased) is likely to be at the expense of another group of patients (89). This is a basic principle in economic evaluation, *opportunity cost* (88, 89). In health care it means that devoting resources to one health intervention also implies a cost in the sense that opportunities for improving health or saving lives elsewhere are forgone.

There are three types of full economic evaluations: cost effectiveness analysis (CEA), cost utility analysis (CUA) and cost benefit analysis (CBA) (87). In short, the methods are distinguished according to how the health outcomes are valued. In CEA, health benefits are measured in natural units such as life years gained, hip fractures avoided, or as in our study, cases of chlamydia cured. This is useful when striving for the optimal use of resources to maximize a specific health outcome. In CUA, the measure of benefit is quality adjusted life years (QALY) or disability adjusted life years (DALY), making it possible to compare interventions with widely different health outcomes. The CUA is a variant of the CEA, and in published medical literature, economic analyses with DALYs or QALYs as the health outcome are often labelled "cost-effectiveness analysis". In CBA, the benefit is measured in monetary terms, which enables comparing projects across sectors. Partly due to the problem of valuing and expressing health benefits in monetary terms, CBA is rarely used for economic evaluations in health care.

The costs included in an economic evaluation are dependent on the perspective of the analysis. In the societal perspective, all costs and health consequences should be captured, irrespective of who pays or who benefits: health sector costs; costs on other sectors; all relevant costs to the patient and family; and productivity losses. A health care provider perspective includes only the costs that are borne by the health care services.

Cost-effectiveness analysis

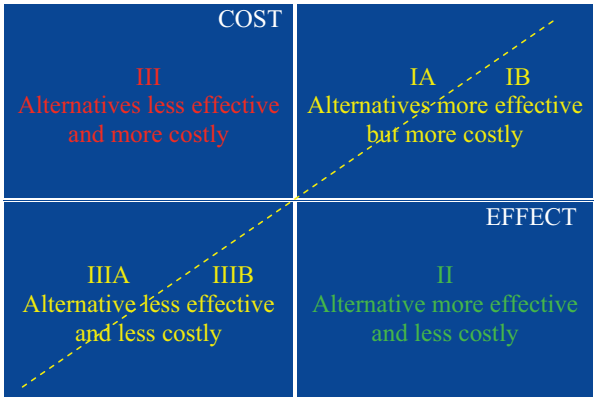
The economic study presented in this thesis is a cost-effectiveness analysis. The aim of such an analysis is to estimate the difference in cost (C) and the difference in effects (E)

between interventions. The result can be summarized as the *incremental* cost-effectiveness ratio (ICER):

$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

The concept of a cost-effectiveness analysis can be illustrated graphically on the cost-effectiveness plane (Figure 3) (87, 90). The x-axis divides the plane according to incremental costs, and the y-axis divides the plane according to incremental effects.

Figure 3 The cost-effectiveness plane

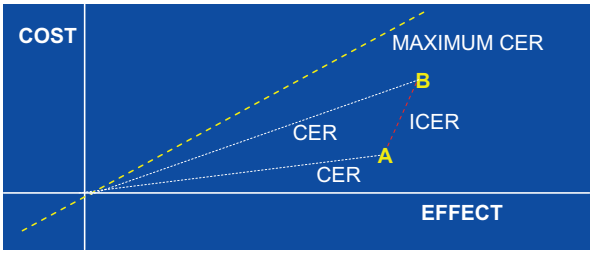


Alternative strategies can be represented by a point in this plane, defined by the effectiveness and cost of the alternative relative to those of a reference standard. This reference, placed in the origin, represents either the current standard or a "do-nothing"-strategy. Strategies in quadrant II are equally costly and more effective, or less costly and equally or more effective than the reference, and will by definition be categorized as cost-effective relative to this reference. Interventions in quadrant IV are not cost-effective.

In order to decide if strategies in quadrant I and III are worthwhile, their cost per effect gained must be compared to a specified monetary threshold; the maximum amount that the decision makers are *willing to pay* for a given health effect (yellow dashed line). A strategy is by convention defined as cost-effective if its incremental cost-effectiveness ratio is less than the maximum acceptable cost-effectiveness ratio (IB or IIIB) (90).

In practice, most interventions fall into quadrant I (Figure 4). For each strategy, the average cost-effectiveness ratio (CER) is given by the slope of the line from the origin. Strategy A and strategy B have average CERs lower than the willingness to pay, and viewed separately, they would both be considered cost-effective. For meaningful comparison between two strategies, however, we have to examine the ICER, visualised by the slope of a line between one strategy and the next more effective treatment. In this case, the additional cost per additional outcome gained by moving from A to B is higher than the maximum CER. This is important to consider before it is decided whether the price is worth paying (87).

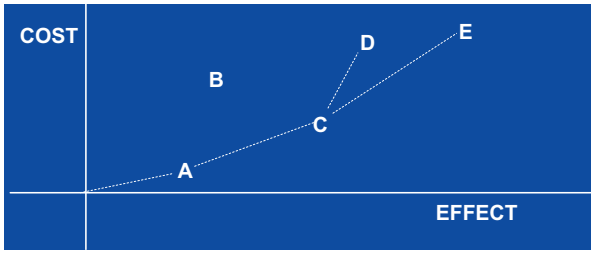
Figure 4 Average and incremental cost-ef fectiveness atios



When three or more strategies are compared, they can be arranged according to ncreasing costs (Figure 5). Of the alternatives A-E, strategy B is *strongly dominated* by alternative C, because the latter is less costly and more effective (Figure 5). Alternative D is

extendedly dominated by alternative E; it has higher ICER than the next, more effective alternative. If the objective was to be taken based on cost-effectiveness principles, strongly and extendedly dominated strategies should be rejected. The remaining strategies A, C and E are ordered according to their ICER. To maximize the effect within a given budget, the strategy with the lowest ICER is adopted first (strategy A). Then independent strategies are successively added, or mutually exclusive strategies replaced, until the budget is exhausted. An alternative approach is to define the maximum acceptable CER, adopt all strategies with ICERs below this ceiling, and see what size of the budget this implies (87).

Figure 5 Dominance and incremental cost-effectiveness ratios



Knowledge and knowledge gaps in economic evaluations of chlamydia

Being the most common bacterial STI in Europe and the United States, numerous cost-effectiveness analyses of screening for chlamydia with laboratory based diagnostic tests have been published, most commonly among female out-patients (91-93). The most recent systematic review of the economic evaluations of screening for *C trachomatis* identified 713 papers and included 57 formal economic evaluations and two cost studies - none from developing countries (91). Many of the studies use 'infection treated' or 'infection cured' as the outcome measure, whereas some use complications averted, such as pelvic

inflammatory disease and infertility (91, 92). In general, it is found that the cost-effectiveness ratio decrease with increasing disease prevalence (93). The cost-effectiveness is also highly dependent of the risk of complications in untreated patients, but the magnitude of this risk is yet to be determined (94).

I have identified two economic evaluations of chlamydia screening programs specifically for pregnant women. Both papers present static cost-effective decision models and use 'major outcomes averted' as outcome. A study conducted in the Netherlands concludes that screening with advanced laboratory methods for asymptomatic *C trachomatis* infection in pregnant Dutch women would render net savings at a minimum prevalence rate of 3% or more (92). Nettleman and Bell in England evaluated culture and direct antigen testing of pregnant women, assuming different prevalences of infection. The probabilities of major outcomes averted were derived from published literature. They conclude that screening all pregnant women would not be cost-effective, but characterized the additional costs as 'modest' when direct antigen tests were used (95).

It has been said that cost-effectiveness analyses do not travel well (25). There are several reasons why the results of these evaluations are not transferable to resource poor settings. The diagnostic tests used in industrialized countries are out of reach, and the differences in health and disease patterns, health care systems as well as economic systems are obvious. Economic evaluations of STI management in developing countries exist, although the so-called research gap[1] is found also in this field. Common to these evaluations is that they mainly focus on STI syndromes, not specific STIs/RTIs. Broadly, they can be divided into two categories. The first includes studies examining the cost of

[1] The 10/90 gap states that less than 10% of the global health research targets diseases affecting the poorest 90% of the world population.

treating curable STIs/RTIs, using ‘treatment provided’ or ‘infection treated’ as the outcome measure. The service delivery modes which are evaluated include management of symptomatic STI clients; case finding among family planning clients or antenatal care attendees; and services aiming to reach specific high risk groups. A recent review reports that heterogeneity of methods and outcome measures used in the analyses, and the fact that methods are often not clearly documented, complicate the synthesis and interpretation of the results (96). Nevertheless, the authors conclude that clinics serving symptomatic patients were consistently less costly than outreach services, that syndromic management had lower cost than other management strategies and that unit costs decreased with scale.

Analyses in the second category use ‘number of HIV-infections averted’ as outcome in the economic analyses, reflecting that STI management in developing countries is seen as one of many strategies to combat the spread of HIV/AIDS (97). With this outcome measure, the costs per DALYs or QALYs gained can be estimated, enabling comparison between STI management and other health interventions. The CHOICE group in WHO has published a series of papers examining the cost effectiveness of different strategies to achieve the millennium development goals. They found that reducing HIV transmission could most efficiently be achieved through mass media campaigns, interventions for sex workers and syndromic management of STIs (provided in primary health care facilities and available to the general population) (97). Other STI management strategies were not evaluated.

When the work with this thesis was initiated, there were no economic evaluations of the use of simple POC tests for chlamydia. Since then, one group of researchers has modelled the cost-effectiveness of using a combined POC test for chlamydia and

gonorrhoea, versus syndromic management, among sex workers in Benin. With the use of HIV infections averted as the outcome measure, the test strategy was considered cost effective and reduced inappropriate treatment (66). To our knowledge, there are still no economic evaluations of chlamydia management in pregnancy in resource poor settings. In conclusion, there is an obvious lack of cost-effectiveness studies from developing countries comparing the costs and health consequences of current or alternative chlamydia management strategies, including the use of POC test, in pregnant women.

Objectives

My vision throughout this work has been to contribute to reduced levels of STIs and their complications in developing countries, thereby preventing HIV transmission, and ultimately improving the health status of the population. It is visionary, indeed, but with the origin in the established knowledge that the current STI management in developing countries had substantial potential for improvement. The resources allocated to the health services in developing countries are scarce. My hypothesis was that investing in the use of specific diagnostic tests for STIs would pay off because of reduced expenses to manage the complications of undetected and untreated infections. Concretely, the main objective of this thesis was to

> Compare the costs and health consequences of testing with specific diagnostic tests versus using the existing syndromic management of STIs among antenatal care attendees in sub-Saharan Africa.

As has been argued for, we chose to focus on diagnostic and treatment alternatives to the vaginal discharge algorithm among pregnant women. We evaluated the syndromic management of all microbes within this syndrome, whereas the economic evaluation focused on chlamydia. The specific objectives were as follows:

1. To estimate the prevalence of chlamydia, gonorrhoea, trichomoniasis, bacterial vaginosis and vulvovaginal candidiasis in a sample of pregnant women in Gaborone, Botswana. [Included in paper 1-3]

2. To assess treatment success among the attendees who had been diagnosed with syndromic approach and prescribed treatment for cervical infections during the routine antenatal care earlier in pregnancy. [Paper 2]
3. To evaluate the syndromic approach for the detection of chlamydia, gonorrhoea, trichomoniasis and bacterial vaginosis in pregnancy, using laboratory tests as the reference standard. [Paper 2 and 3]
4. To determine whether risk scores could improve the diagnostic accuracy of cervical infections. [Paper 3]
5. To compare costs and health consequences of the syndromic management with using point-of-care (POC) tests to diagnose chlamydia among antenatal care attendees in sub-Saharan Africa, including an evaluation of azithromycin versus erythromycin treatment and universal versus age-based management. [Paper 4]
6. To suggest cost-effective modifications, additions or alternatives to the current syndromic management of STIs in sub-Saharan Africa. [Paper 4]

Finally, I hope that we manage to distribute our findings to national health ministries, donor countries and other parties involved the STI management, having the great task of ensuring the most cost-effective use of resources and improve the functioning and performance of the health sector.

Methods

The epidemiological study

Sample and sample size

A proportionate sample of attendees was recruited from each of 13 locations, based on the percentage of all antenatal care attendees who attended that facility the previous year. There were 6 300 women attending antenatal care in Gaborone yearly in 2000 and in 2001 – approximately 525 per month. With a study sample of 703, we included 27% of the antenatal care attendees in Gaborone in the data collection period in our study. Participating in this study were 703 antenatal care attendees in Gaborone, Botswana, none were included twice. There are substantial differences between the richer and poorer areas of Gaborone, and we aimed at getting a sample representative of the population of ANC attendees in the city. Seventeen facilities provided antenatal care at this point of time. We included women from the 13 main facilities providing antenatal care: 12 primary health clinics and one outpatient department. For practical reasons, five facilities with less than 700 antenatal care consultations the previous year (range 15-690) were not included in the study. These clinics were Sebele (outside Gaborone), two university clinics, the prison clinic and the police clinic, the two latter catering for employees and their families.

Facilities were visited one-by-one by a medical doctor (the author) from the 5th of October 2000 to the 1st of March 2001. Each day at the clinic, the women were consecutively invited to be included in the study from the morning. The number of patients per day was limited by either the total number of women that day, or by the number of specimens that the laboratory could handle (usually 12, it varied because of varies in staff and other activities at the lab). In the majority of clinics, all attendees were included in the

study. In the busiest clinics, only a sample of the attendees was included; the selection of attendees in these clinics was incidental. These clinics have many consulting rooms and several midwives conducting antenatal care simultaneously. The study doctor would work in a separate consulting room, conducting the ordinary pregnancy control and collecting data for the study. In a clinical setting like this, systematic randomization of the patients is virtually impossible to accomplish. It was incidental which women who were seen by a clinic midwife and subsequently sent home, and which were seen by the study doctor. We no reason to believe, however, that any systematic bias was involved in the selection of this attendee sample or that our sample is less representative than it would have been had our attendees been randomly chosen.

The only exclusion criterion was the use of antibiotics during the previous two weeks.

Interview and clinical examination

A structured interview (Appendix 1), supplied with information from the patient-held antenatal record (Appendix 2) were used to obtain data on sociodemographic and behavioral factors and current RTI symptoms. When a patient is diagnosed with an STI syndrome during pregnancy, the syndrome and the prescribed drugs are documented in the antenatal record. Prescribed treatment for any STI during the current pregnancy was recorded along with the syndrome diagnosis.

All patients underwent a genital examination; appropriate specimens were collected; and abnormal signs from external and internal genitalia were recorded in detail. Amount, consistency, color and odor of vaginal discharge were described. Signs of a sexually

transmitted infection were classified into defined syndromes following the national guidelines and were treated accordingly.

Laboratory analyses

Urine was checked on site with a dipstick; all other specimens were transported at ambient temperature the same day for processing at the National Health Laboratory (NHL) in Gaborone. A desired outcome of this study pronounced by the NHL in addition to the specific study objectives was to develop human and technical laboratory competence on STI/RTI analysis in Botswana. Two laboratory technicians were trained in STI analysis prior to the study (in Center for Disease Control and Prevention in Atlanta, USA, and in South African Institute for Medical Research). The remaining staff was trained when the study was ongoing. A ligase chain reaction (LCR) machine was bought for study purposes and subsequently donated to the laboratory.

A cervical smear was gram-stained to count polymorphonuclear leukocytes per high power field. For the identification of trichomoniasis and bacterial vaginosis, one high vaginal swab was placed in Stuart transport media; another was used for a vaginal smear. Wet-mounts made from the swabs in transport media were examined for motile trichomonads by light microscopy. The swabs were then agitated into bottles of Diamond's modified medium, the bottles were incubated in Oxoid gaspack jars, and wet-mounts were examined for trichomonads once daily for up to five days.

The vaginal smears were Gram-stained and scored for bacterial vaginosis by an experienced laboratory technician according to Nugent's criteria (72). On a 0-10-point

scale, a score of <4 is considered normal, 4-6 intermediate, and 7 and above is classified as bacterial vaginosis (Table 4).

Table 4 Nugent's criteria: Scoring system (0 to 10) for Gram-stained vaginal smears[a]

Score [b]	Lactobacillus morphotypes	*Gardnerella* and *Bacteroides* spp. morphotypes	Curved gram-variable rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

[a]Morphotypes are scored as the average number seen per oil immersion field. Total score = lactobacilli + G. vaginalis and Bacteroides spp. + curved rods.
[b] 0, No morphotypes present; 1, <1 morphotype present; 2, 1 to 4 morphotypes present; 3, 5 to 30 morphotypes present; 4, 30 or more morphotypes present.

Culture of *Candida* species was initiated by direct inoculation of Saboraud plates at the clinic, incubated at 35 °C (5% CO_2), and examined after 24 and 48 hours. Smears of colonies from positive cultures were Gram-stained and examined for budding yeast cells and pseudohyphae. The wet-mounts and Gram-stained smears were also examined for candida. Presence of candida was defined as positive growth and/or microscopy.

Cervical swabs were obtained from all women for LCR amplification technology for the direct, qualitative detection of specific target nucleic acid sequences of *C trachomatis* and *N gonorrhoeae*. The swabs were placed in LCx® transport media and stored at –20^{o} C prior to batch processing. The LCx® Assays (Abbott Laboratories, IL) were performed according to the manufacturer's instructions. A case of *C trachomatis* or *N gonorrhoeae* infection was defined as an individual with a positive LCR analysis. Culture of *N. gonorrhoeae* was also performed. Last, venous blood samples were collected, and the

maternal sera were tested with the RPR test and the specific *Treponema pallidum* haemagglutination assay (TPHA).

Selected specimens were sent to Norway for analyses at the Norwegian Insistute for Public Health, including examining antibiotic susceptibility patterns of *N gonorrheae* isolates and typing of the *Candida* isolates. These results and the data on syphilis (98) are not included in this thesis.

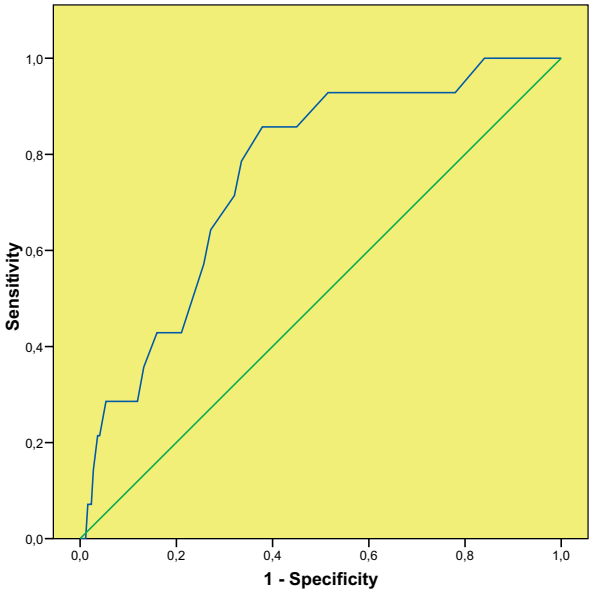
Statistical analyses

Data were analysed using the statistical package SPSS. Univariate logistic regression analyses were used to assess the association between genital symptoms and signs, and the laboratory-verified diagnoses of trichomoniasis and bacterial vaginosis (paper 2) and of cervical infections (paper 3). Socio-demographic risk factors and genital symptoms and signs that, in univariate analysis, were associated at a 0.2 level (*P*-value of odds ratios [OR]), were included in multivariate logistic regression analyses. Validity of the vaginal discharge algorithm, of clinical screening and of risk scores for cervicitis were assessed by measuring sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-), and positive and negative predictive values, using the laboratory diagnosis as the reference standard.

Three levels of risk scores were computed and retrospectively applied, and each of them were assessed for their usefulness as a diagnostic tool to manage cervical infections in pregnancy (Table 1, paper 3). Receiver Operating Characteristic (ROC) curves were used to compare the different risk scores (Figure 6). The ROC curve was first used during the World War II for the analysis of radar signals. In medicine, ROC analysis has been

extensively used in the evaluation of diagnostic tests, as a graphical plot illustrating the trade-off between high sensitivity and high specificity. The test result can be in a continuous output in which the disease must be determined by a cut-off value, for instance to determine whether a person has hypertension based on blood pressure measure, or it can be in a discrete value, for instance a positive or negative pregnancy test. The best possible diagnostic test would yield a point in the upper left corner of the ROC space, representing 100% sensitivity and specificity. A completely random guess would give a point along a diagonal line.

Figure 6 Receiver operating characteristic (ROC) curve (from Wikipedia)



Ethical considerations

The study was approved without questions by the relevant ethical committees: The Norwegian Committee for Medical Research Ethics, the Health Research Development Committee in Botswana and the Hospital Research and Ethical Committee at Princess Marina Hospital. The Ministry of Health granted permission to transport specimens to Norway for quality control.

Information about the study was distributed to the antenatal care clients in English and Setswana. All clients did also receive personal information and got the possibility to ask questions to the clinics' midwives, in particular to those who did not speak English or could not read. Women who did not participate in the study received ordinary care, whereas among the consenting women, the short interview and the gynaecological examination were conducted as a part of the visit. Testing for STIs is not routinely provided, and most women expressed that they appreciated the advantages of the additional examination and tests.

The patients were informed that they could return for their laboratory results after one week; otherwise they would receive the results at the next ANC visit. All participants received a number which all information was linked to anonymously. In the laboratory records, the results were coupled to both names and number, to ensure feedback to the patients. All laboratory findings were sent to the clinics for distribution, and in case of positive results, the specific diagnosis and correct treatment was written explicitly on the form. Anecdotic, in all clinics where I stayed more than a week, I frequently participated in providing attendees with results – and treatment.

HIV-status would have been an interesting and important variable in the epidemiological study. At the time when the field work was planned and permissions to be

applied for, HIV-testing for research purposes was a controversial and loaded issue in Botswana, and could therefore not be included. In the routine antenatal care program, all attendees were invited to participate in the PMTCT program on a voluntary basis, but the uptake was far from optimal.

Table 5 Core issues in the economic evaluation

Research question	In the management of chlamydia infection among antenatal care attendees, what are the costs and health benefits of a) Syndromic management versus point-of-care tests? b) Erythromycin versus azithromycin treatment c) Universal management versus age-based selective management strategies?
Type of economic analysis	Cost-effectiveness analysis performed within a static decision tree model
Comparators	Syndromic approach versus point-of-care tests. For each of these main strategies, we also compared universal and selective management strategies, and treatment with erythromycin or azithromycin.
Perspective	Health care provider
Patient group	New antenatal care attendees
Evidence of effectiveness	Indirect evidence from a study on chlamydia among antenatal care attendees in Botswana, and other published literature
Utilization of health care	Expert judgment
Unit costs	Costs of prescribing and providing treatment; cost of point-of-care test
Measure of effectiveness	Successfully treated and cured infection
Time horizon	The model captures events from a possible diagnosis of chlamydia at the first visit to the partner is treated (1 month)
Discounting	Not applicable due to the limited time perspective
Sensitivity analyses	One-way and probabilistic sensitivity analyses

The economic evaluation

The core issues of the economic evaluation are listed in Table 5. The model is described in detail in a technical report (http://www.hero.uio.no/publicat/2007/HERO2007_10.pdf) (99).

The decision analytic model

We used TreeAge Pro software to develop a decision analytic model comparing chlamydia management strategies in a hypothetical cohort of antenatal care attendees (Figure 1). The structure of the decision tree is shown as one main tree and three partner sub-trees (Figure 1, paper 4). The decision tree is a branching structure in which decision nodes (squares) symbolise choices facing the decision maker. Chance nodes (circles) symbolize events where the possible outcomes are outside the decision maker's control. The node's branches represent the alternatives or outcomes associated with that event, and a terminal node (triangle) denotes the endpoint of a scenario. Information to feed the model was based on the epidemiological study of antenatal care attendees in Gaborone, literature reviews and expert opinions.

The literature reviews consisted of extensive searches in MEDLINE, EMBASE, The Cochrane Library, text books, reports and other relevant sources, including local literature searches in Botswana. The reviews do not formally qualify for categorization as systematic as it was not feasible to do a full and systematic review for all the parameters in the model with such detail. The expert panel consisted of six medical doctors with wide clinical, administrative and research experience from the field. Issues discussed in the expert panel were also discussed with nurses in the primary health care in Botswana and with other resource persons in the country. The model parameters and their probabilities are shown in Table 1, paper 4 and described in detail in Appendix 3. The searches and the search results are described in the technical report (99).

Health outcomes associated with treating chlamydia

To fully capture the costs and health benefits of the different chlamydia management strategies, all prevented complications in chlamydia infected women, their partners and their offspring, and the resulting cost savings to the health system, should have been included in the model. Reviews of literature on complications of chlamydia in developing and developed countries revealed that published data are limited and inconclusive. These reviews are described in detail in the technical report (99). After substantial efforts to interview experts (medical doctors and nurses, health statisticians, health economists and officers in the health ministry) and collect health statistics, national health accounts and health budgets, we concluded that there is a lack of research, statistics and empirical experience on consequences and long term complications of *C trachomatis* infection in Botswana and similar settings. The health outcome estimated for each strategy is therefore limited to the number of cured infections among the attendees and their partners. We also estimated re-infections and the number of patients unnecessarily treated with the different strategies.

Resource consequences and cost measures

Our analysis adopted a health care provider's perspective. The costs were presented in 2006 US$ (Table 2, paper 4). For the syndromic management we modelled treatment costs ($C_{♀treatment}$), which include the direct drug costs ($C_{azithromycin}$ or $C_{erytrhromycin}$) and the cost of a pharmacy technician at the clinic outlet dispensing and informing about the drugs (Δt in hours x C_{staff2}). The modelled costs of partner treatment ($C_{♂treatment}$) also include the direct drug costs ($C_{azithromycin}$ or $C_{doxycyclin}$) and the dispensing process. For the use of POC tests we

also included the test costs (C_{test} per test) and the cost of the extra time needed to undertake each test (Δt in hours x C_{staff1}). In the base case analysis, we used salary costs from Botswana and drug costs from Botswana and the International Drug Price Indicator Guide. Upper and lower ranges for the costs were estimated and evaluated in the sensitivity analyses to ensure relevance to countries with different personnel costs.

STI management in pregnancy takes place within the framework of the antenatal care and the STI management programs. We modelled the direct costs of chlamydia management, assuming that following costs are covered in the antenatal program. 1. Capital costs: building costs, equipment and land and other capital-intensive items. 2. Overhead costs: resources that service different programs, as expenses related to the building (e.g. power, rates), and costs associated with administration, transport, maintenance, cleaning etc. We did not estimate intangible costs such as work time and leisure time forgone for care-givers and patients. The attendees routinely come to the clinic, and the individuals' costs (travel costs and expenditure on goods and services) will not be affected by the STI management strategy. We also assumed that the STI management program, routinely training health workers, could cover the additional training needs.

Deterministic and probabilistic sensitivity analyses

To test the robustness of the model results, we undertook a range of sensitivity analyses. We first explored the consequences of parameter uncertainties in deterministic one-way sensitivity analyses, where one parameter at a time was varied up and down within the pre-specified uncertainty bounds (Table 1 and 2, paper 4) while maintaining the others at their base-case values. In these analyses, screening all new antenatal care attendees with a 50-85% sensitive POC test was compared to syndromic management in the same population

using azithromycin as treatment. We also performed probabilistic sensitivity analyses using Monte Carlo simulation in which the model was run 10 000 times, allowing the effects of joint uncertainty across all the parameters of the model to be considered. Universal testing, first with a 50% sensitive and then with a 75% sensitive POC test, was compared to syndromic management, using azithromycin as the drug of choice. We adopted β-distributions for the probabilities to constrain the values between 0 and 1, and γ-distributions for the costs because of their skewness. The probabilities in the two strategies were linked to account for interdependencies.

Results and summary of the papers

General results from the epidemiological study

We did not register any women refusing to participate. All women were asked about antibiotic use, and 25 were excluded; all of them because they were currently taking STI/RTI treatment. Additionally, 9 women were excluded after interview, examination and specimen collection because information on antibiotic use (all for STIs/RTIs) was discovered later.

Background characteristics of the study population and genital symptoms and signs are presented in Table 1, paper 2. Of the 703 women, 67 (10%) had laboratory-confirmed cervical infection: 51 (8%) were infected with *C trachomatis* and 21 (3%) with *N gonorrhoeae*. *T vaginalis* was identified in 131 (19%) women and bacterial vaginosis in 268 (38%) women. Candida species were identified by microscopy and/or culture in 416 (59%) of the women. In a total of 561 (80%) of the antenatal care attendees, one or more of these five infections and conditions were identified.

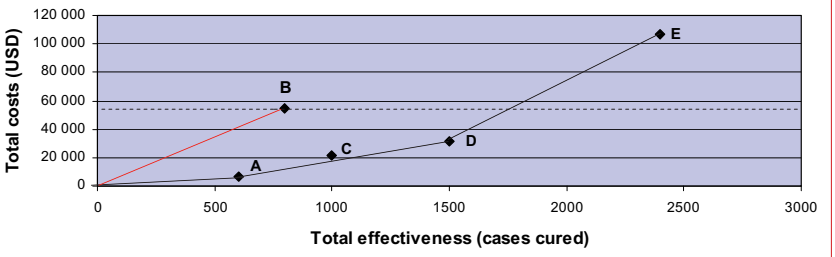
We did not perform specific laboratory tests on microbes causing other syndromes. Few women reported other symptoms than vaginal discharge. Clinical signs of genital warts and genital ulcers were found in 4 % and 1 %, respectively. Five women had been diagnosed with genital warts and genital ulcers earlier in the current pregnancy, compared to 161 women who had been diagnosed with vaginal discharge.

Chlamydia management strategies in the cost-effectiveness plane

In the following, selected results from the cost-effectiveness analysis are illustrated graphically. Figure 7 presents the evaluation of the syndromic approach and of POC-testing

strategies with a currently available 50% sensitive test. Figure 8 presents the results with a 75% sensitive test. The costs and cases of chlamydia cured with the different strategies are plotted relative to a "do-nothing"-strategy. Noteworthy, additional benefits of the POC-tests, such as reduced overtreatment and improved partner management are not included here. The uncertainty of the results is presented in paper 4.

Figure 7 Chlamydia management strategies in the cost-effectiveness plane (POC-testing with a 50% sensitive test)



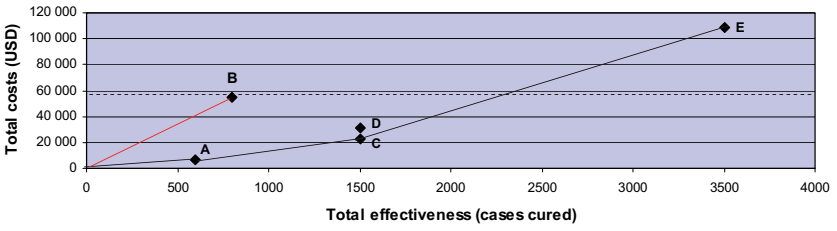
Strategy	CER	ICER
A Syndromic approach with azithromycin treatment among teenagers	10	10 (Ref*→A)
B Syndromic approach with erythromycin treatment among all attendees	66	*241 (A→B)*
C Point-of-care test (50% sensitive) with azithromycin treatment among teenagers	22	*43 (A→C)*
D Syndromic approach with azithromycin treatment among all attendees	21	28 (A→D)
E Point-of-care test (50% sensitive) with azithromycin treatment among all attendees	45	84 (D→E)

*ICER relative to the reference "do-nothing"

All strategies with erythromycin treatment, regardless of the test sensitivity, were *strongly dominated* by the same management using azithromycin, exemplified by changing treatment regimen within the current management (moving from strategy B to strategy D). With a 50% sensitive POC-test, POC-testing among teenagers (strategy C), was *extendedly dominated*, albeit weakly. Strategy A, syndromic approach among teenagers, would imply the lowest cost per cured case and the lowest total cost. Neither the maximum accepted cost

for a cured case of chlamydia is defined, nor is the budget for chlamydia management in sub-Saharan Africa. The black dashed line represents the estimated current budget, and strategy B represents the estimated current cost per case cured. The ICERs of strategy A, C and D were all lower than the CER of the current management. Implementing any of these strategies would imply reduced budget costs. If the objective was to maximize effectiveness within the existing budget, POC-testing could be partly implemented.

Figure 8 Chlamydia management strategies in the cost-effectiveness plane (POC-testing with a 75% sensitive test)



Strategy	CER	ICER
A Syndromic approach with azithromycin treatment among teenagers	10	10 (Ref*→A)
B Syndromic approach with erythromycin treatment among all attendees	66	*241 (A→B)*
C Point-of-care test (75% sensitive) with azithromycin treatment among teenagers	15	18 (A→C)
D Syndromic approach with azithromycin treatment among all attendees	21	*∞ (C→D)*
E Point-of-care test (75% sensitive) with azithromycin treatment among all attendees	31	43 (C→E)

*ICER relative to the reference "do-nothing"

The effectiveness and the cost per case cured with the POC-testing strategies improve with increasing test sensitivity. With a 75% sensitive POC-test, syndromic approach among all attendees was strongly dominated both with erythromycin and with azithromycin treatment. Strategy A, syndromic approach among teenagers, was still the

most cost-effective of the strategies. The ICERs of strategies A, C, D *and* E were all lower than the CER of the current management.

Paper 1: Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana

Optimal performance of all levels of the STI program is essential; improvement can have a substantial effect on the overall burden of disease. After adequate clinical assessment, patients with an STI must obtain prescribed drugs, comply with treatment, and ensure that their partners are treated to avoid reinfection.

In Botswana, more than 100 000 STI clients are prescribed multiple drug regimens yearly and STI drugs constitute a substantial share of the total drug use in the country (100). Despite the large number of prescriptions, treatment success among STI patients in the primary health care remains unknown. The aim of this paper was to draw attention to the consequences of prescribing antibiotics to STI patients in Botswana and to discuss possibilities for improving the cure rates. In our study among ANC clients, we evaluated if there was a lower prevalence of *C trachomatis* and *N gonorrhoeae* among ANC clients who had drugs against these bacteria prescribed to them in their current pregnancy, compared to ANC clients who did not have these drugs prescribed.

There was no significant difference in the prevalence of chlamydia among the women who had and the women who had not been prescribed erythromycin four times daily for ten days (7% vs. 8%). Contrarily, none of the women who had been prescribed a single dose of ceftriaxone had gonorrhoea; whereas 4% of the women who had not had this drug prescribed did have gonorrhoea. Thus, the prescribing of erythromycin seemed to have had a limited effect on chlamydia in this population, whereas the prescribing of ceftriaxone lead to the curing of gonorrhoea. Ceftriaxone is provided as a single-dose injection at the point of care, and the differential effectiveness between the two drugs may

reflect low compliance with the complex erythromycin regimen. We conclude that interventions to increase compliance could improve cure rates, and that the use of a simpler drug regimen should be considered when low compliance is likely.

Paper 2: Trichomoniasis and bacterial vaginosis in pregnancy: inadequately managed with the syndromic approach

Trichomoniasis (TV) and bacterial vaginosis (BV) may contribute substantially to the risk of preterm delivery, low birth weight and increased HIV transmission in sub-Saharan Africa (29, 45, 101-103). Although there are few studies from developing countries on effective strategies to prevent the adverse outcomes associated with TV and BV in pregnancy, it appears to be critical to diagnose and treat these conditions, especially in high-prevalence settings. The aim of this paper was to present results on the prevalence of TV and BV among antenatal care attendees in Botswana, examine the use of the vaginal discharge algorithm earlier in the current pregnancy, and evaluate the syndromic approach and clinical case finding in the diagnosis of these two conditions in pregnancy.

TV and/or BV was present in as many as 359 (51%) of the antenatal care attendees, and three of four were asymptomatic. Symptoms of vaginal discharge was only weakly associated with TV (OR 1.6; 95%CI 1.0 to 2.5), only in the univariate analysis, and not associated with BV. The vaginal discharge algorithm detected only one of five cases of TV and BV. Also, women diagnosed by the algorithm were not significantly more likely to have TV and BV than women not diagnosed as diseased (LR+ 1.35, 95%CI, 0.97 to 1.89). Signs of non-candida-like vaginal discharge identified half of the cases and gave an LR+ of 3.00 (95%CI, 2.31 to 3.92) in the diagnosis of the two conditions combined.

TV prevalence was 15% for the new attendees, compared to 20% among the repeat attendees who had already been provided with standard care (p=0.22). BV prevalence was 41% for new and 37% for repeat attendees (p=0.44). Prevalence of TV and BV was similar among women with and without a history of vaginal discharge, to a large extent explained

by the finding that treatment guidelines were not followed appropriately. Consistent with the guidelines, metronidazole had not been prescribed to any of the 13 women diagnosed with vaginal discharge in first trimester. In the 143 cases an attendee was diagnosed in the second or third trimester, metronidazole had been prescribed to only 17 women (12%). None of these had a *T vaginalis* infection, compared to 132 (19%) of the remaining 686 women. The difference in prevalence between the two groups is reduced, although not significant (Fisher's Exact Test = 0.054 [2-sided]). Similarly, 3 (18%) of the 17 women had bacterial vaginosis, compared to 265 (39%) of the women who had not been prescribed metronidazole (Fisher's Exact Test = 0.127 [2-sided]).

There is a high prevalence of TV and BV among pregnant Batswana women, and no indication that the current STI management reduces the prevalence of these conditions. The vaginal discharge algorithm had low accuracy in diagnosing TV and BV. Although more effective, clinical case finding did also result in undetected cases and overtreatment. Apparently, diagnosis and treatment strategies for TV and BV among pregnant women in this setting require reconsideration. Simple tests could contribute to improving diagnosis and reducing the disease burden of these conditions in sub-Saharan Africa.

Paper 3: Chlamydia and gonorrhoea in pregnant Batswana women: Time to discard the syndromic approach

Chlamydia and gonorrhoea are major causes of morbidity among women in developing countries (31). Both infections have been associated with pregnancy-related complications, and case detection and treatment in pregnancy is essential (32). In countries without laboratory support, the diagnosis and treatment is based on the syndromic approach, but for cervical infections, this strategy is neither sensitive nor specific (6). As case finding with specific diagnostic tests have been out of reach, risk scores based on sociodemographic risk factors, symptoms or signs of infection, urine sticks and microscopy have been explored as screening tools to identify asymptomatic infections among pregnant women (2, 48, 54, 56).

In this study we measured the prevalence of chlamydia and gonorrhoea among antenatal care attendees in Botswana. We evaluated the syndromic approach for the detection of cervical infections in pregnancy, and determined if risk scores could improve the diagnostic accuracy.

Of the 703 women, 51 (8%) were infected with *C trachomatis,* and 21 (3%) with *N gonorrhoeae*. Age was the strongest predictor of cervical infection. The prevalence of infection was highest among teenagers (22%, 95% confidence interval (CI): 13 to 32), whereas two-thirds of the infections were within the largest age group: women 20-29 years. No symptoms predicted cervical infection, and subsequently, the VDS algorithm did not identify infected women (LR+ 1.1, 95% CI: 0.6 to 1.9). The current practice of clinical screening for signs of vaginal discharge (excluding candida-like discharge) also had low discriminative ability (LR+ 1.5, 95 % CI 1.1-1.9).

The sociodemographic, clinical, and microscopy-based risk scores performed similar in the management of *N gonorrhoeae* and *C trachomatis* infection; all suffered from the choice between low sensitivity and low specificity. With a cut-off taken at an acceptable sensitivity of minimum 0.7, six pregnant women would be prescribed multiple antibiotic regimens unnecessarily per true case treated. With a cut-off at a sensitivity of 0.4, the majority of the cervical infections would remain untreated, and four pregnant women would still be unnecessary treated with multiple antibiotics per infected women.

Most of the antenatal care attendees in Botswana with cervical infection go undetected through normal antenatal care services. Our results show that the vaginal discharge algorithm is no better than random treatment in this population. A substantial improvement of the management of cervical infections in antenatal care in developing countries seems impossible without specific diagnostic tests. We argue that Botswana could well serve as an exploratory site for the use of rapid tests for chlamydia and gonorrhoea. Without such tests, health authorities in sub-Saharan Africa should consider reallocating their resources to other STI measures rather than diagnosing and treating cervical infections inadequately in antenatal care.

Paper 4: Costs and health consequences of chlamydia management strategies among pregnant women in sub-Saharan Africa

Chlamydia trachomatis infection is the most common bacterial STI worldwide, with highest prevalences in sub-Saharan Africa (29). It is a major cause of morbidity, particularly among women and neonates (31). The majority of infected women is asymptomatic and will not be diagnosed with the current syndromic management – thereby risking the development of complications and transmission of the infection. Low specificity of the strategy results in high levels of overtreatment, which increases drug costs and the risk of drug resistance (45). Simple, affordable and preferably on-site tests are needed to improve the management of *C trachomatis* infections in the developing world (12).

The aim of this economic evaluation was to compare the costs and health consequences in sub-Saharan Africa of screening with a POC test versus syndromic management of chlamydia in the antenatal care – from the health care providers' perspective. Two treatment alternatives in pregnancy were evaluated: erythromycin and azithromycin; doxycycline was modelled to partners. Three screening options were evaluated: screening all women, screening women under 30, and screening women less than 20 years.

A decision analytic model was developed to compare the diagnostic and treatment strategies, using Botswana as a case. Model input was based upon 1) our study of 703 antenatal care attendees in Botswana, 2) literature reviews and 3) experts' opinions. Probabilities and costs were given a base case value and upper and lower values - to capture and evaluate the uncertainty, and to ensure relevance to other countries. We expressed the

study outcome in terms of costs (US$), cases cured, magnitude of overtreatment and successful partner treatment.

The results of this study indicate that there may be substantial benefits from changing current diagnostic and treatment strategies for chlamydia in the antenatal care in sub-Saharan Africa. Azithromycin was less costly and more effective than was erythromycin. Compared with syndromic management, testing all attendees at the first visit with a 50%-sensitive POC test increased the number of cases cured from 1 500 to 2 400 in a population of 100 000 women, at a cost of US$ 87 per additional case cured. With a 75%-sensitive POC test, the number of cases cured increased to 3 500, at a cost of US$ 38 per additional case cured. This cost was lower in high-prevalence populations or if testing was restricted to teenagers. The POC tests provided the advantage of substantial reductions in overtreatment with antibiotics and improved partner management. In conclusion, using POC tests to diagnose chlamydia during antenatal care in sub-Saharan Africa entails greater health benefits than syndromic management does. Changes in diagnostic strategy and treatment regimens may improve people's health and even reduce health care budgets.

Discussion

General comments

The prevalence of cervical and vaginal infections among pregnant women in Botswana is very high. The results in this thesis indicate that there may be substantial benefits in improving the management of these conditions in antenatal care in sub-Saharan Africa. In the decision analysis of diagnostic and treatment strategies for chlamydia, the prevailing syndromic management of all attendees was the least effective, it incurred high costs per case cured and entailed considerable overtreatment.

Methodology of the epidemiological study

Study design

We used a cross-sectional study design to determine the prevalence of STIs/RTIs and to evaluate the syndromic approach among antenatal care attendees in Botswana. This type of observational study is well suited and commonly used to find prevalences and risk factors of disease. The method provides a description of the population only at the time when information is collected. The use of confidence intervals reduces the uncertainties in prevalence related to sample size and enables us to generalize from the study population to the antenatal care population in Gaborone. The incidences of the STIs/RTIs, or any increase or decrease in the prevalences over time is not studied with this design.

Not all aspects of the vaginal discharge syndrome are captured in this thesis. I performed the clinical examinations of all the attendees myself, and the evaluation of the algorithm is based on my clinical findings in a study setting. Thus, this study can indicate, but not provide exact information of sensitivity and specificity of the algorithm performed

by nurses in routine practice. Clinical signs – as the assessment of normal versus abnormal vaginal discharge in pregnancy – are to a certain extent subjective, and nurses' assessment may differ from mine. In addition, a study setting is close to ideal, measuring efficacy rather than effectiveness. As discussed in the introduction, the syndromic approach is vulnerable to performance of the clinicians. An observational study of the STI management in Botswana showed that among female STI patients, adequate history was taken in 25% of the consultations, adequate examination in 23% (7).

Sample and representativeness

As described in the methods, we made an effort to ensure a study population representative of antenatal care attendees in Gaborone. The age distribution in the sample is comparable to the antenatal care attendees in Gaborone and in Botswana in 2000 (Appendix 4). Age is the most important predictor of having an STI. There are 10% teenaged participants in our study, compared to 14% in the population of antenatal care attendees in Gaborone and 20% in Botswana in the year 2000. If anything, this may result in an underestimate of the STI prevalences.

The level of health care is comparable throughout Botswana, and HIV prevalence among pregnant women is similar in urban and rural areas (76). In a previous national study, we found slightly, but significantly higher prevalences of trichomoniasis, gonorrhoea and/or syphilis in rural areas. Combined with an antenatal coverage of 95%, this situation leads us to believe that we present an adequate picture of the prevalence and management challenges of cervical and vaginal infections in pregnant women in the country as a whole (104).

Both new and repeat attendees were included in this study. By including repeat attendees, we also included attendees who had been diagnosed with and treated for STIs/RTIs earlier in pregnancy. This gave us epidemiological data to examine the effectiveness of the vaginal discharge syndrome, such as prevalence of infection among women who had and women who had not received treatment. To the extent the treatment had been effective; this may have resulted in an underestimation of the RTI/STI prevalences. To exclude 34 women on STI treatment may also have led to an underestimate of these prevalences.

Validity

When determining RTI/STI prevalence, and in the evaluation of the vaginal discharge syndrome algorithm, we immediately encounter "*The gold standard problem*". Most infectious diseases do not have a perfect reference test which can reveal the true infection status in an individual. When evaluating the sensitivity and specificity of a diagnostic tests in the absence of a gold standard, discrepant analysis has been widely used to solve this methodological challenge (105). In discrepant analysis, the samples which are positive with the new diagnostic test and negative with the imperfect reference test are subjected to additional testing – usually with a third test. Subsequently, cases which are positive with the additional test will be reclassified. The method is criticized as severely biased, but other statistical methods do also have to rely on "empirically unverifiable assumptions about the unknowns of the situation" (106).

The exact sensitivity and specificity of the diagnostic tests we have used to identify STIs/RTIs in this study, and following, the exact prevalences, can not be determined. The

performance of a diagnostic test in a given setting is dependent on the sampling procedures and transport, the qualities of the test, the reference standard used and the experience and skills of the laboratory staff. The literature provides approximate estimates for sensitivity and specificity – with the limitations described above. The specimens were tested at the NHL by either a very experienced laboratory technician or technicians who were trained in STI analyses prior to the study. We have not performed reproducibility testing or more than standard quality control of the laboratory analyses, mainly due to resource constraints.

If the sensitivity and specificity of a diagnostic method had been known exactly, the true prevalence can be calculated using the equation below:

$$\textit{True prevalence} = \frac{\textit{(Observed prevalence + Specificity – 1)}}{\textit{(Sensitivity + Specificity - 1)}}$$

Chlamydia and gonorrhoea were identified with LCR amplification technology of cervical specimens. Published evaluations of test have found a sensitivity of 85-97% and a specificity of 97-100% (ref). Assuming for example a sensitivity of 85% and a specificity of 95% in the diagnosis of chlamydia, the true prevalence in our study population would have been:

$$\textit{True prevalence} = \frac{\textit{(7.5+ 0.95 – 1)}}{\textit{(0.85 + 0.95 - 1)}} = 8.75$$

Trichomoniasis was identified with wet-mounts and culture. With the development of molecular techniques to identify *T vaginalis*, it has become evident that culture and microscopy miss a substantial proportion of the infections (68, 70). With the use of molecular techniques as a reference standard, the sensitivity of wet-mounts and culture combined has been found to be approximately 70%. The techniques identify live, motile

trichomonads, resulting in close to 100% specificity. This implies that the true prevalence of trichomoniasis is higher than found in this study. However, it is common practice to report unadjusted prevalences.

Bacterial vaginosis is a clinical syndrome presenting with a malodorous vaginal discharge and increased vaginal pH. It is associated with a group of genital microorganisms rather than a single agent, and the alteration of the normal vaginal flora is a continuum - making the diagnosis challenging. There are two well described diagnostic methods for bacterial vaginosis: Amsel's criteria, a clinical diagnosis including a wet smear, and Nugent's criteria based on a Gram stain of vaginal fluid. As the clinical signs are subtle and dependent on the clinician performing the test, bacterial vaginosis was identified using Gram stain, acknowledged as a reproducible and reliable test and commonly used as the diagnostic standard (72). The slides which were used to identify bacterial vaginosis were meant to be re-read in Norway, but they were stolen together with other valuables from my suitcase at Johannesburg airport. Thus, we have no quality control of the diagnosis of bacterial vaginosis.

Candida species were identified with wet-mounts, gram stain and culture, and patients with positive results were classified having variants of vulvovaginal candidiasis according to their presence of symptoms and signs of infection. The identification and typing of candida species will presented and discussed in a separate paper.

In our evaluation of the vaginal discharge algorithm, we have used laboratory verified diagnosis as the reference standard, illustrated in Table 6. This is in line with other research evaluating the syndromic approach (107-109), but the method is unavoidably biased. As the reference standard is imperfect, *all cells* will have misclassified cases (false

positive or false negative laboratory results), affecting the calculation of sensitivity and specificity. In our example below, 93 cases in which the algorithm was positive and the laboratory results negative were classified as false positive. The disconcordance might have been due to a false negative laboratory result, and if so, the evaluation renders the algorithm less sensitive than correct. Among the 11 cases in which the algorithm and the laboratory test was positive, there may be false positive test results, rendering the algorithm more sensitive than correct – and so on. We acknowledge the described misclassification, but have not attempted to adjust for it.

Table 6 Evaluation of the vaginal discharge algorithm diagnosis of cervicitis

		Cervical infection					
		Positive		Negative		N	(%)
		n	(%)	n	(%)		
Syndromic approach	Positive	11	(16)	93	(15)	104	(15)
	Negative	56	(84)	543	(85)	599	(85)
	Total	67	(100)	636	(100)	703	(100)

Methodology of the economic evaluation

Knowledge gaps in the burden of STIs

Major challenges in performing economic evaluations of chlamydia management lie in estimating the health- and economic benefits of the interventions (Box 5). The main objectives, or benefits, of diagnosing and treating chlamydia are to prevent complications and reduce onward transmission. However, the natural history of *C trachomatis* is not fully known and the risk of developing complications not firmly determined (110). Some of the complications caused by the infection are immediate, whilst the majority occur after a long time and are difficult to measure. In addition, pelvic inflammatory disease, extrauterine

pregnancy, premature labour, neonatal infections and HIV transmission occur both because of and independent of chlamydia. Next, trial evidence for the long term effectiveness of chlamydia screening or case management is very limited, and there are no trials on the use of POC tests.

Box 5 Benefits of a health intervention

1. Health consequences
a) Reduced morbidity and complications
b) Reduced mortality

2. Economic consequences
a) Direct benefits
   Saved future health care costs
b) Indirect benefits
   Improved future working capacity
   The value of less personal pain and loss

In Botswana, as in most developing countries, estimates of the occurrence of chlamydia related complications are largely unavailable. To the extent any information or statistics exists, the proportion of these conditions that may be attributed to chlamydia is unknown. Similarly, evidence is too weak to estimate the proportion of HIV-infections attributable to and preventable by treating chlamydia in this population, or to estimate any reduction in the mother-to-child transmission of HIV. Consequently, modelling DALYs or QALYs lost due to *C trachomatis* infections in the population was virtually impossible.

The costs to the health services in sub-Saharan Africa of a given complication of STIs or of a HIV infection are also nearly impossible to estimate – and thereby also the economic benefits of diagnosing and treating STIs/RTIs. In Botswana, the public health sector operates with overall lump sums, for example salaries or drug use in primary health care (111). There are no separate budgets at hospitals and clinics or for specific programs

such as antenatal care, and the cost of for example, a hospital stay or specific diagnostic or treatment procedures is unknown.

Our reluctance to use chlamydia related complications or HIV-infections averted as the outcome in our analysis concurs with an ongoing debate on chlamydia screening in high income countries (91, 94, 110). Authors of systematic reviews of the evidence point out that the excess risk of pelvic inflammatory disease and infertility in women who have had chlamydia is not adequately studied (112, 113). As the complication rates are based on data from high-risk populations, case-control studies and data not accounting for misdiagnosis, it is argued that an overestimation of the current complication rates is likely. This has obvious implications for the interpretation of cost-effectiveness studies which have used these probabilities, rendering the benefits of chlamydia screening too optimistic. A recent editorial in *Sexually Transmitted Infections* concluded that 'more work is required before we can fully justify and appropriately design chlamydia control programs' in this setting (114).

Similarly, the effect of STI management on HIV transmission in a specific population is very difficult to predict (36, 37). The size and range chosen for the co-factor parameter in a cost-effectiveness model will directly influence the results. Several reviews of cost-effectiveness analyses as applied to HIV/AIDS prevention strategies have noted the paucity of data, and in particular, the dearth of studies from low and middle income countries (115, 116).

Validity and generalizability of the model

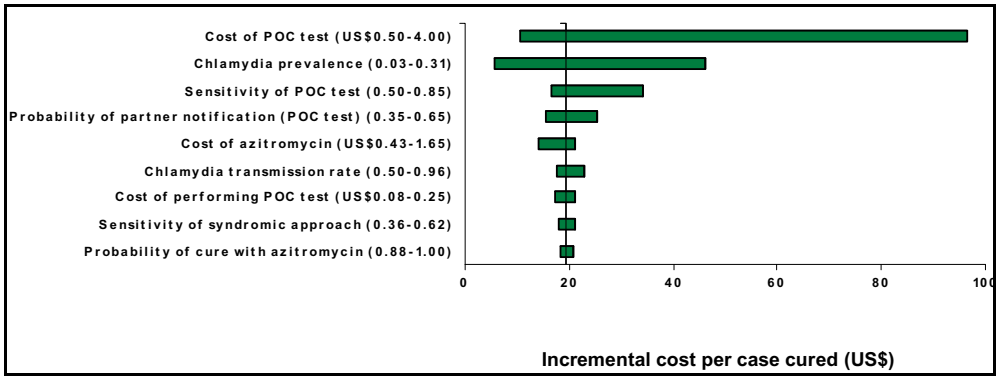
There is a particular need to exercise caution when interpreting results of an economic evaluation. The uncertainty is pervasive, entering the evaluation process at every stage (117). To a large extent, the uncertainty in an analysis reflects a true, real world uncertainty. A model is only as good as the input, and the availability, quality and generalizability of data will influence the results. In addition, there is uncertainty related to the choice of model and the model structure, and to how the analyses are conducted.

The choice of a static model is discussed below. Obviously, our decision tree is a simplification of the reality. We did not attempt to assess the effect of the model uncertainties, whereas the parameter uncertainties were explored using sensitivity analysis. The one-way sensitivity analysis showed how higher or lower parameter values would change the incremental cost per case cured of the POC-tests strategy. In the tornado diagram, the results of the one-way sensitivity analysis are brought together in a single graph, illustrating to what extent the parameter uncertainty has an effect on the results (Figure 8). The bars are arranged in order, with the widest bar at the top (the most critical uncertainty).

Test costs and drugs purchased in international markets are the cost drivers in the model, and these prices will be relatively similar across countries. The cost of the POC test was the largest source of variation in the results. As prevalences may differ in other settings or change over time, we analysed a prevalence range from 3% to 31%, representing the range of prevalences reported in other studies among antenatal care attendees in sub-Saharan Africa (118). This broad range made prevalence the second most important source of variation in the results. Authorities who consider implementing a POC test strategy are

likely to have more exact estimates for the three most critical parameters in the model: the chlamydia prevalence in the population, the POC test sensitivity as well as cost proposals for the test. The model is also available to anyone who wants to modify the decision trees or run the analysis with other model input parameters.

Figure 8 Tornado diagram



Static versus dynamic modelling

The majority of published cost-effectiveness analyses of chlamydia screening are based on static models, commonly a decision tree model (91). Decision trees work well in analysing relatively simple events over a limited time horizon (88). In 2000, the first dynamic transmission models of chlamydia screening were published (119, 120). These models aim to incorporate the complexity of an infectious disease, including the impact of re-infection, continued transmission and the change of prevalence over time. Welte *et al.* have compared a static and a dynamic model of opportunistic chlamydia screening of in the Netherlands, and showed that the different model approaches produced different results (121). The static model estimated a cost-effectiveness of US$ 700 per complication averted, whereas the

dynamic model rendered net savings. The diverging outcomes were explained with the transmission chains considered in the dynamic model and the assumptions about the screening program's influence on chlamydia prevalence.

There is a role for both static and dynamic models in the evaluation of *C trachomatis* screening programs (122). We chose to develop a static model on the basis of three arguments: First, the use of dynamic models has been advocated in the evaluation of large-scale screening programs. Programs targeting smaller groups such as pregnant women have been specifically mentioned as an exception, as they are less likely to lower the force of infection (92). Second, due to the use of intermediate outcomes as discussed above, the analysis has a limited time horizon. Third, dynamic models require much more data, such as the population's sexual behavior and the natural history of *C trachomatis* infections. How is the formation and termination of steady and casual partnerships or the frequency of sexual intercourse in these relations? For our population, such information is at best very imprecise, and the additional data needed would be based on unreliable estimates or "educated guesses". For example, in our epidemiological study, almost all women stated that they had one partner the last year. Simultaneously, the prevalences of STIs were very high. With these premises, it is questionable whether a dynamic model would perform better than a static model.

Prevalence of sexually transmitted infections

Systematic and comprehensive STI surveillance to facilitate disease control efforts is almost non-existing in developing countries, and most epidemiological data have been obtained from prevalence studies (45). In Botswana, STI surveillance is based on STI

syndromic case reports and periodically performed studies of syndrome etiology to guide therapy. These activities are not reliable for assessment of STI incidence or prevalence or to measure the impact of STI/HIV prevention program s (123).

In the prevalence assessment in this study, we find that 54% of antenatal care attendees in Gaborone have chlamydia, gonorrhoea, trichomoniasis or bacterial vaginosis. Published studies of STIs among pregnant women in other countries in sub-Saharan Africa show similar trends in the prevalence of cervical and vaginal infections. In our study, 8% have chlamydia, compared to rates between 6% in Tanzania and 13% in Cape Verde (2, 124). Gonorrhoea is found in 3% of the women, compared to rates that range from 2% in Gabon to 8% in South Africa (125, 126). The prevalence of trichomoniasis in Gaborone was 18%, in other studies of low-risk women in sub-Saharan Africa, the prevalence ranges from 10–31% (45, 101). The bacterial vaginosis prevalence of 38% also corresponds well with other studies. Bacterial vaginosis is shown to be particularly common in the sub-Saharan region, where prevalences up to 50% are not uncommon (102).

There are four other studies on STI epidemiology in Botswana, from 1993-2003, of which three are unpublished. There are indications that the etiology of the STI syndromes has changed since syndromic management was introduced in Botswana in 1992; with a reduction in bacterial STIs and trichomoniasis (127). However, the populations studied are small, from different health facilities in different towns, and the studies are conducted by different researchers using different laboratory methods. Bearing this in mind, we have aggregated the prevalence results for comparison (Table 7).

Table 7 Studies on STI epidemiology in Botswana*

	Chlamydia	Gonorrhoea	Trichomoniasis	Bacterial vaginosis	Candida species
1993 study					
STI clients (102)	16	16	13	53	49
FP clients (102)	20	7	17	47	49
1997 study					
STI clients (57)	-	4	11	-	35
FP clients (131)	-	4	13	-	28
ANC clients (341)	-	5	28	-	46
2000-2001 study					
ANC clients	**8**	**3**	**18**	**38**	**58**
2002 study					
STI clients (431)	14	6	10	59	15
FP clients (269)	12	3	7	49	10
2001-2003 study					
ANC clients (HIV+) (717)	10	5	21	-	-

*The study presented in this thesis is the 2000-2001-study, with prevalences in bold

The effectiveness of syndromic management

This study has evaluated the effectiveness of the vaginal discharge syndrome from two perspectives. First, we measured the prevalence of infections among new compared to repeat attendees who had already been provided with standard care. The high prevalences among repeat clients indicate low effectiveness of the syndromic management. Second, the sensitivity and specificity of the vaginal discharge algorithm were estimated using laboratory verified diagnosis as the reference standard. For cervical infections as well as for trichomoniasis and bacterial vaginosis, the algorithm was no better than random treatment. We conclude that most of the women with these conditions go untreated through normal antenatal care services, and that the currently provided standard management is inappropriate. *Candida* species were identified in 59% of the women, strongly associated with symptoms of vaginal discharge, and probably the pathological cause most often leading to this complaint in pregnancy. Candida is not associated with any serious

complications, and we observed during the data collection that vulvovaginal candidiasis was under-emphasized among the nurses when managing symptomatic women.

Improving health care seeking, clinical management, the prescription of effective drugs, patient compliance and partner notification may all have an effect of the overall burden of STIs. Research has tended to focus on the performance of syndromic management (43). Not all evaluations are directly comparable to ours, due to differences in populations studied, the laboratory methods used or differences in the protocols evaluated. However, our results concur with the overall finding that the vaginal discharge algorithm is neither sensitive nor specific in the diagnosis of chlamydia and gonorrhoea, or trichomoniasis or bacterial vaginosis - particularly not in antenatal care attendees (43, 45, 57). It can be argued that this part of the study fall into the "me too"-research category. However, it is a major concern that this strategy continuously and frequently is in use in the antenatal care. I believe that it is essential to continue to express that the current management of these potentially serious infections among pregnant women in Sub-Saharan Africa is inadequate, and to highlight the need for a replacement.

There is also a need for attention to what happens to the STI clients after the encounter with the health care provider. Most governments are interested in ensuring availability and access to drugs, but the issue of *adequate drug use* should receive increased attention (128, 129). We find that antenatal care clients with a recent history of STI symptoms who have been prescribed ceftriaxone are successfully treated for gonorrhoea. This drug is provided as a single injection in the "dressing room" at the clinic immediately after the consultation. Clients who have been prescribed erythromycin have identical prevalence of chlamydia as the clients without such history. When erythromycin

is prescribed during a consultation, the patients have to collect the tablets at the clinic's "dispensary" and then take one tablet four times daily the next week. It is known that complex treatment regimens as well as side effects of drugs reduce patient compliance (50). The efficacy of erythromycin is high (130, 131), and we argued that low compliance most probably the main cause of the low treatment effect.

Seventeen of 703 women had been prescribed metronidazole during their pregnancy. None of these had a *T vaginalis* infection when included in the study, while 3 (18%) of them had bacterial vaginosis. The reduction in prevalence of *T vaginalis* and bacterial vaginosis among the treated women is not significant, but it is not unlikely that the lack of significance is due to low statistical strength. The results are in line with the knowledge that metronidazole is known to be effective against *T vaginalis* (132). The drug is slightly less effective against bacterial vaginosis, and more than 50% may have recurrence within two months of treatment (133).

Chlamydia management strategies

We compared the number of cases cured, overtreatment and partner treatment in our evaluation of chlamydia management strategies: intermediate, but reliable and meaningful outcome measures. Short-term outcomes are not ideal for making policy recommendations, but as the existing management requires substantial resources, information about possibilities for more advantageous resource use should be highly relevant to health policy makers. We found that in Botswana, the current costs for a cured infection, and thereby the current willingness to pay, were higher than for any of the evaluated alternatives.

Treatment for chlamydia

In practice, there are three recommended treatment alternatives to treat chlamydia in pregnancy: erythromycin 500 mg orally 4 times a day for 7 days, amoxicillin 500 mg orally 3 times a day for 7 days and azithromycin 1 g orally in a single dose (6, 134, 135). In the national guidelines in Botswana, the erythromycin regimen is the first choice. The epidemiological study of the effectiveness of erythromycin (Paper 1) indicated that low compliance to the erythromycin regimen reduces cure rates. The cost-effectiveness study (Paper 4) showed quite clearly that single-dose azithromycin was more effective and less costly than erythromycin. We evaluated azithromycin as an alternative to erythromycin because of the advantage that adherence can be guaranteed (131). Amoxicillin has not been discussed in this thesis. In general, the week-long regimen with amoxicillin has similar costs, cure rates and levels of adverse effects as azithromycin (130, 136).

Efficacy, tolerance, compliance, and cost are factors to consider when preparing guidelines for antibiotic treatment. After losing its patent, the price of azithromycin is lower than of erythromycin (136). With regards to compliance, erythromycin regimen is complex in itself, and patients who are diagnosed with the vaginal discharge syndrome are prescribed multiple drug regimens that require many tablets to be administered correctly. Compared to the alternatives, erythromycin has a significantly higher level of gastrointestinal side effects, which frequently discourages patients from complying with the regimen (134, 137). This may be especially problematic in women who experience pregnancy nausea.

Erythromycin has been on the market in more than 50 years and has been considered safe in pregnancy (131). There is less experience with azithromycin, but no

evidence of adverse effects when used in pregnancy (130, 131). In 2005, an epidemiological study from Sweden suggested a possible association between maternal erythromycin use and infant cardiovascular malformations (138). This resulted in a change in Norwegian guidelines, now recommending amoxicillin in the first and azithromycin in the second and third trimester (139). In 2008, the same Swedish research group presented the results of a new large study not confirming the association suggested earlier (140). The most recent STI management guidelines from the WHO are from 2003, and recommends erythromycin or amoxicillin to treat chlamydia in pregnancy. The use of azithromycin is commented as follows: "Preliminary data suggest that azithromycin is safe to use in pregnant women. However, the number of women in the trials so far is too small to assess safety for use in pregnancy as rare adverse outcomes are unlikely to be detected" (6).

An area of concern in Botswana as well as other sub-Saharan countries is that the pregnant women may be enrolled in the PMTCT program or be on treatment with highly active anti-retroviral therapy (HAART). Erythromycin is a strong inhibitor of the enzyme cytochrome P450 CYP3A4, which metabolize many of the antiretroviral drugs. The interactions are most problematic with concomitant use of erythromycin and protease inhibitors, used as second line HIV drugs – due to a risk of of QT prolongation. In general, azithromycin is a weaker inhibitor of CYP3A4, and will have less interaction with HIV drugs (personal communication with the Liverpool HIV Pharmacology Group and RELIS).

To summarize, countries recommending erythromycin to treat chlamydia in pregnancy should consider changing the treatment guidelines.

Point-of-care tests for chlamydia

In the cost-effectiveness model, even a POC test with 50% sensitivity increased the cases cured with 60%, reduced the over-treatment to 6% and reduced the number of partners who should not have been notified with 87% compared to the current level. These results concur with the body of knowledge that POC tests for chlamydia are necessary to improve effectiveness, reduce the excessive overtreatment and improve partner notification with the syndromic management (61).

The health benefits of improved case detection and treatment is not captured in this analysis. If successful chlamydia treatment reduces complications such as neonatal and post-partum infections, or reduces HIV transmission, the advantage of using POC tests increases (92). Further, the benefits of reducing the substantial over-treatment with POC tests do not only imply reduced costs of drug wastage. We estimated that 20 persons with syndromic approach and less than one with the POC test strategy were treated unnecessary with antibiotics per chlamydia infection cured. Although difficult to measure, the value for individuals of not being unnecessary diagnosed and treated for an STI, and the value of reducing the risk of antibiotic resistance in the population are aspects that need to be taken into account. Targeted partner notification is another important argument for introducing specific POC tests. Managing sexual partners of STI patients is essential to prevent re-infection, cure partners, break the chain of transmission and prevent complications (45). In studies from Africa, partner notification has been associated with potential harm, including domestic violence, and using an unspecific syndrome diagnosis as a basis for notifying partners is questionable (45, 49).

With regards to *introducing* POC tests, any new diagnostic technology should be assessed adequately to determine whether their application improves public health (106). Before recommending the routine use of POC tests for cervical infections in developing countries, carefully designed impact evaluations are needed.

Age-based case finding

Youth was the single factor most strongly associated with chlamydia among pregnant women in Botswana (141), which is consistent with established knowledge on STI epidemiology (44, 142). This is already utilized in the syndromic management guidelines: WHO recommends adding a risk assessment to the diagnosis of chlamydia and gonorrhoea with the vaginal discharge flowchart. The assessment should include population specific demographic and behavioral risk factors such as being less than 21 years, being unmarried and having more than one partner (6). In Botswana, the risk assessment is considered positive if the patient is under 21 years (Figure 2).

If POC tests are introduced, age can be useful as a screening tool in the traditional sense, to minimize the number of standard diagnostic tests by identifying people with a higher-than-average prevalence of infection (143). Chlamydia screening programs in high income countries commonly select people for testing based on their age (134, 144). The cost-effectiveness analysis indicates that adoption of age-restricted chlamydia treatment will entail lower program costs and be more cost-effective than would the management of all pregnant women. Testing pregnant teenagers may be a feasible and reasonable way of introducing POC tests for chlamydia to antenatal care programs in sub-Saharan Africa.

Should POC tests for chlamydia have priority in sub-Saharan Africa?

Ideally, research should provide policy makers with the answer to the question "Is diagnosing and treating STIs worthwhile, compared to health benefits that could be achieved from an alternative use of the resources?" Currently, evidence is too scarce to ensure that economic evaluations can assist optimally in ensuring allocative efficiency in the health sector in sub-Saharan Africa. A complete and credible database might be decades away, and priorities and decisions are made continuously. What can be said about prioritizing STI management in sub-Saharan Africa with our current knowledge? And what about POC tests for chlamydia?

Improving maternal and perinatal conditions and combating HIV/AIDS received substantial attention in the Millennium Declaration (15, 17) In general, diagnosing and treating STIs in developing countries have been considered highly cost-effective[2] (145, 146). Treatment of STIs is a strategy area that has already been prioritized in sub-Saharan Africa (97). It has been said that if countries are to have any chance of achieving their development goals, they need to re-evaluate existing strategies and replace less effective strategies with more effective ones (16). Chlamydia management in pregnancy is well within the scope of the development goals, and this study points to changes in diagnosis and treatment which may contribute to achieving these goals more efficiently. There is a critical health worker shortage the Region, but improving the current strategy is not likely to require allocation of additional human resources to STI management.

[2] The WHO has deemed interventions to be highly cost effective if they cost less than the gross domestic product (GDP) per capita to avert each disability adjusted life years (DALY) and cost effective if each DALY could be averted at a cost of between one and three times the GDP per capita - compared to a do nothing strategy

The Countdown to 2015 for Maternal, Newborn, and Child Survival monitors coverage of priority interventions to achieve the MDGs. With the publishing of the Countdown 2008 results, the need to better integrate and link program s and initiatives was advocated as one of four new directions that should be vigorously pursued (147). Introducing the use of POC tests to diagnose chlamydia in pregnancy is a clear example of a single, biologically based intervention that calls for cooperation between two existing programs and enables mutual benefits. A shift in the diagnostic strategy of chlamydia in antenatal care fits well within the ongoing training and supervision activities of the national STI management programs. Integrating POC testing with antenatal care can relatively easily be incorporated in the routine management of the attendees, and thereby facilitate the uptake and coverage of the intervention. The Countdown has shown that improvements in services that can be routinely scheduled, such as antenatal care, are easier to achieve than in curative services (148).

With regard to need principles for allocation of health resources, it can not be said that chlamydia management is an intervention towards the most severely ill patients. As the morbidity related to STIs disproportionately affects women, it could be argued that it reduces inequities in health between different groups in the population. Due to the high antenatal care coverage in sub-Saharan Africa, improved diagnosis of chlamydia in pregnancy is absolutely a health investment which many could benefit from (30, 118). To introduce a service that aims to cover all reproductive women and subsequently their children and their partners promotes a high degree of fairness in resource distribution.

Concluding remarks

This thesis demonstrates severe shortcomings of the management of cervical and vaginal infections in pregnant women in Botswana, and indicates that changing diagnostic and treatment strategies may improve maternal and infant health as well as resource use. The economic evaluation provides policy makers with information to decide whether to continue the current chlamydia management or to implement new strategies - given that chlamydia management should be funded.

During the work with the economic analysis model, it became evident that using DALYs or QALYs as an outcome measure for the chlamydia management was out of reach; the knowledge gaps were too large. There is an overall lack of data, from the natural history of STIs to the health- and economic benefits of health interventions in sub-Saharan Africa. If the international research community was willing to prioritize their resources differently, and need principles, maximizing principles or egalitarian principles were included in their criteria, this is a possible research area.

I hope this work can contribute to an increased awareness of the need to improve the management of STIs in pregnant women in sub-Saharan Africa. I also hope that it has illuminated the potential of cost-effectiveness analysis to aid decision making and priority setting in health care in resource constrained settings.

References

1. World Bank. World Development Report 1993: Investing in health. New York: Oxford University Press, 1993.
2. Mayaud P, Uledi E, Cornelissen J, ka-Gina G, Todd J, Rwakatare M, *et al.* Risk scores to detect cervical infections in urban antenatal clinic attenders in Mwanza, Tanzania. *Sexually Transmitted Infections* 1998;**74** Suppl 1:139-146.
3. Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sexually Transmitted Diseases* 1992;**19**:61-77.
4. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, *et al*. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530-536.
5. UNAIDS. The public health approach to STD control: UNAIDS Technical Update. Geneva: UNAIDS, 1998.
6. World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003.
7. Boonstra E, Lindbaek M, Klouman E, Ngome E, Romoren M, Sundby J. Syndromic management of sexually transmitted diseases in Botswana's primary health care: quality of care aspects. *Tropical Medicine & International Health* 2003;**8**:604-614.
8. Vuylsteke BL, Ettiegne-Traore V, Anoma CK, Bandama C, Ghys PD, Maurice CE, *et al*. Assessment of the validity of and adherence to sexually transmitted infection algorithms at a female sex worker clinic in Abidjan, Cote d'Ivoire. *Sexually Transmitted Diseases* 2003;**30**:284-291.
9. Kane BG, Degutis LC, Sayward HK, D'Onofrio G. Compliance with the Centers for Disease Control and Prevention recommendations for the diagnosis and treatment of sexually transmitted diseases. *Academic Emergency Medicine* 2004;**11**:371-377.
10. Moses S, Elliott L. Sexually transmitted diseases in Manitoba: evaluation of physician treatment practices, STD drug utilization, and compliance with screening and treatment guidelines. *Sexually Transmitted Diseases* 2002;**29**:840-846.
11. Buve A, Changalucha J, Mayaud P, Gavyole A, Mugeye K, Todd J, *et al*. How many patients with a sexually transmitted infection are cured by health services? A study from Mwanza region, Tanzania. *Tropical Medicine & International Health* 2001;**6**:971-979.
12. Mabey D, Peeling RW, Perkins MD. Rapid and simple point of care diagnostics for STIs. *Sexually Transmitted Infections* 2001;**77**:397-398.
13. World Health Organization. World Health Statistics 2007. Geneva: WHO, 2007.
14. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;**367**:1747-1757.
15. United Nations. United Nations Millennium Declaration. New York: UN, 2000. Available at: http://www.un.org/millennium/declaration/ares552e.pdf.
16. Evans DB, Adam T, Edejer TT, Lim SS, Cassels A, Evans TG, *et al.* Time to reassess strategies for improving health in developing countries. *BMJ* 2005;**331**:1133-1136.

17. World Health Organization. Health and the Millennium Development Goals. Geneva: WHO, 2005. Available at: http://www.who.int/hdp/publications/mdg_en.pdf.
18. Robberstad B. Economic evaluation of health interventions in sub-Saharan Africa. Bergen: University of Bergen, 2005.
19. Nordstrom A, Tan-Torres Edejer T, Evans D. What will it cost to attain the health MDGs? *Bulletin of the World Health Organization* 2007;**85**:246.
20. World Health Organization. Working together for health. The World Health Report 2006. Geneva: WHO, 2006.
21. Folland F, Goodman AG, Stano M. The economics of health and health care. New Jersey: Prentice-Hall, 2001.
22. Baltussen R, Niessen L. Priority setting of health interventions: the need for multi-criteria decision analysis. *Cost Effectiveness and Resource Allocation* 2006;**4**:14.
23. Williams I, Bryan S. Understanding the limited impact of economic evaluation in health care resource allocation: a conceptual framework. *Health Policy* 2007;**80**:135-143.
24. Hutubessy R, Baltussen R, Tan Torres-Edejer T, Evans D. Generalised cost-effectiveness analysis: an aid to decision making in health. *Applied Health Economics and Health Policy* 2002;**1**:89-95.
25. Hutubessy R, Chisholm D, Edejer T, WHO-CHOICE. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost Effectiveness and Resource Allocation* 2003;**1**:8.
26. World Bank. The World Bank list of economies. July, 2008. Avalilable at: http://siteresources.worldbank.org/DATASTATISTICS/Resources/CLASS.XLS
27. Wikipedia. Sub-Saharan Africa. Available at: http://en.wikipedia.org/wiki/Sub-Saharan_Africa
28. United Nations Population Fund. UNFPA Worldwide: Sub-Saharan Africa. Available at: http://www.unfpa.org/africa/overview.cfm.
29. World Health Organization. Global prevalence and incidence of selected curable sexually transmitted infections. Geneva: WHO, 2001. Available at: www.who.int/hiv/pub/sti/pub7/en/.
30. World Health Organization. Antenatal care in developing countries: promises, achievements and missed opportunities: anaanalysis of trends, levels and differentials, 1990-2001. Geneva: WHO, 2003.
31. Over M, Piot P. HIV infections and sexually transmitted diseases. In: Jamison DT MW, Measham AR, Bobadilla JS, eds. Disease control priorities in developing countries. Oxford: Oxford University Press: 1993:455-527.
32. Mullick S, Watson-Jones D, Beksinska M, Mabey D. Sexually transmitted infections in pregnancy: prevalence, impact on pregnancy outcomes, and approach to treatment in developing countries. *Sexually Transmitted Infections* 2005;**81**:294-302.
33. UNAIDS. The public health approach to STD control. Geneva: UNAIDS, 1998.
34. World Bank. World Development Report 1993, Investing in health. New York: Oxford University Press, 1993.
35. UNAIDS/WHO. Consultation on STD interventions for preventing HIV: what is the evidence? Geneva: UNAIDS/WHO, 2000.

36. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sexually Transmitted Infections* 1999;**75**:3-17.
37. Sexton J, Garnett G, Rottingen JA. Metaanalysis and metaregression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infection. *Sexually Transmitted Diseases* 2005;**32**:351-357.
38. Gilson L, Mkanje R, Grosskurth H, Mosha F, Picard J, Gavyole A, *et al.* Cost-effectiveness of improved treatment services for sexually transmitted diseases in preventing HIV-1 infection in Mwanza Region, Tanzania. *Lancet* 1997;**350**:1805-1809.
39. Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, *et al.* Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet* 1999;**353**:525-535.
40. Grosskurth H, Gray R, Hayes R, Mabey D, Wawer M. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet* 2000;**355**:1981-1987.
41. World Health Organization. Sexually transmitted and other reproductive tract infections. A guide to essential practice. Geneva: WHO, 2005.
42. Vuylsteke B. Current status of syndromic management of sexually transmitted infections in developing countries. *Sexually Transmitted Infections* 2004;**80**:333-334.
43. Dallabetta GA, Gerbase AC, Holmes KK. Problems, solutions, and challenges in syndromic management of sexually transmitted diseases. *Sexually Transmitted Infections* 1998;**74** Suppl 1:1-11.
44. Brabin L. Clinical management and prevention of sexually transmitted diseases: a review focusing on women. *Acta Tropica* 2000;**75**:53-70.
45. Mayaud P, Mabey D. Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. *Sexually Transmitted Infections* 2004;**80**:174-182.
46. Blankhart D, Muller O, Gresenguet G, Weis P. Sexually transmitted infections in young pregnant women in Bangui, Central African Republic. *International Journal of STD & AIDS* 1999;**10**:609-614.
47. Fonck K, Kidula N, Jaoko W, Estambale B, Claeys P, Ndinya-Achola J, *et al.* Validity of the vaginal discharge algorithm among pregnant and non-pregnant women in Nairobi, Kenya. *Sexually Transmitted Infections* 2000;**76**:33-38.
48. Mulanga-Kabeya C, Morel E, Patrel D, Delaporte E, Bougoudogo F, Maiga YI, *et al*. Prevalence and risk assessment for sexually transmitted infections in pregnant women and female sex workers in Mali: is syndromic approach suitable for screening? *Sexually Transmitted Infections* 1999;**75**:358-359.
49. Hawkes S, Mabey D, Mayaud P. Partner notification for the control of sexually transmitted infections. *BMJ* 2003;**327**:633-634.
50. Sanson-Fisher R, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. *Diagnostic Microbiology & Infectious Disease*1992;**15** Suppl4:103-109.
51. Kirungi WL, Ball M, Rahman M, Rogoeng M. Observational health facility survey for the evaluation of STD case management in primary health care facilities in Botswana. Gaborone: Ministry of Health, 1998.

52. Paxton LA, Kiwanuka N, Nalugoda F, Gray R, Wawer MJ. Community based study of treatment seeking among subjects with symptoms of sexually transmitted disease in rural Uganda. *BMJ* 1998;**317**:1630-1631.
53. World Health Organization. Global strategy for the prevention and control of sexually transmitted infections: 2006-2015. Geneva: WHO, 2007.
54. Vuylsteke B, Laga M, Alary M, Gerniers MM, Lebughe JP, Nzila N, *et al*. Clinical algorithms for the screening of women for gonococcal and chlamydial infection: evaluation of pregnant women and prostitutes in Zaire. *Clinical Infectious Diseases* 1993;**17**:82-88.
55. Temmerman M, Njagi E, Nagelkerke N, Ndinya-Achola J, Plummer FA, Meheus A. Mass antimicrobial treatment in pregnancy. A randomized, placebo-controlled trial in a population with high rates of sexually transmitted diseases. *Journal of Reproductive Medicine*1995;**40**:176-180.
56. Mayaud P, Grosskurth H, Changalucha J, Todd J, West B, Gabone R, *et al.* Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics. *Bulletin of the World Health Organization* 1995;**73**:621-630.
57. Hylton-Kong T, Brathwaite AR, Del Rosario GR, Kristensen S, Kamara P, Jolly PE, *et al.* Marginal validity of syndromic management for reproductive tract infections among pregnant women in Jamaica. *International Journal of STD & AIDS* 2004;**15**:371-375.
58. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: a barrier to effective health care. *Clinical Infectious Diseases* 2006;**42**:377-382.
59. Gift TL, Pate MS, Hook EW, Kassler WJ. The rapid test paradox: when fewer cases detected lead to more cases treated: a decision analysis of tests for Chlamydia trachomatis. *Sexually Transmitted Diseases* 1999;**26**:232-240.
60. Mabey D, Peeling RW. Rapid diagnostic tests for sexually transmitted infections. *IPPF Medical Bulletin* 2002;**36**:1-3.
61. World Health Organization. Mapping the landscape of diagnostics for sexually transmitted infections. Geneva: WHO, 2004.
62. Peeling RW, Mabey D, Herring A, Hook EW. Why do we need quality-assured diagnostic tests for sexually transmitted infections? *Nature Reviews Microbiology* 2006;**4**:909-921.
63. Yin Y-P, Peeling RW, Chen X-S, Gong K-L, Zhou H, Gu W-M, *et al.* Clinic-based evaluation of Clearview Chlamydia MF for detection of Chlamydia trachomatis in vaginal and cervical specimens from women at high-risk in China. *Sexually Transmitted Infections* 2006;**82**:33-37.
64. Witkin SS, Bongiovanni AM, Inglis SR. Detection of endocervical anti-Chlamydia trachomatis immunoglobulin A in pregnant women by a rapid, 6-minute enzyme-linked immunosorbent assay: comparison with PCR and chlamydial antigen detection methods. *Journal of Clinical Microbiology* 1997;**35**:1781-1783.
65. Swain GR, McDonald RA, Pfister JR, Gradus MS, Sedmak GV, Singh A. Decision analysis: point-of-care Chlamydia testing vs. laboratory-based methods. *Clinical Medicine & Research* 2004;**2**:29-35.

66. Vickerman P, Watts C, Peeling RW, Mabey D, Alary M. Modelling the cost effectiveness of rapid point of care diagnostic tests for the control of HIV and other sexually transmitted infections among female sex workers. Sexually Transmitted Infections 2006;**82**:403-412.
67. Benzaken AS, Galban EG, Antunes W, Dutra JC, Peeling RW, Mabey D, *et al.* Diagnosis of gonococcal infection in high risk women using a rapid test. *Sexually Transmitted Infections* 2006;**82** Suppl 5: 26-28.
68. van Der Schee C, van Belkum A, Zwijgers L, van Der Brugge E, O'Neill E L, Luijendijk A, *et al.* Improved diagnosis of Trichomonas vaginalis infection by PCR using vaginal swabs and urine specimens compared to diagnosis by wet mount microscopy, culture, and fluorescent staining. *Journal of Clinical Microbiology* 1999;**37**:4127-4130.
69. Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. *JAMA* 2004;**291**:1368-1379.
70. Smith KS, Tabrizi SN, Fethers KA, Knox JB, Pearce C, Garland SM. Comparison of conventional testing to polymerase chain reaction in detection of Trichomonas vaginalis in indigenous women living in remote areas. *International Journal of STD & AIDS* 2005;**16**:811-815.
71. Adu-Sarkodie Y, Opoku BK, Danso KA, Weiss HA, Mabey D. Comparison of latex agglutination, wet preparation, and culture for the detection of Trichomonas vaginalis. *Sexually Transmitted Infections* 2004;**80**:201-203.
72. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *Journal of Clinical Microbiology* 1991;**29**:297-301.
73. Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, *et al.* Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *American Journal of Obstetrics & Gynecology* 1998;**178**:203-211.
74. Evans EG. Diagnostic laboratory techniques in vaginal candidosis. *British Journal of Clinical Practice Supplement* 1990;**71**:70-72.
75. Michel CE, Solomon AW, Magbanua JP, Massae PA, Huang L, Mosha J, *et al.* Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study. *Lancet* 2006;**367**:1585-1590.
76. Ministry of Health. Botswana second generation HIV/AIDS surveillance 2006. Gaborone:Ministry of Health, 2007.
77. Health Statistics Unit. Health Statistics Report 2000. Gaborone: Central Statistics Office, 2003.
78. Health Statistics Unit. Health Statistics Report 2002. Gaborone: Central Statistics Office, 2005.99
79. Ministry of Finance and Development Planning. National Development Plan 8, 1997/98-2002/03. Gaborone: Ministry of Finance and Development Planning, 1997.
80. AIDS/STD Unit. Botswana HIV and AIDS Second Medium Term Plan 1997-2002. Gaborone: Ministry of Health, 1997.
81. Ministry of Health. Management of Sexually Transmitted Infections. Reference Manual for Health Workers. Gaborone: Ministry of Health, 2005.

82. Ministry of Health. Guidelines for antenatal care and the management of obstetric emergencies and prevention of mother-to-child transmission of HIV. Gaborone: Ministry of Health, 2005.
83. World Health Organization. World Health Report 2004: Changing history. Geneva: WHO, 2004. Available at: http://www.who.int/whr/2004/en/report04_en.pdf.
84. AVERT. HIV and AIDS in Botswana. Available at: http://www.avert.org/aidsbotswana.htm
85. UNICEF. Botswana statistics 2008. Available at: http://www.unicef.org/infobycountry/botswana_statistics.html.
86. World Health Organization. Botswana statistics 2008. Available at: http://www.who.int/countries/bwa/en/.
87. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press, 1997.
88. Hunink M, Glasziou P. Decision making in health and medicine. Cambridge: Cambridge University Press, 2001.
89. Donaldson C, Currie G, Mitton C. Cost effectiveness analysis in health care: contraindications. *BMJ* 2002;**325**:891-894.
90. Black WC. The CE plane: a graphic representation of cost-effectiveness. *Medical Decision Making*1990;**10**:212-214.
91. Roberts TER, S; Barton, P; Bryan, S; Low, N. Screening for Chlamydia trachomatis: a systematic review of the economic evaluations and modelling. Sexually Transmitted Infections 2006;**82**:193-200.
92. Welte R, Jager, H., Postma, MJ. Cost-effectiveness of screening for genital Chlamydia trachomatis. *Expert Review of Pharmacoeconomics & Outcomes Research* 2001;**1**:145-156.
93. Honey E, Augood C, Templeton A, Russell I, Paavonen J, Mardh PA, *et al.* Cost effectiveness of screening for Chlamydia trachomatis: a review of published studies. *Sexually Transmitted Infections* 2002;**78**:406-412.
94. Adams EJ, Turner KM, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. *Sexually Transmitted Infections* 2007;**83**:267-274.
95. Nettleman MD, Bell TA. Cost-effectiveness of prenatal testing for Chlamydia trachomatis. *American Journal of Obstetrics & Gynecology* 1991;**164**:1289-1294.
96. Terris-Prestholt F, Vyas S, Kumaranayake L, Mayaud P, Watts C. The costs of treating curable sexually transmitted infections in low- and middle-income countries: a systematic review. *Sexually Transmitted Diseases* 2006;**33** Suppl 10:153-166.
97. Hogan DR, Baltussen R, Hayashi C, Lauer JA, Salomon JA. Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries. *BMJ* 2005;**331**:1431-1437.
98. Romoren M, Rahman M. Syphilis screening in the antenatal care: a cross-sectional study from Botswana. *BMC International Health and Human Rights* 2006;**6**:8.
99. Romoren M, Hjortdahl P, Velauthapillai M, Steen T, Hussein F, Rahman M, *et al.* Costs and health consequences of chlamydia management strategies in pregnant women in sub-Saharan Africa. Technical Report 2007. Available at: http://www.hero.uio.no/publicat/2007/HERO2007_10.pdf.

100. Health Statistics Unit. Health Statistics Report 2002. Gaborone: Central Statistics Office, 2005.
101. Bowden FJ, Garnett GP. Trichomonas vaginalis epidemiology: parameterising and analysing a model of treatment interventions. *Sexually Transmitted Infections* 2000;**76**:248-256.
102. Demba E, Morison L, van der Loeff MS, Awasana AA, Gooding E, Bailey R, *et al.* Bacterial vaginosis, vaginal flora patterns and vaginal hygiene practices in patients presenting with vaginal discharge syndrome in The Gambia, West Africa. *BMC Infectious Diseases* 2005;**5**:12.
103. Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. *Clinical Obstetrics & Gynecology* 2004;47:796-807.
104. National AIDS Coordinating Agency. Botswana AIDS Impact Survey II 2004. Gaborone: NACA, 2005.
105. Pfeiffer RM, Castle PE. With or without a gold standard. *Epidemiology* 2005;**16**:595-597.
106. Hadgu A, Dendukuri N, Hilden J. Evaluation of nucleic acid amplification tests in the absence of a perfect gold-standard test: a review of the statistical and epidemiologic issues. *Epidemiology* 2005;**16**:604-612.
107. Tann CJ, Mpairwe H, Morison L, Nassimu K, Hughes P, Omara M, *et al.* Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. *Sexually Transmitted Infections* 2006;**82**:285-289.
108. Hawkes S, Morison L, Foster S, Gausia K, Chakraborty J, Peeling RW, *et al.* Reproductive-tract infections in women in low-income, low-prevalence situations: assessment of syndromic management in Matlab, Bangladesh. *Lancet* 1999;**354**:1776-1781.
109. Mayaud P, ka-Gina G, Cornelissen J, Todd J, Kaatano G, West B, *et al.* Validation of a WHO algorithm with risk assessment for the clinical management of vaginal discharge in Mwanza, Tanzania. *Sexually Transmitted Infections* 1998;**74** Suppl 1: 77-84.
110. Low N. Screening programmes for chlamydial infection: when will we ever learn? *BMJ* 2007;**334**:725-728.
111. Government of Botswana. 2004/2005 Estimates of expenditure from the consolidated and development funds. Gaborone: The Government printer, 2004.
112. van Valkengoed IG, Morre SA, van den Brule AJ, Meijer CJ, Bouter LM, Boeke AJ. Overestimation of complication rates in evaluations of Chlamydia trachomatis screening programmes -implications for cost-effectiveness analyses. *International Journal of Epidemiology* 2004;**33**:416-425.
113. Wallace LA, Scoular A, Hart G, Reid M, Wilson P, Goldberg DJ. What is the excess risk of infertility in women after genital chlamydia infection? A systematic review of the evidence. *Sexually Transmitted Infections* 2008;**84**:171-175.
114. Garnett GP. How much infertility does chlamydia cause? *Sexually Transmitted Infections* 2008;**84**:157-158.
115. Walker D. Cost and cost-effectiveness of HIV/AIDS prevention strategies in developing countries: is there an evidence base? *Health Policy & Planning* 2003;**18**:4-17.

116. Creese A, Floyd K, Alban A, Guinness L. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet* 2002;**359**:1635-1643.
117. Briggs A. Economics notes: handling uncertainty in economic evaluation. *BMJ* 1999;**319**:120.
118. National AIDS Coordinating Agency. Botswana 2003 second generation HIV/AIDS surveillance. Gaborone: NACA, 2003.
119. Townshend JRP, Turner HS. Analysing the effectiveness of Chlamydia screening. *Journal of the Operational Research Society* 2000;**51**:812-24.
120. Welte R, Kretzschmar M, Leidl R, van den Hoek A, Jager JC, Postma MJ. Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. *Sexually Transmitted Diseases* 2000;**27**:518-529.
121. Welte R, Postma M, Leidl R, Kretzschmar M. Costs and effects of chlamydial screening: dynamic versus static modeling. *Sexually Transmitted Diseases* 2005;**32**:474-483.
122. Hu D, Hook EW, Goldie SJ. Screening for Chlamydia trachomatis in women 15 to 29 years of age: a cost-effectiveness analysis. *Annals of Internal Medicine* 2004;**141**:501-513.
123. World Health Organization. Guidelines for Sexually Transmitted Infections Surveillance. Geneva: WHO, 1999.
124. Wessel HF, Herrmann B, Dupret A, Moniz F, Brito C, Bergstrom S. Genital infections among antenatal care attendees in Cape Verde. *African Journal of Reproductive Health* 1998;**2**:32-40.
125. Bourgeois A, Henzel D, Dibanga G, Malonga-Mouelet G, Peeters M, Coulaud JP, *et al.* Prospective evaluation of a flow chart using a risk assessment for the diagnosis of STDs in primary healthcare centres in Libreville, Gabon. *Sexually Transmitted Infections* 1998;**74** Suppl 1: 128-132.
126. Sturm AW, Wilkinson D, Ndovela N, Bowen S, Connolly C. Pregnant women as a reservoir of undetected sexually transmitted diseases in rural South Africa: implications for disease control. *American Journal of Public Health* 1998;**88**:1243-1245.
127. Paz-Bailey G, Rahman M, Chen C, Ballard R, Moffat HJ, Kenyon T, *et al.* Changes in the etiology of sexually transmitted diseases in Botswana between 1993 and 2002: implications for the clinical management of genital ulcer disease. *Clinical Infectious Diseases* 2005;**41**:1304-1312.
128. Homedes N, Ugalde A. Improving the use of pharmaceuticals through patient and community level interventions. *Social Science & Medicine* 2001;**52**:99-134.
129. Homedes N, Ugalde A, Chaumont C. Scientific evaluations of interventions to improve the adequate use of pharmaceuticals in Third World countries. *Public Health Reviews* 2001;**29**:207-230.
130. Low N. Chlamydia (uncomplicated, genital). Clinical Evidence 2006:2129-35.
131. Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. Cochrane Database of Systematic Reviews, 2000.
132. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. Cochrane Database of Systematic Reviews, 2003.
133. Joesoef MR, Schmid G. Bacterial vaginosis. *Clinical Evidence* 2007:1968-1978.

134. Center for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. Atlanta: CDC, 2006.
135. British Association for Sexual Health and HIV. 2006 UK National Guideline for the Management of Genital Tract Infection with Chlamydia trachomatis. London: BASHH, 2006.
136. Management Sciences for Health. International Drug Price Indicator Guide. Available at: http://erc.msh.org/dmpguide/index.cfm?language=english&action=newyear&display=yes&module=dmp&year=2005.
137. Kingston M, Carlin E. Treatment of sexually transmitted infections with single-dose therapy: a double-edged sword. *Drugs* 2002;**62**:871-878.
138. Kallen BA, Otterblad Olausson P, Danielsson BR. Is erythromycin therapy teratogenic in humans? *Reproductive Toxicology* 2005;**20**:209-214.
139. Statens Legemiddelverk. Bruk av antibiotika under graviditet. Available at: www.legemiddelverket.no/upload/AB%20graviditet%20til%20publikasjon.pdf
140. Kallen KBM. Maternal drug use in early pregnancy and risk of cardiovascular defect in infant - A follow-up study. Abstract presented at the 36th Annual Conference of the European Teratology Society, August 2008.
141. Romoren M, Sundby J, Velauthapillai M, Rahman M, Klouman E, Hjortdahl P. Chlamydia and gonorrhoea in pregnant Batswana women: Time to discard the syndromic approach? BMC Infectious Diseases 2007:**7**.
142. Cates W, Jr. Contraception, unintended pregnancies, and sexually transmitted diseases: why isn't a simple solution possible? *American Journal of Epidemiology* 1996;**143**:311-318.
143. Sloan NL, Winikoff B, Haberland N, Coggins C, Elias C. Screening and syndromic approaches to identify gonorrhea and chlamydial infection among women. *Studies in Family Planning* 2000;**31**:55-68.
144. The National Chlamydia Screening Programme. Available at: http://www.chlamydiascreening.nhs.uk/.
145. Piot P, Rowley J. Economic impact of reproductive tract infections and resources for their control. In: Germain A, edt. Reproductive Tract Infections: global impact and priorities for women's health. New York: The Plenum Press, 1992.
146. Evans DB, Lim SS, Adam T, Edejer TT, *et al.* Evaluation of current strategies and future priorities for improving health in developing countries. *BMJ* 2005;**331**:1457-1461.
147. Salama P, Lawn J, Bryce J, Bustreo F, Fauveau V, Starrs A, et al. Making the Countdown count. *Lancet* 2008;**371**:1219-1221.
148. Bryce J, Daelmans B, Dwivedi A, Fauveau V, *et al.* Countdown to 2015 for maternal, newborn, and child survival: the 2008 report on tracking coverage of interventions. *Lancet* 2008;**371**:1247-1258.

Appendix 1

Questionnaire

Inclusion criteria	☒ ANC patient, any gestational age ☐ New ☒ Repeat: routine visit number 02 ☐ Referred:_____ ☒ No antibiotics last two weeks
Date	11.10.2000
Name of clinic	Ext 7 = 02
Patient number	0330
Age	20
Birth year	1980
Highest education completed	☐ Never went to school ☐ Primary ☒ Junior secondary Form II ☐ Post secondary ☐ Higher ☐ Other:_____
Marital status	☒ Unmarried ☐ Married ☐ Separated/Divorced ☐ Widowed ☐ Other:_____
If currently not married:	
Steady partner?	Yes☒ No☐
If married/steady partner	
Living together ?	Yes☒ No☐
Present partner since	>24 (months)
Number of partners last 12 months	01
Date of last menstruation	4.5.2000
Expected delivery date	11.02.2001
Symphysis-fundus height	22 (cm)
Week of gestation	24
Non-pregnant weight	65.5 Height (if <1.5m) 1.60
Hb first visit	Date____ Result____ Action____
Hb 34-36 week	Date____ Result____ Action____
VDRL/RPR	Date____ Result____ Action____
VDRL/RPR 34-36 week	Date____ Result____ Action____

Treatment for STDs during pregnancy

Date__ __.__ Diagnosis_____
Treatment_____
_____
_____

Past pregnancies

Gravida 0 ;
Para 0 0
Abortions \
Ectopics _____
__ __ Age of youngest (years)
__ __ Age of oldest (years)
Complications (number)
__ Premature labour
__ Small for gestational age
__ Stillbirth
__ Other: _____

Subjective symptoms

Do you think you might have a disease in your private parts now? Yes X No__Not sure__
Do you have any of the following symptoms?

Dysuria (pain when you pee) Yes__No X Not sure__
More discharge than usual Yes__No X Not sure__
☐ White discharge
☐ Yellow/green/brown discharge
☐ Smelly discharge
Itching or soreness in private parts Yes__No X Not sure__
Sores or ulcers in private parts Yes__No X Not sure__
Warts on private parts Yes__No X Not sure__
Lower abdominal pain Yes X No__Not sure__

Clinical data obtained from genital examination

External genitalia	Normal	Yes X No__
	Irritation/redness	Yes__ No X
	Swelling	Yes__ No X
	Blisters	Yes__ No X
	Sores/ulcers	Yes__ No X
	Genital warts	Yes__ No X
	Inguinal node enlargement	Yes__ No X
Internal genitalia	Normal	Yes__ No X
	Irritation/redness	Yes__ No X
	Blisters	Yes__ No X
	Sores/ulcers	Yes__ No X
	Genital warts	Yes__ No X
Vaginal secretion	Normal	Yes X No__
	Amount	X Scarce ☐ Moderate ☐ Profuse
	Colour	☐ Clear ☐ White ☐ Brown X Cream/yellow
	Consistency	X Thick ☐ Thin
		☐ Foamy ☐ Curdlike X Homogenous
	Coating the vaginal walls	Yes__ No X
	Smelling	Yes__ No X
Cervix	Normal	Yes__ No X
	Cervical secretion	Yes X No__
		☐ Clear
		X Mucopurulent
	Cervical bleeding	Yes__ No X
		☐ Immediately
		☐ When taking samples
	Erythroplaque cervix	Yes__ No X

Comments UH lod. fra cervix. Veldig ømtelig/smertefull v/ us.
Cervicitt, PID? Treatment: Cef
d/o LAP hvor lenge Ery
Metro
Clotrimazol

Urine dipstick test	Nitrites	neg
	Leucocyte esterase	neg
	Proteins	neg
	Glucose	neg
	Blood	neg
pH-level		7
Amine test	Pos__ Neg X	

Appendix 2

ANTENATAL SECTION

Surname..... Date of Birth..... Age..... yrs.

Forenames..... Place of Birth.....

Address..... Home Village.....

..... Nationality.....

Single/Married/Widowed/Divorced Education..... Occupation.....

Next of Kin..... Relationship.....

Address.....

Gravida..... Para..... Ab..... LNMP..... EDD.....

PAST OBSTETRIC HISTORY

Date	Place	Gestation (wks)	Duration of Labour(hrs.)	Method of Delivery	Sex	Fetal Outcome	Complications

ADMISSIONS DURING PREGNANCY

	1	2	3	4
Health Facility				
Date of Admission				
Date of Discharge				
Hospital Number				
Diagnosis				
Treatment				
Followup				

CONSENT FORMS

For Complications of Pregnancy

I give consent for the registered Health Worker to give an anaesthetic and perform any operation on myself/my dependant that may be necessary.

Signed..... Rel'p.....
Witness..... Date.....

For Tubal Ligation

I/We give consent for the registered Health Worker to perform an operation to tie the tubes to prevent further pregnancies.

Signed..... Husband.....
Guardian..... Rel'p.....
Witness..... Date.....

(2)

Date .....

HISTORY

No. of Risks

MENSTRUAL HISTORY: LNMP_____
Usual cycle_____/_____ days
If only month known early/mid/late
Bleeding since LNMP yes/no
Details_____

Uncertain dates_____

FAMILY PLANNING:
Has practised? yes/no
Method used_____
Date stopped_____
Wants FP after delivery? yes/no
Method chosen_____

FAMILY HISTORY:
HPT Diabetes Twins Genetic Oth.
Details_____

MEDICAL COMPLICATIONS:
Cardiac Renal STD TB Diabetes
Anaemia HPT
Other_____
On treatment?_____

Allergies_____
Details_____

OPERATIONS AND ACCIDENTS:
Details_____

PAST PREGNANCIES: Grav Para Ab
No. alive Age of youngest yrs.

Complications (1 point for each risk)

	Comment/Indic'n
Prolonged labour (>24 hrs.)	
Precipitate labour (< 2 hrs.)	
Vacuum/Forceps	
Symphysiotomy	
Caesarian Section	
APH	
PPH	
PIH/Eclampsia	
SB or NND	
Recurrent Abortion	

PRESENT PREGNANCY

No. of Risks

OTHER RISKS:
Under 16 yrs._____
Over 35 yrs._____
Primig. over 30 yrs._____
Late booker_____
Unsatisfactory home conditions_____
Unwise habits - alcohol_____
- tobacco_____
- obesity_____
Other_____

GENERAL EXAMINATION:
Nutrition_____ Breasts_____
Thyroid_____ Nipples_____
Heart_____ Varicose veins_____
Chest_____ Xray req'd yes/no
Details if abnormal_____

Height (if under 150 cm.)_____
Shoe size_____
Non-pregnant weight_____kg.

VAGINA EXAMINATION:
Vulva_____Vagina_____Cervix_____
Uterine size___wks. Adnexa_____
Pelvic size small/borderline/norm.
Pap smear done/not done
Details if abnormal_____

LABORATORY RESULTS:

	Date	Result	Action
HB 1st visit			
HB 34-36 wk.			
VDRL			
Blood group			
Pap smear			
MSU			
RH antibodies			
CXR(if req'd)			

TETANUS TOXOID: (write in the date)
Booster only_____
1st of 2_____ 2nd of 2_____

TOTAL NO. OF RISKS AT BOOKING

NOTES AND SPECIAL PROBLEMS: _____

SPACING OF PREGNANCIES: (Fill in the year)
0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2

(3)

Appendix 3

Model input parameters: The female decision tree

The expert panel assumed that the probability of correct prescription by nurses, patients' compliance to prescribed drugs and partner notification will be higher if an antenatal care attendee is diagnosed with chlamydia using point-of-care (POC) tests than with the syndromic management strategy. This is because when a pregnant woman is diagnosed with 'vaginal discharge syndrome', she may have candida, bacterial vaginosis, trichomoniasis, chlamydia or gonorrhoea, physiologically increased discharge or abdominal pain related to pregnancy. The treatment for vaginal discharge syndrome includes a multiple and complex drug regimen, and both the nurses' adherence to the treatment guidelines and patients' compliance to this regimen is known to be low. As the condition most likely is not sexually transmitted, it is understandable that neither nurses nor patients are dedicated to ensure partner notification, not risking domestic disturbance unnecessarily.

All POC tests for chlamydia have high specificities, and thereby the advantages of a specific test which the syndromic approach is lacking. A positive test requires the prescription of and compliance to one drug; and partner treatment is imperative. For the POC test strategy, there are no data on these events. The expert panel inflated the values used for the probabilities in the syndromic strategy, assuming that the additional confidence in the POC test result would improve management. The possibility that this is not the case was covered by using large uncertainty bounds, including in the lower bound a value that represents syndromic management. The upper bound represents much better performance, as found in developed countries where specific chlamydia tests are in use.

Chlamydia prevalence

Chlamydia prevalence is based on data from our study among 703 antenatal care attendees in Gaborone, Botswana. In this population, young age was the factor most strongly associated with cervical infection (Table A1). Based on this knowledge, we modelled different management strategies: to include all women, selective management of women under 30, and selective management of teenagers. Chlamydia incidence is not included in the model. As prevalences may differ in other settings as well as change over time, we used broad uncertainty ranges to assess the effect of prevalence on the cost-effectiveness

estimates in one-way sensitivity analysis. The prevalence range from 3% to 31% represents the range of prevalences found in other studies among antenatal care attendees in sub-Saharan Africa (1).

Table A1 Chlamydia prevalence by age among 703 antenatal care attendees in Gaborone, Botswana

Age	N (%)	Prevalence (95% Confidence interval)
<20	76 (10.8)	15.8 (9.3-25.6)
20-29	432 (61.5)	8.1 (5.9-11.1)
30+	195 (27.7)	3.1 (1.4-6.5)
Total	703 (100)	7.5 (5.8-9.7)

Sensitivity and specificity of the POC test

Several POC tests for *C trachomatis* are commercially available. The evaluated specificity of the tests is consistently found to be high and was therefore set at 98.5% (97.0-100%) (Table A2). The sensitivity has not yet been firmly determined. It has varied widely across tests and the populations being tested, ranging from 25 to 85% (2, 3). The evaluations have also differed with respect to reference standard used. Introduction of a test with a sensitivity of at least 50% is a current option, and most likely, more sensitive tests will be available within the next few years. We therefore modelled a baseline sensitivity of the test of 50%, with a range from 50% to 85%. Tests with sensitivities lower than 50% were not considered, as they would detect fewer infections than the syndromic approach.

Table A2: Sensitivity and specificity of *Chlamydia trachomatis* point-of-care tests

Point-of-care test	Patient group	Sensitivity	Specificity	Reference
Antigen detection assay	"High risk women"	49.7%	97.9%	Yin *et al.* 2006 (4)
Chlamydia optical immunoassay	Female STI clients	73.8%	100%	Pate *et al*. 1998 (5)
Chlamydia optical immunoassay	"Female clients"	31.6%	98.9%	Widjaja *et al*. 1999 (6)
Chlamydia optical immunoassay	Female STI clients	64.2%	99.1%	Swain *et al*. 2004 (7)
Direct fluorescent antibody test	Female STI clients	73.6%	99.9%	Swain *et al*. 2004 (7)
IgA Rapid Sero Test (ELISA)	Pregnant women	69.6%	97.2%	Witkin *et al*. 1997 (8)

Sensitivity and specificity of syndromic management

The sensitivity and specificity of the syndromic approach were based on data on the 157 new antenatal care attendees in our epidemiological study. Pregnant women coming for

their first antenatal care visit who complain of vaginal discharge or lower abdominal pain will be managed with the vaginal discharge algorithm. In addition, all new attendees are clinically screened for STIs. This strategy, in which symptoms and/or signs are used as entry points to the vaginal discharge algorithm, has a sensitivity of 49% (95% CI 0.36-0.62) and a specificity of 65% (95% CI 0.61-0.69) in the diagnosis of chlamydia.

Probability of drug being prescribed

The probability of nurses' adherence to prescription guidelines for the syndromic diagnosis is also based on study data. Among 165 attendees who had been diagnosed with vaginal discharge syndrome, 140 (85%, 95% CI 79-90%) had been prescribed erythromycin. This is consistent with other studies from sub-Saharan Africa. In an observational study from Botswana including 66 female STI clients who were diagnosed with vaginal discharge syndrome and 33 who were diagnosed with lower abdominal pain, health workers prescribed treatment for chlamydia to 92 (93%) of the clients (9). This prescription rate is likely to be higher than in an antenatal care population: The health workers know they are observed, the probability of chlamydia is higher among STI clients, and with the lower abdominal pain syndrome, only drugs for chlamydia and gonorrhoea is recommended. Buve *et al* estimated in their report from Tanzania that 80% of the STI clients were prescribed adequate drugs (10).

The probability of prescription of the recommended drug is likely to be higher if the specific POC test is positive. The nurse can rely on the diagnosis, and if the attendee is asymptomatic, only one drug regimen is necessary. Numerous discussions with nurses in primary health clinics in Botswana revealed that low rates of prescription in accordance with the treatment guidelines in the syndromic management strategy are caused by the uncertainty in the diagnosis and the complexity of the treatment regimens. The nurses reported using their own judgement and clinical experience to prescribe drugs for what they think is causing the patient's symptoms or signs. Their knowledge of type and dosage of drugs to treat chlamydia is high. Cost-effectiveness analyses of chlamydia screening from developed countries are all operating with 100% probability of correct prescription (11, 12). A Medline search yielded no studies on health workers' prescription of treatment for chlamydia specifically (see the technical report (13)). The expert panel agreed that if a

specific POC test for chlamydia is positive, it is unrealistic to assume full adherence. The nurses may forget the prescription or prescribe ineffective drugs, and it is was concluded that this is likely to happen in about one in 15 test positive cases. We therefore used 93% (85-100%) probability of correct prescription with the POC test strategy.

Compliance and drug effectiveness

A correct prescription does not necessarily lead to a successful cure of chlamydia. Treatment failures may be due to non-compliance, microbiological cure failure or re-infection. It is generally accepted that the drugs recommended for chlamydia are nearly 100% effective when taken as recommended. We have therefore used a combined probability for drug efficacy and compliance (Box A1). The risk of reinfection is captured in a separate variable.

Studies, primarily from developing countries, have measured compliance and partner notification in randomized, controlled trials (Table A3) (14-16). These methods are hampered by methodological challenges such as observational bias (patients are likely to perform better in a defined research setting), or there may be a self-selection of patients, in that the less conscientious individuals will be lost during the follow-up stage. Additionally, most studies have focused on "treatment failures" without being able to tell if it is insufficient compliance, incomplete efficacy of the drug or reinfection from an infected partner which has caused the failure to obtain cure.

Box A1 Probability of cure with the two alternative drug- and management strategies

Compliance and drug efficacy with **erythromycin**

- Probability of cure with syndromic management = 0.50 (0.30-0.70)
- Probability of cure with point-of-care tests = 0.86 (0.50-0.95)

Compliance and drug efficacy with **azithromycin**

- Probability of cure with syndromic management = 0.95 (0.88-1.00)
- Probability of cure with point-of-care tests = 0.95 (0.88-1.00)

There are few papers published in Medline on patient compliance to STI drugs in developing countries. With the syndromic management of STIs, information on drug efficacy or reinfection rates is unachievable. As it is unknown which infection or condition

the patient is suffering from, only clinical cure rates can be measured. Buve *et al* estimate the proportion of symptomatic patients with a bacterial sexually transmitted infection cured by primary health care services in Mwanza, Tanzania. Within this project, patients with an STI syndrome assessed at outpatient clinics were requested to report back after 1 week. Of the female returners, 69% said they took the full treatment. The authors assume that the selection of dutiful patients results in an overestimate of the total compliance rate (10).

It is consistently shown that the compliance and drug effectiveness for single dose treatment with azithromycin is very high. For optimal compliance, directly observed treatment can be introduced. Cure rates for erythromycin are lower, as the more complex treatment regimen and a greater occurrence of adverse effects reduce compliance (17, 18). In original studies and reviews from developed countries where the chlamydia diagnosis is based on a specific laboratory test, the probabilities of cure with erythromycin were 0.86 (0.72-0.95). The expert panel believe that the cure rates for attendees diagnosed with a POC test are likely to be similar, but assigned large uncertainty bounds (0.50-0.95).

The estimated 0.50 (0.30-0.70) probability of cure when erythromycin is prescribed to attendees diagnosed with syndromic approach is based on expert opinions and indirect data from our study among antenatal care attendees. Patients diagnosed with the vaginal discharge syndrome must simultaneously administer up to four drug regimens correctly, and often don't know what condition they are suffering from - both aspects obviously having a negative impact on compliance. In our study from Botswana, the prevalence of chlamydia was identical (7.5%) among women who had been prescribed erythromycin earlier in the current pregnancy and among women who had not. Low compliance was a core factor in explaining why the prescribing of erythromycin did not necessarily cure the *C trachomatis* infection. The attendees, who in the study setting are diagnosed with a cervical infection using the vaginal discharge algorithm, had an insignificantly higher prevalence of chlamydia compared to those who have not been diagnosed. I can tell numerous anecdotes from my experience during the field work illustrating a high level of non-adherence to erythromycin among pregnant women diagnosed with vaginal discharge syndrome. A common error was to take one tablet daily in four weeks instead of one tablet four times daily for one week.

Table A3 Probability of cure with different drug regimens to treat chlamydia

Source	Patient group	Correct prescription	Azithromycin		Erythromycin‡		Doxycycline	
			Compliant	Effectiveness	Compliant	Effectiveness	Compliant	Effectiveness
Postma (11) CE	Female index Male partners	100% 100%	90% 90%	95% 95%		95% 95%		
Welte (12) CE-R	Unspecified		100%	95%			80%	95%
Roberts (19) CE-R	Unspecified	100%	100%				75-87%	
Romoren (20) OD	Pregnant women				"low"			
Guaschino (21) R	Unspecified		Effectiveness 95-100% Clinical cure rate 89-97%		Effectiveness 95-100% Clinical cure rate 80%		Effectiveness 88-100% Clinical cure rate 94-99%	
Turrentine (22) M	Pregnant women				Clinical cure 95%			
Adimora (23) R Thorpe OD Brihmer OD McCormack OD1 McCormack OD2	Unspecified Female index Female index Male index Female index	 NA NA	Effectiveness† 95-100% Clinical cure rate 80-95% NA (100%) 97% NA (100%) 100%				Effectiveness 99% Clinical cure rate NA (100%) 99% NA 97% NA 99% NA 99%	
Townshend (24) CE	Unspecified	100%	Treatment success rate 90% (80-100%), re-infections included (AB unspecified)					
de Vries (25) CE	Male and female	100%	90%	95%	Based on the same operational research as Postma			
Adair (14) OD	Pregnant women	NA	NA	97.5%	(53.5%)	95.3%		
Rustomjee (15) OD	Female index	NA	100%	100%				
Miller (26) R			99 (93-100)	95 (88-100)	80% (54-89)	86 (72-95)		
Abstracts Silverman OD Bush OD Alger OD Alary	 Pregnant women Pregnant women Pregnant women Pregnant women	 NA NA NA NA	100%	100%	Overall cure rate 84.6% Overall cure rate 93% Overall cure rate 83% Overall cure rate 100%			

CE, Cost-effectiveness study; R, Review; OD, original data; M, meta analysis. †Bacterial cure within 2-4 weeks

‡ Many studies report side-effects followed by non-compliance to erythromycin. However, the cure-rate is always reported to be higher than the treatment failure.

Model input parameters: The partner decision tree

The risk of reinfection due to failed partner referral was included in the model. In our study among antenatal care attendees, 671 (95%) of 703 women reported one partner during the last 12 months. We therefore assume that the women have, as a median, one partner with whom she will be sexually active during the current pregnancy. We did not include further transmission from the male partner. We are aware that multiple partnerships are common in Botswana (1). This, combined with the high prevalences of STIs among the antenatal care attendees, make us believe that modelling a steady couple may not represent the full reality. If the pregnant women or her partner has more than one partner, the effect of correctly diagnosing and treating chlamydia will be underestimated.

Probability of partner being infected and probability of reinfection

The chlamydia transmission rate between pregnant women and their partners in sub-Saharan Africa is unexamined. The probability of the partner being infected, and a cured female or male being reinfected, is based on co-infection studies from the US, UK or Australia on patients in STI clinics and their steady and casual partners (Table A4). These studies are hampered by the lack of gold standard laboratory tests, by their inability to have included nearly all partners, and by the fact that both steady and casual partners are examined. The probability of transmission will vary from individual to individual and between subgroups, and the studies may therefore not necessarily be relevant to a population of antenatal care attendees with steady partners in a developing country. The studies indicate that the transmission of chlamydia is equal and bidirectional between sexual partners (27). It is also dependent on the number of sexual contacts in the couple, and thus higher among steady partners. The expert panel concluded that the transmission probability will be in the higher range (0.80), but we have used wide uncertainty bounds (0.50-0.96). The panel's main arguments were a) The majority of the pregnant Batswana women in our study reported that they had one steady partner with whom they had had a relationship for one year or more, and b) The prevalences of other STIs/RTIs are very high in this area, most likely increasing the susceptibility and infectiousness of genital infections.

We have not modelled possible chlamydia infections in partners of uninfected women. We assumed that male partners who are effectively treated do not reinfect their female partner before their infection is cured.

Table A4: Studies of infection rates in partners of males and females with chlamydia

Study population	Infection in ♂partners	Infection in ♀partners	Reference
1. STI clinic, USA. 53 couples concordantly infected; in 48 couples one was infected	68%	70%	(27)
2. STI clinic, UK. 97 M and 93 F index cases, half of their partners were tested	75%	75%	(28)
3. STI clinic, UK..404 chlamydia-infected ♀ reported 632 sexual contacts and 147 (23%) were tested	44%	-	(29)
4. Australian study, primary health care and specialist clinics. 87 M/F index cases w/chlamydia	52%	52%	(30)

Probability of infected male being symptomatic

Economic evaluations of chlamydia screening which include partner notification and treatment, estimate that 30-50% of men with chlamydia infection are symptomatic. We have not found any original studies verifying this estimate, such data are virtually non-existing (10). Studies among men seeking care overestimate the symptomatic/asymptomatic ratio, while population prevalence studies underestimate the ratio –as symptomatic men will have sought care and been treated. In a population-based study from Uganda, 92% of men with chlamydia reported no symptoms during the last 6 months (31). In a work-site-based study from Tanzania, 89% of men with chlamydia reported no symptoms (32). In a study among young incarcerated minority males in the US, 90% of men with chlamydia were asymptomatic (33). Two population based studies on urethritis in men from Tanzania showed that 35% of men with chlamydia and/or gonorrhoea were symptomatic (10). As gonorrhoea more often is symptomatic, this value is probably too high for chlamydia infections. Based on these data, we modelled that 0.15 (0.10-0.20) male partners are symptomatic.

Probability of partner notification and health care attendance

Many factors will influence if a partner is notified and subsequently attends a health care facility. The health care worker has to counsel the antenatal care attendee on partner notification, the woman has to notify her partner, and the partner has to attend a health facility. The success of a partner notification attempt is dependent on whether the partners are steady or casual, whether the diagnosis is syndromic or specific, on the notification strategy applied, as well as the cultural setting. We have used the same value for the probability of partner being notified and attend a health facility for all partners of the diagnosed females. The probability will vary in the different subgroups of antenatal care attendees in the model (A2), but this is difficult to estimate.

Box A2 Factors which may influence partner notification and/or attendance at individual level in our model

- If the antenatal care is prescribed correct treatment or not

(The nurse may be less likely to counsel on partner notification, and the antenatal care attendee may be less conscious regarding notification. On the other hand, women who are not prescribed correct treatment are often prescribed other, but inappropriate drugs, a situation which not necessarily will be associated with reduced partner notification).

- If the male partner is symptomatic or not

(Symptomatic males may be more likely to attend a clinic when being notified by their partner. Or; symptomatic males may be less likely to attend a clinic when notified because he may have sought other care (independent care seeking is included in the model).

- If the male partner seek other care independently (mutual influence)

We used an estimate of 8.5% (5-15%) for partner notification within the syndromic approach – based on health statistics data from Botswana. These data are in line with studies from other sub-Saharan countries (Table A5). There were 0.085 male STI contacts registered per female STI client in Botswana in 2002, demonstrating that partner notification is very poor (34). The 91 738 registered STI syndromes among female clients do not include the STI syndromes diagnosed among the approximately 40 000 antenatal care attendees registered the same year. We do not know how many of the men who were referred by a pregnant partner, and thus lack direct data on the partner referral rate among

pregnant women diagnosed with an STI. Two observational studies on STI management in Botswana report that *advice* on partner notification including the issuing of a contact slip was provided to 61% and 66% of the STI clients, respectively (9, 35). Less than five minutes in total was spent per STI client, in a consultation which is meant to contain history taking, clinical examination, diagnosis, treatment and counselling. These data underpin that the number of partners who will be notified by the women and subsequently attend a health facility is low.

The participants in the expert panel have wide theoretical knowledge and clinical experience with partner notification in developing countries. They concluded that with the use of specific point-of-care tests, a realistic estimate of the probability of partner notification and attendance will be 25% (0.085-0.65%). The lower bound of partner notification and attendance with the POC test strategy represents the current partner attendance, whereas data from studies in developed countries was used as a basis for the upper bound. Medline searches and the studies identified are described in the technical report (13). Many studies on partner notification are performed under optimal conditions, often with the aim of improving the partner management, and may not represent routine care.

Table A5 Studies used as a basis for the modelled probability of partner notification and attendance

Description of study	Partners		Reference
	Notified	Attend	
Syndromic management/African countries			
Male partners per female STI client in Botswana		8.5%	(34)
Female STI clients in Uganda. A study to improve partner notification		22%	(36)
Female STI clients in Uganda	4%		(31)
STI clients in South Africa		<20%	(16)
Diagnostic test/western countries			
STI clients in the Netherlands. Optimal conditions.		60-82%	(37)
STI clients in the UK. Optimal conditions.		<65%	(38)

Probability of symptomatic males seeking other care and being cured

Symptomatic males may seek care independently of their pregnant partner, and the care providers will range from street vendors and faith healers to pharmacies, private doctors

and public clinics. Data on health care seeking among symptomatic males and the quality of care provided is scarce. Buve *et al*. has reported from Tanzania that 51% of males and females with genital discharge or genital ulcer sought care (10). How many of the partners who seek care after being notified by a partner and how many who seek care independently is not reported –and probably not known. In a population-based study in Botswana, 85% of the male respondents who ever had STI symptoms had been to a public health facility (which may or may not be because he has been notified by his partner), 26% had sought a traditional healer, 16% had been to the pharmacy and 14% to a private doctor (1). The number of symptomatic episodes among these males was not reported.

The probability of cure among symptomatic males seeking other health care is the sum of a correct diagnosis, a correct prescription, sufficient compliance and avoidance of reinfection. We lack accurate data from public clinics in sub-Saharan Africa on cure rates among males with urethral discharge. The described study by Buve *et al*. estimated cure among male STI clients in public health facilities: 63% were diagnosed correctly, 73% were prescribed correct treatment and 84% were compliant (10). In an observational study from primary health care in Botswana, adequate history taking among male STI clients was performed in 54% and clinical examination in 57% of the cases (9). Of the males who were diagnosed with urethral discharge syndrome, 91% received an appropriate prescription. Compliance was not measured in this study, and the authors noted that nurses may perform better when being observed. We have not found any literature estimating cure rates of the management of patients with genital symptoms in private clinics, in pharmacies or among traditional or faith healers.

The probability of symptomatic males seeking other care and subsequently being cured are expert opinions. The expert panel based their estimates on available studies, their common clinical experience (for example that many patients don't seek health care before their symptoms are severe), knowledge of and literature on the wide use of alternative medicine in sub-Saharan Africa, and on discussions with nurses in the primary health care. The panel agreed that the parameters have a large degree of uncertainty, and estimated that 50% (30-70%) of the symptomatic males who do not attend a health facility as a result of partner notification seek the health services independently. They estimated that 50% (30-70%) of the symptomatic males who seek care independently are cured for their chlamydia

infection. We have not accounted for the fact that an infected male partner may notify his pregnant partner resulting in her treatment and cure.

Probability of correct prescription to male partner

We have not identified studies on quality of prescription to partners, but we assume that the probability of correct prescription will be similar to the probability among index patients. A 0.85 (0.76-1.00) probability of correct prescription to male partners with the syndromic approach strategy is based on the two observational studies on syndromic management of STI clients in Botswana. The first study among 33 males with urethral discharge found that 70% were prescribed ceftriaxone for gonorrhoea and 76% were prescribed doxycycline for chlamydia (35). In the second study, all 32 males with urethral discharge syndrome were prescribed ceftriaxone and doxycycline (9).

As discussed under the description of the parameters in the female decision tree, the expert panel assumed that the probability of correct prescription to male partners will be higher if a specific POC test is positive than with the syndromic approach. The expert panel assumed that with the POC test strategy, it is realistic with a 93% (85-100%) probability of prescription of treatment. Cost-effectiveness analyses of chlamydia screening from developed countries are all operating with 100% correct prescription, but we added a dose of realism (the nurses may forget the prescription or prescribe ineffective drugs).

Probability of compliance and drug effectiveness among male partners

In Botswana, the standard treatment for chlamydia in males and non-pregnant women is doxycycline 100 mg tablets twice daily in one week (39, 40). Doxycycline and azithromycin are juxtaposed by the WHO, Center for Disease Control and Prevention and others, but the former drug is cheaper (40, 41). We modelled doxycycline treatment to partners, although single-dose treatment with 1g azithromycin may be considered to improve compliance. We mainly found data on compliance to doxycycline from developed countries (Table A3), and we did not identify any studies on compliance and cure rates in partners as such. The probability used for the syndromic management strategy, 0.80 (0.60-1.00), was adjusted by the experts based on their knowledge of the local conditions and assigned large confidence intervals. Further, the expert panel assumed that partners of

patients with a positive POC chlamydia test will be more compliant than partners of patients diagnosed with vaginal discharge syndrome: The male will know that their partner had chlamydia, and for partners of asymptomatic attendees only one drug regimen is necessary. The lower bound of the 0.90 (0.80-1.00) probability with the POC strategy is identical to the estimate of the current level, whereas the upper bound is based on the original studies and reviews from developed countries. As data on compliance among symptomatic versus asymptomatic partners are lacking, we used the same probability of compliance and drug effectiveness for all male partners regardless of symptoms.

References

1. National AIDS Coordinating Agency. Botswana 2003 second generation HIV/AIDS surveillance. Gaborone: National AIDS Coordinating Agency, 2003.
2. Vickerman P, Watts C, Alary M, Mabey D, Peeling RW. Sensitivity requirements for the point of care diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae in women. *Sexually Transmitted Infections* 2003;**79**:363-367.
3. Watson EJ, Templeton A, Russell I, Paavonen J, Mardh PA, Stary A, *et al*. The accuracy and efficacy of screening tests for Chlamydia trachomatis: a systematic review. *Journal of Medical Microbiology* 2002;**51**:1021-1031.
4. Yin Y-P, Peeling RW, Chen X-S, Gong K-L, Zhou H, Gu W-M, *et al*. Clinic-based evaluation of Clearview Chlamydia MF for detection of Chlamydia trachomatis in vaginal and cervical specimens from women at high-risk in China. *Sexually Transmitted Infections* 2006;**82**:33-37.
5. Pate MS, Dixon PB, Hardy K, Crosby M, Hook EW. Evaluation of the Biostar Chlamydia OIA assay with specimens from women attending a sexually transmitted disease clinic. *Journal of Clinical Microbiology*. 1998;**36**:2183-2186.
6. Widjaja S, Cohen S, Brady WE, O'Reilly K, Susanto, Wibowo A, *et al*. Evaluation of a rapid assay for detection of Chlamydia trachomatis infections in outpatient clinics in South Kalimantan, Indonesia. *Journal of Clinical Microbiology* 1999;**37**:4183-4185.
7. Swain GR, McDonald RA, Pfister JR, Gradus MS, Sedmak GV, Singh A. Decision analysis: point-of-care Chlamydia testing vs. laboratory-based methods. *Clinical Medicine & Research* 2004;**2**:29-35.
8. Witkin SS, Bongiovanni AM, Inglis SR. Detection of endocervical anti-Chlamydia trachomatis immunoglobulin A in pregnant women by a rapid, 6-minute enzyme-linked immunosorbent assay: comparison with PCR and chlamydial antigen detection methods. *Journal of Clinical Microbiology* 1997;**35**:1781-1783.
9. Boonstra E, Lindbaek M, Klouman E, Ngome E, Romoren M, Sundby J. Syndromic management of sexually transmitted diseases in Botswana's primary health care: quality of care aspects. *Tropical Medicine & International Health* 2003;**8**:604-614.
10. Buve A, Changalucha J, Mayaud P, Gavyole A, Mugeye K, Todd J, *et al*. How many patients with a sexually transmitted infection are cured by health services? A

study from Mwanza region, Tanzania. *Tropical Medicine & International Health* 2001;**6**):971-979.
11. Postma MJ, Welte R, van den Hoek JA, van Doornum GJ, Jager HC, Coutinho RA. ost-effectiveness of partner pharmacotherapy in screening women for asymptomatic infection with Chlamydia Trachomatis. *Value in Health* 2001;**4**:266-275.
12. Welte R, Jager, H., Postma, MJ. Cost-effectiveness of screening for genital Chlamydia trachomatis. *Expert Review of Pharmacoeconomics & Outcomes Research* 2001;**1**:145-156.
13. Romoren M, Hjortdahl P, Velauthapillai M, Steen T, Hussein F, Rahman M, *et al*. Costs and health consequences of chlamydia management strategies in pregnant women in sub-Saharan Africa. Technical Report. University of Oslo, 2007. Available at: http://www.hero.uio.no/publicat/2007/HERO2007_10.pdf.
14. Adair CD, Gunter M, Stovall TG, McElroy G, Veille JC, Ernest JM. Chlamydia in pregnancy: a randomized trial of azithromycin and erythromycin. *Obstetrics & Gynecology* 1998;**91**:165-168.
15. Rustomjee R, Kharsany AB, Connolly CA, Karim SS. A randomized controlled trial of azithromycin versus doxycycline/ciprofloxacin for the syndromic management of sexually transmitted infections in a resource-poor setting. *Journal of Antimicrobial Chemotherapy* 2002;**49**:875-878.
16. Mathews C, Guttmacher SJ, Coetzee N, Magwaza S, Stein J, Lombard C, *et al.* Evaluation of a video based health education strategy to improve sexually transmitted disease partner notification in South Africa. *Sexually Transmitted Infections* 2002;**78**:53-57.
17. Sanson-Fisher R, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. *Diagnostic Microbiology & Infectious Disease* 1992;**15**, Suppl 4:103-109.
18. Robinson AJ, Ridgway GL. Concurrent gonococcal and chlamydial infection: how best to treat. *Drugs* 2000;**59**:801-813.
19. Roberts TER, S; Barton, P; Bryan, S; Low, N. Screening for Chlamydia trachomatis: a systematic review of the economic evaluations and modelling. *Sexually Transmitted Infections* 2006;**82**:193-200.
20. Romoren M, Rahman M, Sundby J, Hjortdahl P. Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana. *Sexually Transmitted Infections* 2004;**80**:395-400.
21. Guaschino S, Ricci G. How, and how efficiently, can we treat Chlamydia trachomatis infections in women? *Best Practice & Research in Clinical Obstetrics & Gynaecology* 2002;**16**:875-888.
22. Turrentine MA, Newton ER. Amoxicillin or erythromycin for the treatment of antenatal chlamydial infection: a meta-analysis. *Obstetrics & Gynecology* 1995;**86**:1021-1025.
23. Adimora AA. Treatment of uncomplicated genital Chlamydia trachomatis infections in adults. *Clinical Infectious Diseases* 2002;**35**, Suppl 2:183-186.
24. Townshend JRP, Turner HS. Analysing the effectiveness of Chlamydia screening. *Journal of the Operational Research Society* 2000;**51**:812-824.

25. de Vries R, van Bergen JE, de Jong-van den Berg LT, Postma MJ, *et al*. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. *Value in Health* 2006;**9**:1-11.
26. Miller JM, Martin DH. Treatment of Chlamydia trachomatis infections in pregnant women. *Drugs* 2000;**60**:597-605.
27. Quinn TC, Gaydos C, Shepherd M, Bobo L, Hook EW, 3rd, Viscidi R, *et al*. Epidemiologic and microbiologic correlates of Chlamydia trachomatis infection in sexual partnerships. *JAMA* 1996;**276**:1737-1742.
28. Markos AR. The concordance of Chlamydia trachomatis genital infection between sexual partners, in the era of nucleic acid testing. *Sexual Health*. 2005;**2**:23-24.
29. Manavi K, McMillan A, Young H. Genital infection in male partners of women with chlamydial infection. *International Journal of STD & AIDS* 2006;**17**:34-36.
30. Mak DB, Plant AJ, Bulsara MK. Quality of sexually transmitted infection clinical management and contact tracing outcomes in a remote area of high sexually transmitted infection endemicity. *Sexually Transmitted Diseases* 2004;**31**:449-454.
31. Paxton LA, Kiwanuka N, Nalugoda F, Gray R, Wawer MJ. Community based study of treatment seeking among subjects with symptoms of sexually transmitted disease in rural Uganda. *BMJ* 1998;**317**:1630-1631.
32. Klouman E, Masenga EJ, Sam NE, Klepp KI. Asymptomatic gonorrhoea and chlamydial infection in a population-based and work-site based sample of men in Kilimanjaro, Tanzania. *International Journal of STD & AIDS* 2000;**11**:666-674.
33. Pack RP, Diclemente RJ, Hook EW, 3rd, Oh MK. High prevalence of asymptomatic STDs in incarcerated minority male youth: a case for screening. *Sexually Transmitted Diseases* 2000;**27**:175-177.
34. Central Statistics Office. Health Statistics Report 2002. Gaborone: Ministry of Finance and Development Planning, 2005.
35. Kirungi WL, Ball M, Rahman M, Rogoeng M. Observational health facility survey for the evaluation of STD case management in primary health care facilities in Botswana. Gaborone: AIDS/STD Unit, 1998.
36. Nuwaha F, Kambugu F, Nsubuga PS, Hojer B, Faxelid E. Efficacy of patient-delivered partner medication in the treatment of sexual partners in Uganda. *Sexually Transmitted Diseases* 2001;**28**:105-110.
37. van de Laar MJ, Termorshuizen F, van den Hoek A. Partner referral by patients with gonorrhea and chlamydial infection. Case-finding observations. *Sexually Transmitted Diseases* 1997;**24**:334-342.
38. Low N, McCarthy A, Roberts TE, Huengsberg M, Sanford E, Sterne JA, *et al*. Partner notification of chlamydia infection in primary care: randomised controlled trial and analysis of resource use. *BMJ* 2006;**332**:14-19.
39. Ministry of Health. Management of Sexually Transmitted Infections. Gaborone: Ministry of Health, 2005.
40. WHO. Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization, 2003.
41. Center for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. Atlanta: Center for Disease Control and Prevention, 2006.

Appendix 4

Table A6 Age of ntenatal care attendees in the study compared to new attendees in Botswana

Age groups	Study setting		New antenatal care attendees in Gaborone					
	Year 2000-2001		Year 2000		Year 2001		Year 2002	
	n	(%)	n	(%)	n	(%)	n	(%)
<20	76	(10.8)	7 965	(20.0)	8 594	(20.0)	8 264	(19.1)
20-29	432	(61.5)	21 314	(53.6)	23 257	(54.2)	23 569	(54.6)
30+	195	(27.7)	10 466	(26.3)	11 031	(25.7)	11 333	(26.3)
All	703	(100)	39 745	(100)	42 882	(100)	43 166	(100)
<20	76	(10.6)	7 965	(20.0)	8 594	(20.0)	8 264	(19.1)
<30	508	(72.3)	29 279	(73.7)	31 851	(74.3)	31833	(73.7)
All	703	(100)	39 745	(100)	42 882	(100)	43 166	(100)

Table A7 Age of antenatal care attendees in the study compared new attendees in Gaborone

Age groups	Study setting		New antenatal care attendees in Gaborone			
	Year 2000-2001		Year 2000		Year 2002	
	n	(%)	n	(%)	n	(%)
<15	0	-	14	(0.2)	7	(0.1)
15-19	76	(10.8)	860	(13.6)	633	(10.0)
20-29	432	(61.5)	4164	(66.1)	4008	(63.5)
30-39	179	(25.7)	1163	(18.4)	1529	(24.2)
40-44	16	(2.3)	117	(1.9)	134	(2.1)
45+	0	-	7	(0.1)	4	(0.1)
Total	703	(100)	6325	(100)	6315	(100)

Paper I

Chlamydia and gonorrhoea in pregnancy:

effectiveness of diagnosis and treatment in Botswana

Sexually Transmitted Infections. 80(5):395-400, 2004 Oct.

ORIGINAL ARTICLE

Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana

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Sex Transm Infect 2004;**80**:395–400. doi: 10.1136/sti.2003.007757

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Accepted for publication 15 January 2004

Background: Millions of patients are prescribed drugs for sexually transmitted infections (STIs) in developing countries each year, yet the treatment effect of these prescriptions is largely unknown.
Objectives: To determine if the prescribing of erythromycin and ceftriaxone to pregnant women with STI symptoms leads to a reduction in the prevalence among these women of chlamydia and gonorrhoea, respectively.
Methods: We compared the prevalence of chlamydia among 116 pregnant women who had been prescribed erythromycin for a history of STI symptoms in their current pregnancy with the prevalence in a control group of 557 pregnant women who had not been prescribed this drug. Similarly we compared the prevalence of gonorrhoea among 110 pregnant women who had and 561 women who had not been prescribed ceftriaxone.
Results: There was no significant difference in the prevalence of chlamydia among the women who had and the women who had not been prescribed erythromycin four times daily for 10 days (7% *v* 8%). Contrarily, none of the women who had been prescribed a single dose of ceftriaxone had gonorrhoea, whereas 4% of the women who had not had this drug prescribed did have gonorrhoea.
Conclusions: The prescribing of erythromycin seems to have had a limited effect on chlamydia in this population, whereas the prescribing of ceftriaxone led to the curing of gonorrhoea. Ceftriaxone is provided as a single dose injection at the point of care, and the differential effectiveness between the two drugs may reflect low compliance with the complex erythromycin regimen. Interventions to increase compliance could improve cure rates. The use of a simpler drug regimen should be considered when low compliance is likely.

Sexually transmitted infections (STIs) are a major health problem in many parts of the developing world. STIs cause substantial morbidity and mortality, which disproportionately affect women. Because many of the complications are pregnancy related,[1 2] adequate diagnosis and effective treatment of STIs in pregnancy are critical. Additionally, there is substantial evidence that the presence of other STIs increases both HIV infectiousness and susceptibility,[3 4] and a long term STI control programme is emphasised as one of the cornerstones of HIV prevention.[5] Striving for optimal performance of the STI programme is essential; in countries where healthcare budgets are limited, the potential for improvement is often larger and can have a substantial effect on the overall burden of disease.

Evaluations of STI programmes are usually limited to an assessment of the proportion of patients with an STI that is correctly diagnosed and to the prescribing of effective drugs. Previous studies have tended not to focus on the fact that patients with an STI must overcome a series of hurdles after their encounter with the healthcare system before they can be considered cured. STI clients who are adequately assessed must obtain prescribed drugs, comply with treatment, and ensure that their partners are treated to avoid re-infection.[6] Patient compliance with medical advice and drug regimens is an increasingly significant issue in developing countries. The consumption of drugs is on the rise, and drugs represent a high proportion of healthcare budgets.[7] Although most governments are interested in ensuring availability and access to drugs, addressing the issue of adequate drug use remains a low priority.[8]

In Botswana, a country of 1.7 million people, the burden of STIs is high. Extrapolating from the 37% of the pregnant women who are known to be HIV positive, the Ministry of Health has calculated that 275 000 of 15–49 year olds are infected with the virus.[9] Because of a lack of laboratory facilities, STI diagnosis and treatment are usually limited to case management in which algorithms are used to classify presenting symptoms and clinical signs into defined syndromes. There were 180 000 registered STI related outpatient consultations in 2000, 150 000 of which led to a syndrome diagnosis.[10] However, syndromic management leads to diagnostic uncertainty and limits epidemiological surveillance. Patients are prescribed multiple drug regimens to cover every possible microbiological agent that is known to cause each syndrome, and antimicrobials for STIs constitute a substantial share of the total drug use in the country. Despite the large number of prescriptions, treatment success among STI patients in the primary healthcare system remains unknown.

The aim of this article is to draw attention to the consequences of prescribing antibiotics to STI patients in Botswana and to discuss possibilities for improving the cure rates. In a larger research project on STIs among antenatal care (ANC) clients in Botswana, we found that many of the women had a history of STI symptoms in their current pregnancies and had been prescribed the recommended STI treatment. Given the epidemiological data, we present the following research question: Is there a lower prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among ANC clients who have had drugs against these bacteria prescribed to them in their current pregnancy, compared to ANC clients who have not had these drugs prescribed?

METHOD

Included in this study were 703 ANC clients who visited the primary healthcare clinics in Gaborone, the capital of

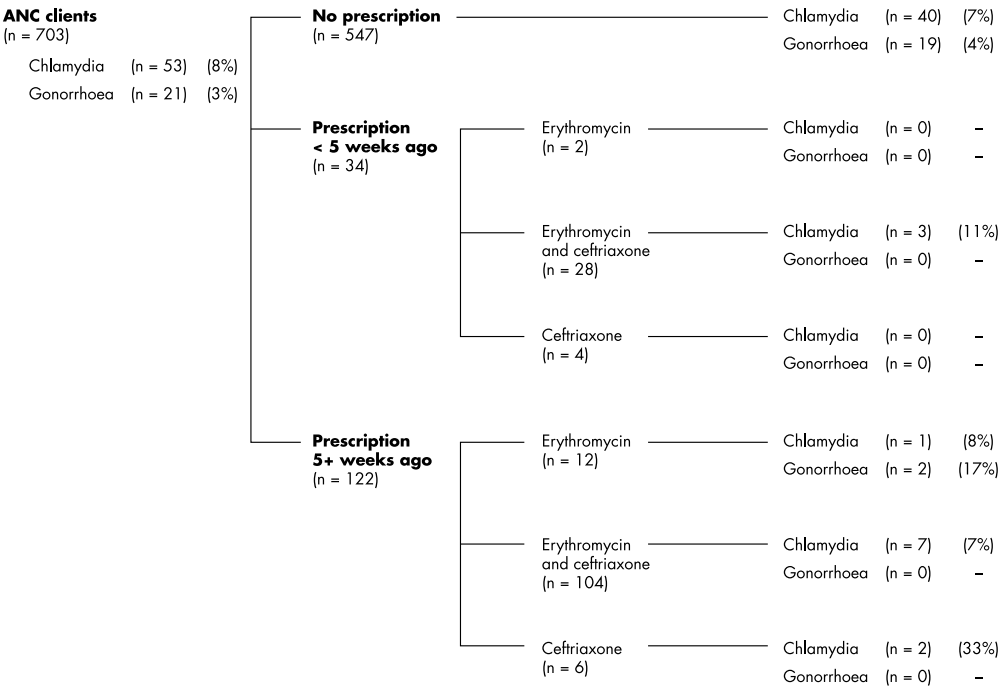

Figure 1 Prescription of erythromycin and ceftriaxone earlier in current pregnancy among 703 antenatal care clients in Gaborone, Botswana, and the distribution of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in this population.

Botswana, between October 2000 and February 2001. A proportionate sample of ANC clients was chosen from each of the clinics, based on the ANC patient load during the same period in the previous year. All volunteers gave written, informed consent, and our only exclusion criterion was the use of antibiotics in the 2 weeks before their visit. A structured interview and data from the patient held obstetric record were used to obtain information on sociodemographic factors, past and current pregnancies, and STI symptoms.

When a patient is diagnosed with an STI syndrome during pregnancy, the syndrome and the prescribed drugs are documented in the obstetric record. In pregnant women, STIs are often diagnosed during the mandatory speculum examination at the first ANC visit. Prescribed treatment for any STI during the current pregnancy was recorded in this study along with the syndrome diagnosis. In Botswana, the recommended treatment for *C trachomatis* is 100 mg of doxycycline taken orally twice daily for 10 days; in pregnancy, the recommended treatment is 500 mg of erythromycin taken orally four times daily for 10 days.[11] The treatment for *N gonorrhoeae* is 250 mg of ceftriaxone given as a single intramuscular injection by a healthcare provider at the point of care.

All patients underwent a genital examination, and clinical signs from external and internal genitalia were recorded. Signs of a sexually transmitted infection were classified into defined syndromes following the national guidelines and were treated accordingly. Cervical swabs were obtained from all women for ligase chain reaction (LCR) amplification technology for the direct, qualitative detection of specific target nucleic acid sequences of *C trachomatis* and *N gonorrhoeae*. The swabs were placed in LCx transport media, transported to the laboratory at ambient temperature the same day, and stored at −20°C before batch processing. The LCx assays (Abbott Laboratories, IL, USA) were performed according to the manufacturer's instructions. A case of *C trachomatis* or *N gonorrhoeae* infection was defined as an individual with a positive LCR analysis. DNA amplification testing methods can remain positive up to 3 weeks after treatment. A positive test performed 3 or more weeks after completed treatment should thus be interpreted as true positive, reflecting either treatment failure or re-infection.[12] In this study, rather than assume that every patient began medication the day she received her prescription, we calculated up to 2 weeks to complete the course of medication. Patients who had been prescribed treatment for either of the two infections under study were therefore divided into two groups: (a) patients for whom treatment was prescribed up to 5 weeks earlier and who were still within the period in which a confirmed case of infection could be a false positive, and (b) patients for whom treatment was prescribed 5 or more weeks previous, and for whom a confirmed case was likely to be true positive. Patients who had not been prescribed treatment were used as controls.

The study was approved by the national ethics committees of Botswana and Norway.

RESULTS

The median age of the 703 ANC clients was 25 years and the median gestational age 30 weeks (range 8–42); 53 (8%) of the women had a laboratory verified *C trachomatis* infection and 21 (3%) had laboratory verified *N gonorrhoeae* infection. Further background characteristics and genital symptoms and signs are described in table 1. Both erythromycin and

Table 1 Background characteristics, genital symptoms and signs, and the prevalence of cervical infections among 703 antenatal care clients in Gaborone, Botswana

	No	(%)
Age groups (years)		
15–19	76	(11)
20–24	249	(35)
25–29	183	(26)
30–34	126	(18)
35–43	69	(10)
Education		
Primary school or less	168	(24)
Junior secondary school	310	(44)
Secondary school or higher	225	(32)
Marital status		
Married	114	(16)
Living with husband	*97*	*(85)*
Non-marital steady partner	572	(81)
Living with partner	*256*	*(45)*
Single	17	(2)
Number of pregnancies		
1st pregnancy	243	(35)
2nd pregnancy	208	(30)
3rd pregnancy	122	(17)
4th+ pregnancy	130	(18)
Number of antenatal care visits		
1st visit	157	(22)
2nd–4th visit	300	(43)
5th–7th visit	182	(26)
8th+ visit	64	(9)
Self reported symptoms of STIs		
Increased vaginal discharge	119	(17)
Itching/soreness	58	(8)
Lower abdominal pain	53	(8)
Genital warts	16	(2)
Genital ulcer	8	(1)
Dysuria	8	(1)
Clinical signs of STIs		
Vaginal discharge syndrome	308	(44)
Genital warts	29	(4)
Genital ulcer	5	(1)
Cervical infection (chlamydia and/or gonorrhoea)	67	(10)
Chlamydia	53	(8)
Gonorrhoea	21	(3)

ceftriaxone had been prescribed to 132 of the women earlier in their pregnancies; erythromycin only had been prescribed to 14 women and ceftriaxone only to 10 women. Figure 1 shows the distribution of confirmed cervical infections among women who had and had not been prescribed erythromycin and/or ceftriaxone.

The diagnosis for which the antibiotics were prescribed is shown in table 2. Vaginal discharge syndrome (VDS) was the most common diagnosis, leading to 137 (86%) of 159 erythromycin prescriptions and 130 (85%) of 153 ceftriaxone prescriptions. According to national syndromic management guidelines,[11] a woman who complains of abnormal vaginal discharge should, if the condition is confirmed at a speculum examination, be prescribed treatment for vulvovaginal candidiasis, trichomoniasis, bacterial vaginosis, chlamydia, and gonorrhoea. How many of these women actually had chlamydia, gonorrhoea or any of the other infections is not known.

There was no significant difference in the prevalence of chlamydia or gonorrhoea among women with and without clinical signs of vaginal discharge syndrome: 27 (9%) of the 308 women with VDS and 26 (7%) of the 395 women without VDS had chlamydia (Fisher's exact test 0.31 (two sided)), and 13 (4%) of the 308 women with VDS and eight (2%) of the 395 women without VDS had gonorrhoea (Fisher's exact test 0.12 (two sided)). Using only clinical signs of abnormal vaginal discharge as a diagnostic tool to identify cervical infections in this study population has a low sensitivity and specificity: VDS has a sensitivity of 0.51 for chlamydia and 0.62 for gonorrhoea and a specificity of 0.57 for both chlamydia and gonorrhoea.

Of the 703 ANC women, 146 (21%) had been prescribed the recommended erythromycin regimen for chlamydia—13 of them twice. The prevalence of chlamydia among women who had and had not been prescribed erythromycin is identical at 8%. Confirmed *C trachomatis* cases in the different erythromycin prescription groups are shown in table 3; none of these prevalences are significantly different. Of the 116 women who had been prescribed erythromycin 5 or more weeks earlier (median 11 weeks), eight (7%) had chlamydia; and 42 (8%) of the 561 women who had not been prescribed this drug during pregnancy had chlamydia (Fisher's exact test 1.0 (two sided)). There were no significant differences in age, median gestational week, parity, educational level, marital status, or length of current relationship among the women who had and had not been prescribed erythromycin earlier in pregnancy.

Of the 703 ANC women, 142 (20%) had been prescribed ceftriaxone in their current pregnancy, 11 of them twice. Among these 142 women, none had a positive *N gonorrhoeae* test result. Among the 110 women who had been prescribed ceftriaxone 5 or more weeks earlier (median 12 weeks), none had gonorrhoea, whereas 21 (4%) of the 561 women who had not been prescribed the drug had gonorrhoea (table 3). The difference in gonorrhoea prevalence between the two groups is significant (Fisher's exact test = 0.035 (two sided)).

Table 2 Diagnosis leading to prescription of erythromycin and ceftriaxone to 156 antenatal care clients in Gaborone, Botswana, of which 132 clients were prescribed both drugs, 14 clients were prescribed erythromycin only, and 10 ceftriaxone only

	No	(%)
Reasons for prescribing 500 mg of erythromycin 1 × 4 in 10 days to 146 women, 13 of whom were diagnosed twice (n = 159)		
Vaginal discharge syndrome	137	(86)
Cervical erosion	18	(11)
Lower abdominal pain	3	(2)
Genital ulcer	1	(1)
Reasons for prescribing 250 mg of ceftriaxone intramuscularly, single dose to 142 women of whom 11 were diagnosed twice (n = 153)		
Vaginal discharge syndrome	130	(85)
Cervical erosion	17	(11)
Lower abdominal pain	2	(1)
Genital ulcer	3	(2)
Syphilis	1	(1)

DISCUSSION

This retrospective study reviews treatment success among ANC clients who were prescribed drugs for *C trachomatis* and *N gonorrhoeae* during pregnancy. We demonstrate that prescribing erythromycin orally four times daily in 10 days does not necessarily lead to a cure for *C trachomatis* in pregnancy and that ceftriaxone prescribed as a single dose injection against *N gonorrhoeae* appears to be effective. The differences in the effect of prescribing these two drug regimens are thought provoking.

When the correct drug has been prescribed, patient compliance and treatment of an infected partner are the main factors necessary for the successful treatment of STIs. Research on these issues can be limited by methodological pitfalls, and different research strategies should complement each other. Studies, primarily from developing countries, have measured compliance and partner notification in randomised, controlled trials.[13–15] Yet these methods are hampered by challenges such as observational bias (patients are likely to perform better in a defined research setting), or there may be a self selection of patients, in that the less conscientious individuals will be lost during the follow up stage.

Epidemiological data have an advantage in evaluating the true effect of STI management from a public health perspective—in this case, illustrating the impact of treating cervical infections among ANC clients in the primary healthcare system in Botswana. A methodological weakness in our study, which is an inherent problem of syndromic management, is the unknown prevalence of infection before the prescription of antibiotics. ANC clients who were and were not prescribed erythromycin earlier in pregnancy demonstrate a similar prevalence of chlamydia. Is there reason to believe that the prevalence of chlamydia among clients who had been prescribed erythromycin was higher before treatment, and was therefore significantly reduced? The answer to this question is mainly dependent on the sensitivity of the clinical signs on which the prescription was based. The majority (85%) of the patients had had erythromycin prescribed to them because of clinical signs of VDS. It is well known that the algorithms currently available for the management of cervical infections are far from ideal.[16–18] Previous research from Africa reports no or poor association between vaginal discharge and cervical infections.[2 19 20] In our data we do not find a significant association between VDS and *C trachomatis* infection among pregnant women. It is also relevant to note that the women who had and the women who had not had erythromycin prescribed to them earlier in their pregnancies are similar in sociodemographic risk factors, including age—a consistent risk factor for cervicitis. Thus, circumstantial evidence indicates that the prevalence of cervical infection among the patients who had been prescribed erythromycin and/or ceftriaxone was probably the same or slightly higher before treatment.

Lack of efficacy in the prescribed antibiotics is not likely in this study. Erythromycin and ceftriaxone have been shown to be effective against *C trachomatis* and *N gonorrhoeae* respectively, and bacterial resistance to these treatment regimens has not yet been found to be of clinical importance.[21] The availability of STI drugs is high in Botswana, even in rural areas, and they are provided to the patients free of charge.[22] Of the 122 women who had had erythromycin and/or

Table 3 Prevalence of chlamydia and gonorrhoea among 703 ANC clients in Gaborone, Botswana, compared to prescription of the drugs recommended for these infections earlier in current pregnancy

	No	(%)	Total No
500 mg erythromycin 1×4 in 10 days	***C trachomatis* infection**		
No erythromycin prescribed	42	(8)	557
Erythromycin prescribed less than 5 weeks earlier	3	(10)	30
Erythromycin prescribed 5 or more weeks earlier	8	(7)	116
Total sample	53	(8)	703
Ceftriaxone 250 mg im in a single dose	***N gonorrhoeae* infection**		
No ceftriaxone prescribed	21	(4)	561
Ceftriaxone prescribed less than 5 weeks earlier	0	–	32
Ceftriaxone prescribed 5 or more weeks earlier	0	–	110
Total sample	21	(3)	703

ceftriaxone prescribed to them 5 or more weeks before this study, 104 (85%) had had both drugs prescribed. No substantial crossover effect between the two drugs is likely, however. Neither drug regimen is satisfactory for treatment of the other microbe,[21] and we found no significant reduction of gonorrhoea among patients who were prescribed erythromycin and no significant reduction in chlamydia among patients who were prescribed ceftriaxone.

Re-infection

Could the treatment failure of erythromycin be due to re-infection or to a newly acquired infection? Chlamydia and gonorrhoea can cause urethral discharge in men, and men with this symptom and partners to women with VDS are usually treated with both doxycycline and ceftriaxone. Among the ANC clients in this study with an *N gonorrhoeae* infection who were prescribed ceftriaxone, all were treated successfully and had not been re-infected by their partners at the time of our study. Two factors can possibly lead to a lower impact of re-infection with *N gonorrhoeae* than with *C trachomatis* in this population. We cannot ignore the fact that the level of healthcare seeking among partners with gonorrhoea (which causes symptoms among men more often than does chlamydia) is likely to be somewhat higher. It is also possible that treatment success with the single dose therapy for gonorrhoea is higher among partners than is the doxycycline regimen for chlamydia.

Theoretically, all women treated for chlamydia could have been re-infected or acquired a new infection after being cured. However, it would have required a substantial failure in the notification and treatment of the partners of ANC clients with *C trachomatis* and complete success in notifying and treating partners of the women with an *N gonorrhoeae* infection—a highly unlikely state of affairs. Sexual abstinence in the gonorrhoea group could explain their lack of re-infection and multiple partners in the chlamydia group could have caused new infections, but there is no reason to believe that that would have been the case. Women in both groups reported one sexual partner the last year and it seems safe to assume that these two groups should not differ systematically in their sexual behaviour. These arguments lead to the conclusion that re-infections or new infections can not be a major cause of the documented failure to treat *C trachomatis*. One is left with the impression that patient compliance is a more important variable.

Patient compliance

Although evidence from developing countries is limited, a substantial level of non-adherence to antibiotic prescriptions in most cultures is well known and reviews of studies from developed countries suggest that at least 30% of patients fail to follow medical advice on drug use.[23] Of the many variables involved in non-adherence, non-modifiable factors include characteristics of the patient, practitioner, or illness; whereas potentially modifiable factors relate to aspects of the interaction between patient and healthcare provider and aspects of the drug regimen. The complexity of the regimen (frequency of administration, number of tablets required daily, and length of treatment) is closely related to adherence.[23] The number of patients who do not comply with prescribed courses of antibiotics may be increased in asymptomatic STI clients, and the occurrence of adverse effects is also associated with non-compliance.[21]

As in most developing countries, ANC clients in Botswana with STI symptoms are prescribed a multiple drug regimen that requires many tablets to be administered correctly, which in itself may reduce compliance. The erythromycin regimen is complex in itself, the medication is frequently followed by gastrointestinal side effects, and the patient's complaint is not severe. We suspect that low compliance is a central factor in explaining why the prescribing of erythromycin orally four times daily in 10 days does not necessarily lead to a cure for *C trachomatis* in pregnancy.

Improving cure rates

According to national guidelines in Botswana, all STI patients should be counselled on patient based partner referral and should receive contact cards with information to give to their partners. However, referred partners to symptomatic STI patients comprise less than 10% of all registered STI outpatients,[10] suggesting that there is room for improvement in the partner notification system. Unfortunately, few studies on this issue have been undertaken in resource poor countries where it is essential that resources be used effectively and efficiently, and the cultural contexts are different.[15] The relatively high levels of overdiagnosis of STIs in syndromic management, especially in women, may not, in fact, provide an appropriate basis for recommending the management of partners, as we may not be sure that the individual is truly infected.[24] Thus, improving partner notification in women with VDS is a complicated issue. A more obvious and simple strategy to improve *C trachomatis* cure rates within the national control programmes is the use of a single, supervised dose of antibiotics.

Several drugs, typically used in combination, can satisfactorily cure cervical infections. If poor compliance is suspected, as is the case with the ANC clients in Gaborone who are treated with erythromycin for *C trachomatis* infections, directly observed single dose therapy should be considered.[25] Gonorrhoea has been treated in this manner since the beginning of the antibiotic era; and with the development and licensing of azithromycin, chlamydia can also be effectively treated with single dose therapy.[26] The oral administration of 1 g of azithromycin has a similar or higher efficacy and similar or fewer side effects than all the alternative week long regimens,[12 27] and has become the drug of choice in most of the developed world. Although azithromycin is still not officially licensed for the treatment of chlamydia in pregnancy, clinical experience and research data suggest that azithromycin is effective and safe for the fetus,[13 28] and the drug is listed as an alternative regimen for pregnant women in the Centres for Disease Control STD treatment guidelines.[29] Compared to azithromycin, erythromycin has a significantly higher level of gastrointestinal side effects, which frequently discourage patients from complying with the regimen and thereby reduces the cure rate.[26 29]

A comparative study on STI drugs from 15 countries in Africa and Asia concludes that azithromycin is not routinely used for chlamydia in developing countries.[30] Single dose therapies were used to treat *N gonorrhoeae* in 12 out of 15 countries, but week long regimens were used in all 15 countries to treat *C trachomatis*. Efficacy, tolerance, compliance, and cost are factors to consider when preparing guidelines for antibiotic treatment of chlamydial infection. An important obstacle to single dose therapy in countries where resources are limited is the higher drug acquisition cost for azithromycin compared to doxycycline. The erythromycin regimen is more expensive than azithromycin, and in pregnant women, azithromycin could be recommended.[31] When it comes to other STI patients, economic analysis clearly favours single dose therapy when the indirect costs of treatment failures are included.[28]

It is also clear that an investment of additional time is necessary during consultation in order to provide patient education and counselling on compliance, partner notification, and safe sex. Female STI patients in Botswana are managed in an average of 5.4 minutes.[22]

Key messages

- In sub-Saharan Africa, the burden of STIs is high, and antimicrobials for STIs constitute a substantial share of the total drug use. Despite the large number of prescriptions, treatment success among STI patients in the primary healthcare system remains unknown
- This study draws attention to what happens after STI patients in Botswana have been diagnosed and prescribed treatment. We find that antenatal care clients with a recent history of STI symptoms who have received prescriptions of ceftriaxone are successfully treated for *Neisseria gonorrhoeae*. ANC clients who have been prescribed erythromycin have identical prevalence of *Chlamydia trachomatis* to ANC clients without such history. We argue that the complexity of the erythromycin regimen is most probably the main cause of the low treatment effect
- Improving patient compliance, but also facilitating partner notification, and promoting sexual abstinence until the patient and partner are treated can be effectivel and cost effective ways to improve treatment with STI drugs. The use of directly observed single dose therapy for the treatment of chlamydia should be considered if low compliance to more complex treatment regimens is likely

CONCLUSION

When assessing the performance and cure rates achieved by STI programmes, it is necessary to focus on the consequences of the STI patient's diagnosis and treatment prescription. Low compliance with recommended drug regimens and lack of partner notification and treatment are the main obstacles that hinder a cure. In this study, many ANC clients in Botswana are successfully treated on the spot for *N gonorrhoeae* with an intramuscular injection with ceftriaxone, whereas many clients who are prescribed one tablet of erythromycin four times daily for 10 days are not cured of *C trachomatis*. We argue that the complexity of the erythromycin regimen most probably is the main cause of the low treatment effect.

Improving patient compliance, but also facilitating partner notification, and promoting sexual abstinence until the patient and partner are treated can be effective and cost effective ways to improve treatment with STI drugs. Healthcare professionals prescribing antibiotics must give their patients clear information that emphasises the importance of adhering to the treatment and examine the patient's health beliefs and understanding of the instructions. Interventions to improve patient compliance as well as partner treatment should be based on area specific research. We also recommend that health authorities in developing countries consider the use of directly observed single dose therapy for the treatment of chlamydia if low compliance is considered to be likely.

CONTRIBUTORS

MRo contributed to the study design, was responsible for data collection and data analysis, and was the primary author of the manuscript; MRa contributed to the study design, and to formal and organisational aspects of the study; JS and PH supervised the study; all co-authors contributed to the drafting of the article and approved the final manuscript.

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REFERENCES

1 **World Bank**. *World development report 1993: investing in health*. New York: World Bank, 1993.
2 **Mayaud P**, Uledi E, Cornelissen J, *et al*. Risk scores to detect cervical infections in urban antenatal clinic attenders in Mwanza, Tanzania. *Sex Transm Infect* 1998;**74**(Suppl 1):S139–46.
3 **Wasserheit JN**. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis* 1992;**19**:61–77.
4 **Grosskurth H**, Mosha F, Todd J, *et al*. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.
5 **UNAIDS**. *The public health approach to STD control: UNAIDS Technical Update*. Geneva: UNAIDS, 1998.
6 **Buve A**, Changalucha J, Mayaud P, *et al*. How many patients with a sexually transmitted infection are cured by health services? A study from Mwanza region, Tanzania. *Trop Med Int Health* 2001;**6**:971–9.
7 **Homedes N**, Ugalde A. Research on patient compliance in developing countries. *Bull Pan Am Health Organ* 1994;**28**:17–33.
8 **Homedes N**, Ugalde A. Improving the use of pharmaceuticals through patient and community level interventions. *Soc Sci Med* 2001;**52**:99–134.
9 **National AIDS Coordinating Agency**. *Botswana 2003 second generation HIV/AIDS surveillance: a Technical Report*. Gaborone: National AIDS Coordinating Agency, 2003.
10 **Central Statistics Office**. *Health statistics report 1999*. Gaborone: Central Statistics Office, 2002.
11 **AIDS/STD Unit**. *The management of sexually transmitted diseases*. Gaborone: AIDS/STD Unit, Ministry of Health, 1994.
12 **Johnson RA**. Diagnosis and treatment of common sexually transmitted diseases in women. *Clinical Cornerstone* 2000;**3**:1–11.
13 **Adair CD**, Gunter M, Stovall TG, *et al*. Chlamydia in pregnancy: a randomized trial of azithromycin and erythromycin. *Obstet Gynecol* 1998;**91**:165–8.
14 **Rustomjee R**, Kharsany AB, Connolly CA, *et al*. A randomized controlled trial of azithromycin versus doxycycline/ciprofloxacin for the syndromic management of sexually transmitted infections in a resource-poor setting. *J Antimicrob Chemother* 2002;**49**:875–8.
15 **Mathews C**, Coetzee N, Zwarenstein M, *et al*. Strategies for partner notification for sexually transmitted diseases (Cochrane Review). In: *The Cochrane Library Issue 4, 2003*. Chichester: John Wiley, 2003.
16 **van Dam CJ**, Becker KM, Ndowa F, *et al*. Syndromic approach to STD case management: where do we go from here? *Sex Transm Infect* 1998;**74**(Suppl 1):S175–8.
17 **Mabey D**. Sexually transmitted diseases in developing countries. *Trans Roy Soc Trop Med Hyg* 1996;**90**:97–9.
18 **Vickerman P**, Watts C, Alary M, *et al*. Sensitivity requirements for the point of care diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae in women. *Sex Transm Infect* 2003;**79**:363–7.
19 **Schneider H**, Coetzee DJ, Fehler HG, *et al*. Screening for sexually transmitted diseases in rural South African women. *Sex Transm Infect* 1998;**74**(Suppl 1):S147–52.
20 **Mayaud P**, ka-Gina G, Cornelissen J, *et al*. Validation of a WHO algorithm with risk assessment for the clinical management of vaginal discharge in Mwanza, Tanzania. *Sex Transm Infect* 1998;**74**(Suppl 1):S77–84.
21 **Robinson AJ**, Ridgway GL. Concurrent gonococcal and chlamydial infection: how best to treat. *Drugs* 2000;**59**:801–13.
22 **Boonstra E**, Lindbaek M, Klouman E, *et al*. Syndromic management of sexually transmitted diseases in Botswana's primary health care: quality of care aspects. *Trop Med Int Health* 2003;**8**:604–14.
23 **Sanson-Fisher R**, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. *Diagn Microbiol Infect Dis* 1992;**15**(Suppl 4):S103–9.
24 **Hawkes S**, Mabey D, Mayaud P. Partner notification for the control of sexually transmitted infections. *BMJ* 2003;**327**:633–4.
25 **Gilson RJ**, Mindel A. Recent advances: sexually transmitted infections. *BMJ* 2001;**322**:1160–4.
26 **Kingston M**, Carlin E. Treatment of sexually transmitted infections with single-dose therapy: a double-edged sword. *Drugs* 2002;**62**:871–8.
27 **Adimora AA**. Treatment of uncomplicated genital Chlamydia trachomatis infections in adults. *Clin Infect Dis* 2002;**35**(Suppl 2):S183–6.
28 **Miller JM**, Martin DH. Treatment of Chlamydia trachomatis infections in pregnant women. *Drugs* 2000;**60**:597–605.
29 **Centers for Disease Control and Prevention**. Sexually transmitted diseases treatment guidelines 2002. *MMWR* 2002;**51**(No RR-6):34.
30 **Van der Veen F**, Fransen L. Drugs for STD management in developing countries: choice, procurement, cost, and financing. *Sex Transm Infect* 1998;**74**(Suppl 1):S166–74.
31 **Pepin J**, Mabey D. Sexually transmitted infections in Africa: single dose treatment is now affordable. *Sex Transm Infect* 2003;**79**:432–4.

Paper II

Trichomoniasis and bacterial vaginosis in pregnancy:

inadequately managed with the syndromic approach

Bulletin of the World Health Organization. 85(4):297-304, 2007 Apr.

Trichomoniasis and bacterial vaginosis in pregnancy: inadequately managed with the syndromic approach

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Objective To measure the prevalence of *Trichomonas vaginalis* (TV) infection and bacterial vaginosis (BV) among pregnant women in Botswana, and to evaluate the syndromic approach and alternative management strategies for these conditions in pregnancy.
Methods In a cross-sectional study, 703 antenatal care attendees were interviewed and examined, and specimens were collected to identify TV, BV, *Candida* species, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Information on reproductive tract infections earlier in pregnancy was obtained from a structured interview and the antenatal record.
Findings TV was found in 19% and BV in 38% of the attendees. Three-fourths of women with TV or BV were asymptomatic. Syndromic management according to the vaginal discharge algorithm would lead to substantial under-diagnosis and over-treatment of TV and BV. Signs of vaginal discharge were more predictive of the presence of these conditions than were symptoms. Among the 546 attendees on a repeat antenatal visit, 142 (26%) had been diagnosed with vaginal discharge earlier in their pregnancy – 14 of them twice. In 143 cases, an attendee was diagnosed with vaginal discharge in the second or third trimester; however, metronidazole had been prescribed only 17 times (12%).
Conclusion Diagnosis and treatment of TV and BV among pregnant women in sub-Saharan Africa presents major challenges. Half the pregnant women in this study were diagnosed with TV or BV, but these conditions were not detected and treated during antenatal care with syndromic management. Also, health workers did not adhere to treatment guidelines. These results indicate that management guidelines for TV and BV in antenatal care should be revised.

Bulletin of the World Health Organization 2007;85:297-304.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Trichomonas vaginalis (TV) infection is the most common curable sexually transmitted infection (STI) worldwide.[1] In studies of low-risk women in sub-Saharan Africa, the prevalence ranges from 10–31%.[2,3] Bacterial vaginosis (BV) is a syndrome characterized by a shift in vaginal flora; it is particularly common in the sub-Saharan region, where prevalences up to 50% are not uncommon.[4] These two vaginal conditions are thought to cause substantial morbidity among women in developing countries. Both infections have been linked to preterm delivery and low birth weight[5] and, as reproductive tract infections (RTIs), they are likely to increase both infectiousness of HIV and susceptibility to the disease.[6,7] It appears to be critical to diagnose and treat TV and BV in pregnancy, especially in high-prevalence settings.[8,9]

There are few studies from developing countries on effective strategies to prevent the adverse outcomes associated with TV and BV in pregnancy. Systematic reviews from developed countries of antibiotic treatment for these conditions in asymptomatic pregnant women show no significant reductions in adverse pregnancy outcomes.[5,10–12] However, antibiotic treatment for BV may reduce the risk of low birth weight and preterm rupture of the membranes among pregnant women with previous preterm deliveries.[13] Provision of treatment for TV or BV in symptomatic pregnant women has not been adequately evaluated.[11,12]

Diagnosis of TV and BV in women in sub-Saharan Africa is based on the vaginal discharge syndrome – the most common syndrome in the syndromic approach (i.e. treating symptoms and signs of disease based on the organisms most commonly responsible for the particular syndrome). In the early 1990s, the World Health Organization developed syndromic management guidelines for symptomatic STI patients for countries without laboratory support. Easily recognized symptoms and signs are combined using flowcharts, and patients are then treated with two or more antibiotic regimens.[14] In Botswana, women reporting vaginal discharge or lower abdominal pain are managed using the vaginal discharge algorithm.[15] Based on a risk assessment and clinical signs, the women are provided with treatment for TV and BV and/or chlamydia and gonorrhoea and/or candidiasis. Where a woman has chlamydia and gonorrhoea, partner treatment is always recommended; however, where a woman has TV, partner treatment is only recommended if the woman's symptoms persist.

For pregnant women, the Botswana STI manual states that asymptom-

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doi: 10.2471/BLT.**06.031922**
(*Submitted: 23 March 2006 – Final revised version received: 2 October 2006 – Accepted: 16 November 2006*)

atic women with a history of previous preterm delivery should be examined for vaginal discharge to detect and treat BV.[15] Syndromic management of asymptomatic antenatal care attendees in general is not recommended in either the national or the World Health Organization's STI management guidelines. In practice, however, all antenatal care attendees in Botswana are clinically screened for RTIs because the country's antenatal care guidelines recommend a routine speculum examination at the first antenatal visit to "exclude genital infections, abnormalities and pelvic tumours".[16] It is not uncommon for abnormal vaginal discharge to be found in women not displaying symptoms. The nurses will act on pathological findings, and asymptomatic women with signs of vaginal discharge are thus provided with syndromic treatment. This management bypasses the original entry point of the syndromic algorithms: symptoms that lead patients to seek health care.

The aim of this paper is to present results on the prevalence of TV and BV among antenatal care attendees in Botswana, to examine the use of the vaginal discharge algorithm earlier in the current pregnancy, and to evaluate the syndromic approach and clinical screening in the diagnosis of these two conditions in pregnancy.

Methods

A total of 703 pregnant women participated in this study. The women were selected from those visiting the 13 main facilities providing antenatal care (12 primary health clinics and one outpatient department) in Gaborone, Botswana, between October 2000 and February 2001. A proportionate sample of attendees was recruited from each location, based on the percentage of all antenatal care attendees who attended that facility the previous year. In most clinics, all attendees were included in the data collection; a sample of the attendees was included from the busiest clinics. All participants gave written, informed consent; the study was approved by the national committees for research ethics in Botswana and in Norway. The only exclusion criterion was the use of antibiotics during the previous two weeks.

A structured interview and data from the patient-held antenatal record were used to obtain information on sociodemographic factors, current RTI symptoms, and diagnosis and prescribed treatment for RTIs earlier in the pregnancy. All attendees underwent a genital examination by a medical doctor, and clinical signs from external and internal genitalia were recorded. Amount, consistency, colour and odour of vaginal discharge were described and categorized as "normal", "*Candida*-like" or "non-*Candida*-like" discharge.

One high vaginal swab was placed in Stuart transport medium; another was used for a vaginal smear. Specimens were transported at ambient temperature to the National Health Laboratory for further processing. Wet-mounts made from the swabs in transport media were examined for motile trichomonads by light microscopy. The swabs were then agitated into bottles of Diamond's modified medium, the bottles were incubated in Oxoid gaspack jars, and wet-mounts were examined for trichomonads once daily for up to five days. The vaginal smears were Gram-stained and scored for BV according to Nugent's criteria[17] by an experienced laboratory technician.

Culture of *Candida* species was initiated by direct inoculation of Saboraud plates at the clinic, incubated at 35 °C (5% CO_2), and examined after 24 and 48 hours. Smears of colonies from positive cultures were Gram-stained and examined for budding yeast cells and pseudohyphae. The wet-mounts and Gram-stained smears were also examined for *Candida*. Presence of *Candida* was verified by positive growth and/or microscopy. Cervical swabs were obtained for ligase chain reaction (LCR) amplification, for direct, qualitative detection of specific target nucleic acid sequences of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.[18]

Data were analysed using the statistical package SPSS, Version 11. To evaluate the clinical diagnosis of TV and BV, univariate logistic regression analyses were used to assess the association between laboratory-verified diagnoses and genital symptoms and signs. Sociodemographic risk factors and genital symptoms and signs that, in univariate analysis, were associated at a 0.2 level (*P*-value of odds ratios [OR]), were included in multivariate logistic regression analysis. Validity of the vaginal discharge algorithm and of the clinical screening were assessed by measuring sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–), and positive and negative predictive values, using the laboratory diagnosis of TV and BV as the reference standard.

Results

General characteristics

The median age of the 703 antenatal care attendees was 25 years (range of 15–43) and median gestational age 30 weeks (range of 8–42). Selected background characteristics, genital symptoms and signs, and the prevalence of RTIs are shown in Table 1. TV and/or BV was present in 359 (51%) of the women, *Chlamydia* and/or gonorrhoea in 67 (10%), and *Candida* species in 416 (59%). Among the 132 women with TV, 100 (76%) reported no symptoms of vaginal discharge or lower abdominal pain. Among the 268 women with BV, 205 (76%) were asymptomatic.

Vaginal discharge and its association with TV and BV

Table 2 (available at http://www.who.int/bulletin) shows selected genital symptoms and signs, and their univariate association with TV and BV. Of the symptoms, only vaginal discharge was associated with TV, albeit weakly (OR 1.6; 95% confidence interval (95%CI), 1.0 to 2.5), and only in the univariate analysis. None of the genital symptoms evaluated were significantly associated with BV. Vaginal discharge and genital itching were, however, significantly associated with *Candida* species. *Candida* was identified in 84 (71%) of the 119 women with symptoms of vaginal discharge, compared with 332 (57%) of the 585 women without this symptom ($P < 0.01$).

In the clinical evaluation of the discharge, non-*Candida*-like vaginal discharge was associated with increased prevalence of TV and BV, whereas *Candida*-like discharge was not (Table 2, available at http://www.who.int/bulletin). Runny, frothy and malodorous discharges were strongly associated with both TV and BV; results from women with one or more of these discharge characteristics were OR 7.1 (95%CI, 4.7 to 10.8) for TV, and OR 3.3 (95%CI, 2.3 to 4.8) for BV. Adjusted odds ratios are shown in Table 3.

Table 4 compares the diagnostic accuracy of the vaginal discharge algorithm, screening for signs of vaginal discharge and for specific discharge characteristics. The vaginal discharge algorithm failed to detect most cases of TV and BV. Also, women diagnosed by the algorithm as diseased were not significantly more likely to have TV and BV than women not diagnosed

as diseased (LR+ 1.35; 95%CI, 0.97 to 1.89).

Signs of non-*Candida*-like vaginal discharge gave an LR+ of 3.00 (95%CI, 2.31 to 3.92) in the diagnosis of the two conditions combined. Screening the women for specific discharge characteristics increased the LR+ to 6.66 (95%CI, 4.25 to 10.5), but also increased the proportion of undetected infections.

Diagnosis and treatment of vaginal discharge earlier in current pregnancy

An indicator of effectiveness of the current RTI management in antenatal care is the prevalence of infections among the repeat attendees because, unlike new attendees, they have already been provided with standard care. TV prevalence was 15% for new and 20% for repeat attendees ($P = 0.22$) and BV prevalence was 41% for new and 37% for repeat attendees ($P = 0.44$).

Among the 546 repeat attendees, 142 (26%) had been diagnosed with vaginal discharge earlier in their current pregnancy – 14 of them twice. Prevalence of TV and BV was similar, whether or not the women had a history of vaginal discharge.

Treatment guidelines for vaginal discharge were usually not followed appropriately. At the time of the study, the recommended regimen to cover TV and BV was 400 mg metronidazole twice daily for 7 days; treatment for these conditions in the first trimester of pregnancy was not recommended. Consistent with the guidelines, metronidazole had not been prescribed to any of the 13 women diagnosed with vaginal discharge in the first trimester. In 143 cases, however, attendees were diagnosed with vaginal discharge in the second or third trimester, but metronidazole had been prescribed only 17 times (12%).

Of the 17 attendees for whom metronidazole was prescribed, none had TV, compared to 132 (19%) of the 686 women who had not been prescribed the drug ($P < 0.05$). Three (18%) of the 17 attendees had BV, compared to 265 (39%) of the women who had not been prescribed metronidazole ($P > 0.1$).

Table 1. **Background characteristics, genital symptoms and signs and prevalence of reproductive tract infections (RTIs) among 703 antenatal care attendees in Gaborone, Botswana**

Characteristics	*n*	(%)
Age groups		
15–19	76	(11)
20–24	249	(35)
25–29	183	(26)
30–34	126	(18)
35–43	69	(10)
Education		
Primary school or less	168	(24)
Junior secondary school	310	(44)
Secondary school or higher	225	(32)
Marital status		
Married	114	(16)
Non-marital steady partner	572	(81)
Single	17	(2)
Living with husband/partner	353	(50)
Not living with husband/partner	350	(50)
Pregnancy number		
1st pregnancy	243	(35)
2nd pregnancy	208	(30)
3rd pregnancy	122	(17)
4th+ pregnancy	130	(18)
Antenatal care visit number		
1st visit	157	(22)
2–4th visit	300	(43)
5th + visit	246	(35)
Self-reported symptoms of RTIs		
Vaginal discharge	119	(17)
Itching/soreness	58	(8)
Lower abdominal pain	53	(8)
Genital warts	16	(2)
Genital ulcer	8	(1)
Dysuria	8	(1)
Clinical signs of RTIs		
Vaginal discharge (not *Candida*-like)	227	(32)
Candida-like vaginal discharge	81	(12)
Genital warts	29	(4)
Genital ulcer	5	(1)
Presence of pathogens		
Chlamydia trachomatis	53	(8)
Neisseria gonorrhoeae	21	(3)
Trichomonias vaginalis	132	(19)
Bacterial vaginosis	268	(38)
Candida species	416	(59)

Discussion

In our study of RTIs in pregnant Batswana women, we found high prevalence of TV and BV, and no indication that syndromic management reduces the prevalence of these conditions. The vaginal discharge algorithm was extensively used by the health workers, but had low accuracy in diagnosing TV and BV. In addition, staff often did not adhere to treatment guidelines. TV and BV may contribute substantially to the risk of preterm delivery, low birth weight and increased HIV transmission in sub-Saharan Africa. Apparently, diagnosis and treatment strategies for TV and BV among pregnant women in this setting require reconsideration.

The study population is representative of antenatal care attendees in Gaborone. The level of health care is comparable throughout Botswana, and

Table 3. **Univariate and multivariate logistic regression analyses[a] of determinants of trichomoniasis and bacterial vaginosis among 703 antenatal care attendees in Gaborone, Botswana**

	Trichomoniasis		N	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	% Positive (*n* = 132)	% Negative (*n* = 571)			
Sociodemographic factors					
Age groups					
< 20	20	9	76	4.55 (2.35–8.82)	7.05 (3.23–15.37)
20–29	65	61	432	2.18 (1.29–3.66)	3.00 (1.66–5.43)
30+	15	31	195	1	1
Education					
Primary school or less	30	23	168	2. 65 (1.52–4.65)	5.25 (2.75–10.02)
Junior secondary school	54	42	310	2.56 (1.54–4.25)	2.68 (1.56–4.60)
Senior secondary or higher	17	35	225	1	1
Antenatal care visit					
New client	17	24	157	1	1
Repeat client	83	77	546	1.45 (0.89–2.37)	1.67 (0.98–2.85)
Symptoms					
More discharge than usual					
No	77	84	584	1	1
Yes	23	16	119	1.59 (1.00–2.54)	1.09 (0.63–1.87)
Clinical signs					
Vaginal discharge					
Negative	36	61	395	1	1
Candida-like discharge	3	14	81	0.38 (0.13–1.07)	0.32 (0.11–0.96)
Other vaginal discharge	61	26	227	3.93 (2.62–5.91)	3.61 (2.31–5.65)
	Bacterial vaginosis				
	% Positive (*n* = 268)	% Negative (*n* = 435)			
Sociodemographic factors					
Age groups					
< 20	14	9	76	2.10 (1.22–3.60)	1.73 (0.75–1.62)
20–29	62	61	432	1.32 (0.92–1.89)	1.10 (0.75–1.62)
30+	24	30	195	1	1
Marital status					
Unmarried	88	81	589	1.63 (1.05–2.52)	1.37 (0.85–2.19)
Married	12	19	114	1	1
Symptoms					
Malodorous discharge					
No	94	96	671	1	1
Yes	6	4	32	1.66 (0.82–3.38)	1.34 (0.62–2.88)
Clinical signs					
Vaginal discharge					
Negative	50	59	395	1	1
Candida-like discharge	4	16	81	0.27 (0.14–0.54)	0.26 (0.13–0.52)
Other vaginal discharge	46	24	227	2.28 (1.63–3.18)	2.13 (1.51–2.99)

[a] Only factors that were associated with the respective conditions at a 0.2 level (*P*-value of odds ratio) in the univariate analysis are presented in the table.

HIV prevalence among pregnant women is similar in urban and rural areas.[19] Combined with an antenatal coverage of 95%, this situation leads us to believe that we present an accurate picture of management challenges of TV and BV in pregnant women in the country as a whole.[20]

Clinical management of TV and BV in pregnancy

In antenatal care, health-care workers manage women who report vaginal discharge and women in whom vaginal discharge is found at the routine examination. The vaginal discharge algorithm recognizes that women reporting vaginal discharge commonly suffer from TV, BV or vulvovaginal candidiasis and, in rarer cases, a cervical infection.[21–23] Symptoms of vaginal discharge or lower abdominal pain are unspecific, especially in pregnancy, where physiological discharge and the presence of candidiasis increase. We found that TV and BV were equally

Table 4. **Accuracy of the vaginal discharge algorithm, and of screening for signs of vaginal discharge or specific discharge characteristics, in the diagnosis of trichomoniasis and bacterial vaginosis among 703 antenatal care attendees in Gaborone, Botswana**

	Confirmed infection (*n*)	Sensitivity	Specificity	LR+[a]	LR–	PPV	NPV
Trichomoniasis (*n* = 132)							
VDS algorithm	28	0.21	0.84	1.35 (0.91–1.94)	0.93	0.24	0.82
Signs of vaginal discharge (other than *Candida*-like)	80	0.61	0.74	2.35 (1.92–2.85)	0.53	0.35	0.89
Signs of specific discharge characteristics (runny and/or frothy and/or malodorous)	71	0.54	0.86	3.84 (2.96–4.95)	0.54	0.47	0.89
Bacterial vaginosis (*n* = 268)							
VDS algorithm	50	0.19	0.84	1.19 (0.86–1.66)	0.96	0.42	0.63
Signs of vaginal discharge (other than *Candida*-like)	123	0.46	0.76	1.92 (1.55–2.37)	0.71	0.54	0.70
Signs of specific discharge characteristics	92	0.34	0.86	2.53 (1.90–3.38)	0.72	0.61	0.68
BV and/or TV (*n* = 359)							
VDS algorithm	69	0.19	0.86	1.35 (0.97–1.89)	0.94	0.59	0.50
Signs of vaginal discharge (other than *Candida*-like)	172	0.48	0.84	3.00 (2.31–3.92)	0.62	0.76	0.61
Signs of specific discharge characteristics	132	0.37	0.95	6.66 (4.25–10.5)	0.67	0.87	0.58

LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; VDS, vaginal discharge syndrome.
[a] The positive likelihood ratios are calculated with 95% confidence interval (score method).

common in both symptomatic and asymptomatic pregnant women, and that the algorithm was neither sensitive nor specific in the management of these conditions in pregnancy.

Candida species were common among the antenatal care attendees, strongly associated with symptoms of vaginal discharge, and probably the pathological cause most often leading to this complaint. *Candida* is not associated with any serious complications, and should therefore be treated only in symptomatic women. Conversely, identification and treatment of chlamydia and gonorrhoeae in pregnancy is critical. We have previously shown that the vaginal discharge syndrome is an inadequate management strategy for cervical infections in pregnant Botswana women.[18]

In this study population, clinical screening for signs of vaginal discharge at the first antenatal care visit appears to be more effective than the use of symptoms as an entry point for metronidazole treatment. The magnitude of undetected cases is the main challenge to clinical screening: six of ten attendees with TV and one of two with BV remained unidentified. However, using this approach, one of four women receiving metronidazole does so unnecessarily. Over-treatment could be substantially reduced by limiting metronidazole prescriptions to women with runny, malodorous or foamy discharge. Different specific discharge characteristics have been associated with both TV and BV,[24] and it could be useful to employ these characteristics in settings where diagnostic tests are unavailable. However, discharge associated with the two conditions in this study population may not be applicable to other populations of pregnant women. Specific clinical criteria are diagnostically demanding for health-care workers, and if specificity increases, so does the proportion of undetected cases.

Studies among pregnant women in other developing countries have shown low correlations between symptoms and signs of vaginal discharge and the presence of TV or BV.[25–28] With the development of molecular techniques to identify *Trichomonas vaginalis*, it has become evident that culture and microscopy miss a substantial proportion of the infections.[29,30] This implies that the sensitivity of syndromic management for identifying TV is likely to be lower than estimated in this and other studies using traditional diagnostic techniques.

Adherence to the syndromic management treatment guidelines

As many as one of four pregnant women who had at least one encounter with the antenatal services had been diagnosed with vaginal discharge syndrome. In most cases, the health workers had not prescribed metronidazole, although the availability of drugs is excellent in Botswana. This finding is consistent with another study on quality of STI management from primary health care in Botswana that showed substantial flaws in history-taking, clinical examination and prescriptions.[31] A tendency to deviate from recommended RTI guidelines is common throughout the world.[32–34] Adherence to clinical guidelines is notoriously difficult to achieve, even when intensively promoted.[35] The uncertainties of the vaginal discharge algorithm may discourage health workers from optimal performance, increasing the number of inadequate prescriptions and untreated infections.

Management of TV and BV in the antenatal care is further complicated by the situation regarding the advisability of using metronidazole in pregnancy.[36] Multiple studies and meta-analyses have concluded that metronidazole does not appear to be associated with an increased teratogenic risk.[37–39] However, two studies have suggested that treatment with metronidazole in women with TV can increase preterm birth.[40,41] This adverse effect has been difficult to explain, but raises a caution about the unnecessary use of metronidazole in pregnancy.

Revised guidelines in Botswana recommend metronidazole 2 g in a single dose to cover TV in pregnancy, and 250 mg three times daily for 7 days to cover BV.[15] This management is based on evidence of optimal treatment effect for each condition, and would minimize metronidazole use in pregnancy if the women were treated for only one of the conditions.[13,37,42] However, as an etiological diagnosis cannot be made in primary health care, this strategy requires the prescription of two regimens to pregnant women with vaginal discharge – a situation that is both confusing and unnecessary. According to recently updated guidelines from the Centers for Disease Control and Prevention, metronidazole 500 mg twice daily for 7 days is the only regimen which effectively treats both conditions.[37]

Simple diagnostic tests to identify TV and BV

Accurate diagnosis and prompt treatment of STIs is important from a public health perspective, and this includes detection of asymptomatic cases. With the demonstrated shortcomings of the management of TV in Botswana, and the lack of treatment for partners of women whose symptoms do not persist, the high prevalence of TV is likely to continue.

A focus on the implementation of the syndromic approach may have superseded an exploration of the use of point-of-care tests for TV and BV in developing countries. Contrary to many other RTIs, simple and cheap tests for TV and BV are available. TV can be identified immediately with a simple latex agglutination test[43] or by saline wet preparation. BV can be diagnosed on-site, with or without the aid of a microscope.[44]

Introduction of point-of-care tests for TV and BV in the antenatal care in countries where prevalences of RTIs and HIV are high requires further exploration. Antenatal screening would identify asymptomatic cases, and testing attendees with vaginal discharge would reduce over-treatment with metronidazole in pregnancy. Health workers' prescriptions and patients' compliance would probably improve with a specific diagnosis, and treatment regimens could be optimized. Treating sexual partners of women with vaginal discharge has been debated because the majority of the identified women do not have an STI.[45] An important benefit of testing for TV is the relative ease of notifying and treating partners of patients with a positive test.

Botswana has a relatively well-functioning health system and could serve as an exploratory site for the use of point-of-care tests for TV and BV. Through the programme to prevent mother-to-child transmission of HIV, all health posts and clinics have lay workers who perform rapid tests for HIV. Simple tests for TV and BV performed by clinicians or lay workers could contribute to improving diagnosis and reducing the disease burden of these conditions in sub-Saharan Africa.

Conclusion

The inaccuracy of vaginal discharge in predicting pathological conditions in pregnancy and the magnitude of asymptomatic TV and BV is a challenge in developing countries, as is the quality of care provided. Guidelines are inadequate and there is a lack of adherence to guidelines by health workers. Our results from Botswana indicate that national health authorities should revise the diagnosis and treatment guidelines for TV and BV in antenatal care. Also, the results of this study may be useful in the process of continuous revision of World Health Organization guidelines for the management of these conditions in developing countries. ■

Competing interests: None declared.

Résumé

Insuffisances de l'approche syndromique pour la prise en charge de la trichomonase et de la vaginite bactérienne chez la femme enceinte

Objectif Déterminer la prévalence des infections à *Trichomonas vaginalis* (TV) et des vaginites bactériennes (VB) chez les femmes enceintes du Botswana et mener une évaluation comparée de l'approche syndromique et d'autres stratégies pour la prise en charge de ces pathologies pendant la grossesse.

Méthodes Dans le cadre d'une étude transversale, on a interrogé et examiné 703 femmes se présentant aux visites prénatales et on a prélevé chez elles des échantillons pour recherche de TV, d'une éventuelle VB, de *Candida*, de *Chlamydia trachomatis* et de *Neisseria gonorrhoeae*. Des entretiens structurés et l'exploitation des dossiers prénatals ont permis de recueillir des éléments sur les infections de l'appareil reproducteur survenues à un stade antérieur de la grossesse.

Résultats On a diagnostiqué une infection à TV chez 19% des femmes examinées et une VB chez 38% d'entre elles. Trois quarts des femmes atteintes d'infection à TV ou VB étaient asymptomatiques. Une prise en charge syndromique selon l'Algorithme pour les pertes vaginales de l'OMS aurait conduit à un sous-diagnostic notable de certaines pathologies et à un surtraitement des infections à TV et des VB. Les pertes vaginales se sont révélées plus fortement prédictives de la présence de ces affections que les symptômes. Parmi les 546 femmes reçues dans le cadre des visites prénatales, 142 (26 %) avaient déjà été diagnostiquées comme présentant des pertes vaginales à un stade antérieur de la grossesse (à deux reprises pour 14 d'entre elles). On a relevé 143 cas de pertes vaginales au deuxième ou au troisième trimestres de grossesse parmi les femmes examinées lors de ces visites prénatales. Néanmoins, ces pertes n'ont donné lieu que 17 fois à la prescription de métronidazole (12 % des cas).

Conclusion Le diagnostic et le traitement des infections à TV et des VB chez les femmes enceintes d'Afrique subsaharienne présentent des difficultés majeures. Cette étude a conduit à diagnostiquer une infection à TV ou une VB chez la moitié des femmes enceintes, mais ces affections n'ont été ni détectées, ni traitées, par la prise en charge syndromique appliquée lors des visites prénatales. De même, le personnel soignant ne suivait par les recommandations thérapeutiques. Ces résultats témoignent de la nécessité d'une révision du Guide pour la prise en charge des IST à TV et des VB dans le cadre des soins prénatals.

Resumen

Tricomoniasis y vaginosis bacteriana en el embarazo: insuficiencias del manejo sindrómico

Objetivo Medir la prevalencia de la infección por *Trichomonas vaginalis* (TV) y la vaginosis bacteriana (VB) entre las embarazadas en Botswana, y evaluar el manejo sindrómico y otras estrategias de tratamiento para esas enfermedades en el embarazo.

Métodos Se realizó un estudio transversal en el que se entrevistó y examinó a 703 mujeres que recibieron atención prenatal. Se obtuvieron muestras para detectar los casos de infección por TV, VB, *Candida*, *Chlamydia trachomatis* y *Neisseria gonorrhoeae*. La realización de una entrevista estructurada y el examen de los registros prenatales permitieron reunir información sobre las infecciones del aparato reproductor sufridas en fases anteriores del embarazo.

Resultados Se detectó TV en el 19% de las mujeres examinadas, y VB en el 38%. Tres cuartas partes de las mujeres con TV o VB no presentaban síntomas. El manejo sindrómico basado en el algoritmo del flujo vaginal llevaría a subdiagnosticar y sobretratar considerablemente la infección por TV y la VB. A la hora de determinar la presencia de esas enfermedades, los signos de flujo vaginal tenían un mayor valor predictivo que los síntomas. Entre las 546 mujeres que ya habían realizado antes una visita prenatal, a 142 (26%) se les había diagnosticado flujo vaginal en fases anteriores del embarazo (a 14 de ellas dos veces). En 143 casos se diagnosticó flujo vaginal en el segundo o tercer trimestre, pero sólo se había prescrito metronidazol en 17 ocasiones (12%).

Conclusión El diagnóstico y tratamiento de la infección por TV y la VB entre las embarazadas en el África subsahariana tropieza con importantes dificultades. A la mitad de las embarazadas participantes en este estudio se les diagnosticó TV o VB, pero esas afecciones no fueron detectadas y tratadas en visitas de atención prenatal en que se aplicaba el manejo sindrómico. Además, los trabajadores sanitarios no seguían las directrices terapéuticas. Estos resultados indican que es necesario revisar las directrices de tratamiento de la infección por TV y la VB en la atención prenatal.

ملخص

عدم كفاية الأسلوب المتلازمي في معالجة داء المشعَّرات والتهاب المهبل الجرثومي لدى الحوامل

الغرض: استهدفت هذه الدراسة قياس مدى انتشار العدوى بالمشعَّرة المهبلية وبالتهاب المهبل الجرثومي لدى الحوامل في بتسوانا، وتقييم الأسلوب المتلازمي والاستراتيجيات البديلة المتبعة لمعالجة هذه الحالات في فترة الحمل.

الطريقة: في هذه الدراسة المستعرضة، تمت مقابلة وفحص 703 من المترددات على عيادات الرعاية السابقة للولادة، وأُخذت منهن عينات لتحري العدوى بالمشعَّرة المهبلية، والتهاب المهبل الجرثومي، وأنواع المبيَضَّات البيض، والمتدثرة الحثرية، والنيسرية البنيَّة. وتم الحصول على معلومات عن عدوى السبيل الإنجابي في فترة مبكرة من الحمل، وذلك من خلال مقابلات منظمة مع الحوامل، ومن خلال سجلات عيادات الرعاية السابقة للولادة.

الموجودات: لوحظ وجود عدوى بالمشعَّرة المهبلية لدى 19% من الحوامل المترددات على العيادات، كم لوحظ التهاب المهبل الجرثومي لدى 38% منهن. وكان ثلاثة أرباع الحوامل المصابات بالمشعَّرة المهبلية والتهاب المهبل الجرثومي لا يشتكين من أعراض. وتبيَّن أن معالجة المتلازمات وفقاً للوغاريثمات قياس النجيج المهبلي، قد تؤدي إلى قصور شديد في التشخيص، وإلى الإفراط في معالجة المشعَّرة المهبلية والتهاب المهبل الجرثومي. وتبيَّن أيضاً أن النجيج المهبلي أكثر دلالة على وجود هذه الحالات، بالمقارنة مع الأعراض. ومن بين 546 من المترددات بشكل متكرر على عيادات الرعاية السابقة للولادة، تم تشخيص 142 منهن (أي نسبة 26%) بوجود نجيج مهبلي في فترة مبكرة من الحمل، مع تعرُّض 14 امرأة منهن لهذا النجيج مرتين. وتم تشخيص 143 حالة من المترددات على العيادات بأنهن مصابات بنجيج مهبلي في الأثلوث الثاني أو الثالث من الحمل. ومع ذلك لم يوصف المترونيدازول إلا 17 مرة فقط (أي بنسبة 12%).

الاستنتاج: يمثِّل تشخيص ومعالجة المشعَّرة المهبلية والتهاب المهبل الجرثومي تحدياً كبيراً أمام الحوامل في البلدان الواقعة جنوب الصحراء الأفريقية. وقد تم في هذه الدراسة تشخيص العدوى المشعَّرة المهبلية وبالتهاب المهبل الجرثومي لدى نصف الحوامل ، ومع ذلك لم يتم اكتشاف أو معالجة هذه الحالات بالأسلوب المتلازمي في الفترة السابقة للولادة. وخلصت الدراسة أيضاً إلى أن العاملين الصحيين لم يلتزموا بالدلائل الإرشادية للمعالجة. وتشير هذه النتائج إلى أن الدلائل الإرشادية لمعالجة هذه الحالات في الفترة السابقة للولادة ينبغي مراجعتها وتنقيحها.

References

1. World Health Organization. *Global prevalence and incidence of selected curable sexually transmitted infections* 2001. Available at: www.who.int/hiv/pub/sti/pub7/en/
2. Mayaud P, Mabey D. Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. *Sex Transm Infect* 2004;80:174-82.
3. Bowden FJ, Garnett GP. Trichomonas vaginalis epidemiology: parameterising and analysing a model of treatment interventions. *Sex Transm Infect* 2000; 76:248-56.
4. Demba E, Morison L, van der Loeff MS, Awasana AA, Gooding E, Bailey R, et al. Bacterial vaginosis, vaginal flora patterns and vaginal hygiene practices in patients presenting with vaginal discharge syndrome in The Gambia, West Africa. *BMC Infect Dis* 2005;5:12.
5. Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. *Clin Obstet Gynecol* 2004;47:796-807.
6. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;346:530-6.
7. Sexton J, Garnett G, Rottingen JA. Metaanalysis and metaregression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infection. *Sex Transm Dis* 2005;32:351-7.
8. Mullick S, Watson-Jones D, Beksinska M, Mabey D. Sexually transmitted infections in pregnancy: prevalence, impact on pregnancy outcomes, and approach to treatment in developing countries. *Sex Transm Infect* 2005; 81:294-302.
9. Bowden FJ, Garnett GP. Why is Trichomonas vaginalis ignored? *Sex Transm Infect* 1999;75:372-4.
10. Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review. *Obstet Gynecol* 2005;105:857-68.

11. Gulmezoglu AM. Interventions for trichomoniasis in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2005.
12. McDonald H, Brocklehurst P, Parsons J. Antibiotics for treating bacterial vaginosis in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2005.
13. Koumans EH, Markowitz LE, Hogan V. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. *Clin Infect Dis* 2002;35:S152-72.
14. *Guidelines for the management of sexually transmitted infections.* Geneva: WHO; 2003. Available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf
15. Botswana Ministry of Health. *Management of Sexually Transmitted Infections. Reference Manual for Health Workers.* Gaborone: MoH; 2005.
16. Botswana Ministry of Health. *Guidelines for antenatal care and the management of obstetric emergencies and prevention of mother-to-child transmission of HIV*. Gaborone: Ministry of Health; 2005.
17. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol* 1991;29:297-301.
18. Romoren M, Rahman M, Sundby J, Hjortdahl P. Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana. *Sex Transm Infect* 2004;80:395-400.
19. Botswana Ministry of Health. *Botswana 2005 second generation HIV/AIDS surveillance.* Gaborone: MoH; 2006.
20. National AIDS Coordinating Agency. *Botswana AIDS Impact Survey II 2004.* Gaborone; 2005.
21. Dallabetta GA, Gerbase AC, Holmes KK. Problems, solutions, and challenges in syndromic management of sexually transmitted diseases. *Sex Transm Infect* 1998;74:S1-11.
22. Mayaud P, ka-Gina G, Cornelissen J, Todd J, Kaatano G, West B, et al. Validation of a WHO algorithm with risk assessment for the clinical management of vaginal discharge in Mwanza, Tanzania. *Sex Transm Infect* 1998;74:S77-84.
23. Fonck K, Kidula N, Jaoko W, Estambale B, Claeys P, Ndinya-Achola J, et al. Validity of the vaginal discharge algorithm among pregnant and non-pregnant women in Nairobi, Kenya. *Sex Transm Infect* 2000;76:33-8.
24. Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. *JAMA* 2004;291:1368-79.
25. Tann CJ, Mpairwe H, Morison L, Nassimu K, Hughes P, Omara M, et al. Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. *Sex Transm Infect* 2006;82:285-9.
26. Hylton-Kong T, Brathwaite AR, Del Rosario GR, Kristensen S, Kamara P, Jolly PE, et al. Marginal validity of syndromic management for reproductive tract infections among pregnant women in Jamaica. *Int J STD AIDS* 2004; 15:371-5.
27. Blankhart D, Muller O, Gresenguet G, Weis P. Sexually transmitted infections in young pregnant women in Bangui, Central African Republic. *Int J STD AIDS* 1999;10:609-14.
28. Sturm AW, Wilkinson D, Ndovela N, Bowen S, Connolly C. Pregnant women as a reservoir of undetected sexually transmitted diseases in rural South Africa: implications for disease control. *Am J Public Health* 1998;88:1243-5.
29. Smith KS, Tabrizi SN, Fethers KA, Knox JB, Pearce C, Garland SM. Comparison of conventional testing to polymerase chain reaction in detection of Trichomonas vaginalis in indigenous women living in remote areas. *Int J STD AIDS* 2005;16:811-5.
30. van Der Schee C, van Belkum A, Zwijgers L, van Der Brugge E, O'Neill EL, Luijendijk A, et al. Improved diagnosis of Trichomonas vaginalis infection by PCR using vaginal swabs and urine specimens compared to diagnosis by wet mount microscopy, culture, and fluorescent staining. *J Clin Microbiol* 1999;37:4127-30.
31. Boonstra E, Lindbaek M, Klouman E, Ngome E, Romoren M, Sundby J. Syndromic management of sexually transmitted diseases in Botswana's primary health care: quality of care aspects. *Trop Med Int Health* 2003;8:604-14.
32. Vuylsteke BL, Ettiegne-Traore V, Anoma CK, Bandama C, Ghys PD, Maurice CE, et al. Assessment of the validity of and adherence to sexually transmitted infection algorithms at a female sex worker clinic in Abidjan, Cote d'Ivoire. *Sex Transm Dis* 2003;30:284-91.
33. Kane BG, Degutis LC, Sayward HK, D'Onofrio G. Compliance with the Centers for Disease Control and Prevention recommendations for the diagnosis and treatment of sexually transmitted diseases. *Acad Emerg Med* 2004; 11:371-7.
34. Moses S, Elliott L. Sexually transmitted diseases in Manitoba: evaluation of physician treatment practices, STD drug utilization, and compliance with screening and treatment guidelines. *Sex Transm Dis* 2002;29:840-6.
35. Mak DB, Holman CD. STDs aren't sexy: health professionals' lack of adherence to clinical guidelines in an area of high STD endemicity. *J Public Health Med* 2000;22:540-5.
36. Owen MK, Clenney TL. Management of vaginitis. *Am Fam Physician* 2004; 70:2125-32.
37. Centers for Disease Control and Prevention. *Sexually transmitted diseases treatment guidelines 2006*. Available at: www.cdc.gov/std/treatment/2006/toc.htm
38. Caro-Paton T, Carvajal A, Martin de Diego I, Martin-Arias LH, Alvarez Requejo A, Rodriguez Pinilla E. Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997;44:179-82.
39. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995;172:525-9.
40. Klebanoff MA, Carey JC, Hauth JC, Hillier SL, Nugent RP, Thom EA, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. *N Engl J Med* 2001;345:487-93.
41. Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, Wawer MJ, Serwadda D, Sewankambo N, et al. Treatment of Trichomonas in pregnancy and adverse outcomes of pregnancy: a subanalysis of a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol* 2003;189:1398-400.
42. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2005.
43. Adu-Sarkodie Y, Opoku BK, Danso KA, Weiss HA, Mabey D. Comparison of latex agglutination, wet preparation, and culture for the detection of Trichomonas vaginalis. *Sex Transm Infect* 2004;80:201-3.
44. *Sexually transmitted and other reproductive tract infections. A guide to essential practice.* Geneva: WHO; 2005. Available at: http://www.who.int/reproductive-health/publications/rtis_gep/rtis_gep.pdf
45. Hawkes S, Mabey D, Mayaud P. Partner notification for the control of sexually transmitted infections. *BMJ* 2003;327:633-4.

Table 2. **Association between symptoms and signs and laboratory-verified trichomoniasis or bacterial vaginosis among 703 antenatal care attendees in Gaborone, Botswana**

	Trichomoniasis		N	Odds ratio (95% confidence interval)	*P*-value
	% Positive (*n* = 132)	% Negative (*n* = 571)			
Symptoms					
More discharge than usual					
No	77	84	584	1	
Yes	23	16	119	1.59 (1.00–2.54)	0.049
Itching or soreness					
No	91	92	645	1	
Yes	9	8	58	1.14 (0.59–2.22)	0.70
Lower abdominal pain					
No	96	92	650	1	
Yes	5	8	53	0.53 (0.22–1.27)	0.15
Clinical signs					
Moderate/profuse discharge					
No	46	68	447	1	
Yes	55	32	256	2.52 (1.72–3.71)	0.000
Runny discharge					
No	62	93	615	1	
Yes	38	7	88	8.55 (5.23–13.84)	0.000
Malodorous discharge					
No	84	96	659	1	
Yes	16	4	44	4.51 (2.41–8.43)	0.000
Frothy discharge					
No	56	90	590	1	
Yes	44	10	113	7.35 (4.73–11.44)	0.000
Specific discharge characteristics					
Negative	46	86	552	1	
Runny/malodorous/frothy	54	14	151	7.14 (4.71–10.83)	0.000
Vaginal discharge					
Negative	36	61	395	1	
Candida-like discharge	3	14	81	0.38 (0.13–1.07)	0.068
Other vaginal discharge	61	26	227	3.93 (2.62–5.91)	0.000
	Bacterial vaginosis				
	% Positive (*n* = 268)	% Negative (*n* = 435)			
Symptoms					
More discharge than usual					
No	82	84	584	1	
Yes	18	16	119	1.12 (.075–1.67)	0.585
Itching or soreness					
No	91	92	645	1	
Yes	9	8	58	1.25 (0.73–2.16)	0.415
Lower abdominal pain					
No	92	93	650	1	
Yes	8	7	53	1.17 (0.66–2.06)	0.598
Clinical signs					
Moderate/profuse discharge					
No	62	65	447	1	
Yes	38	35	256	1.15 (0.84–1.58)	0.383
Runny discharge					
No	82	91	615	1	
Yes	18	9	88	2.16 (1.37–3.38)	0.001

(Table 2, cont.)

	Bacterial vaginosis		N	Odds ratio (95 % confidence interval)	*P*-value
	% Positive (*n* = 268)	% Negative (*n* = 435)			
Malodorous discharge					
No	88	97	659	1	
Yes	12	3	44	4.25 (2.18–8.27)	0.000
Frothy discharge					
No	74	90	590	1	
Yes	26	10	113	3.08 (2.04–4.67)	0.000
Specific discharge characteristics					
Negative	66	86	552	1	
Runny/malodorous/frothy	34	14	151	3.33 (2.30–4.84)	0.000
Vaginal discharge					
Negative	50	59	395	1	
Candida-like discharge	4	16	81	0.27 (0.14–0.54)	0.000
Other vaginal discharge	46	24	227	2.28 (1.63–3.18)	0.000

Paper III

Chlamydia and gonorrhoea in pregnant Batswana women:

time to discard the syndromic approach?

BMC Infectious Diseases. 7:27, 2007.

BMC Infectious Diseases

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Chlamydia and gonorrhoea in pregnant Batswana women: time to discard the syndromic approach?

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Published: 16 April 2007

BMC Infectious Diseases 2007, **7**:27 doi:10.1186/1471-2334-7-27

Received: 4 October 2006
Accepted: 16 April 2007

This article is available from: http://www.biomedcentral.com/1471-2334/7/27

Abstract

Background: Chlamydia and gonorrhoea are major causes of morbidity among women in developing countries. Both infections have been associated with pregnancy-related complications, and case detection and treatment in pregnancy is essential. In countries without laboratory support, the diagnosis and treatment of cervical infections is based on the syndromic approach. In this study we measured the prevalence of chlamydia and gonorrhoea among antenatal care attendees in Botswana. We evaluated the syndromic approach for the detection of cervical infections in pregnancy, and determined if risk scores could improve the diagnostic accuracy.

Methods: In a cross-sectional study, 703 antenatal care attendees in Botswana were interviewed and examined, and specimens were collected for the identification of *C trachomatis*, *N gonorrhoeae* and other reproductive tract infections. Risk scores to identify attendees with cervical infections were computed based on identified risk factors, and their sensitivities, specificities, likelihood ratios and predictive values were calculated.

Results: The prevalence of chlamydia was 8%, and gonorrhoea was found in 3% of the attendees. Symptoms and signs of vaginal discharge did not predict cervical infection, and a syndromic approach failed to identify infected women. Age (youth) risk factor most strongly associated with cervical infection. A risk score with only sociodemographic factors had likelihood ratios equivalent to risk scores which incorporated clinical signs and microscopy results. However, all the evaluated risk scores were of limited value in the diagnosis of chlamydia and gonorrhoea. A cut-off set at an acceptable sensitivity to avoid infected antenatal care attendees who remained untreated would inevitably lead to considerable over-treatment.

Conclusion: Although in extensive use, the syndromic approach is unsuitable for diagnosing cervical infections in antenatal care attendees in Botswana. None of the evaluated risk scores can replace this management. Without diagnostic tests, there are no adequate management strategies for *C trachomatis* and *N gonorrhoeae* in pregnant women in Botswana, a situation which is likely to apply to other countries in sub-Saharan Africa. Screening for cervical infections in pregnant women is an essential public health measure, and rapid tests will hopefully be available in developing countries within a few years.

Background

Sub-Saharan Africa has the highest prevalence of gonorrhoea and chlamydia worldwide. These two sexually transmitted infections (STIs) have a major impact on health, particularly in women and neonates [1]. A cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis* can cause serious complications, such as ascending infections, infertility, cervical cancer, spontaneous abortion, premature delivery and low birth weight [2]. Epidemiological and biological studies have shown that ulcerative and non-ulcerative STIs can enhance HIV transmission [3,4].

It should be part of the mandate of the antenatal care programmes to diagnose and treat *C trachomatis* and *N gonorrhoeae*, due to their association with maternal, foetal and infant morbidity. In developing countries, diagnosis of cervical infections is limited to the syndromic approach, using the 'vaginal discharge syndrome' (VDS) algorithm. In the early 1990s, the World Health Organization developed syndromic management guidelines as a case management of symptomatic STI patients in countries without laboratory support [5]. Easily recognized symptoms and signs are combined using flowcharts, and patients are treated with two or more antibiotic regimens to cover the majority of, or the most serious, organisms responsible for producing a syndrome. The VDS algorithm for the management of vaginal and cervical infections is far from ideal, and for chlamydia or gonorrhea, this simplified approach is neither sensitive nor specific [2,5-8]. Simple, rapid tests for these infections have been requested for more than a decade [9,10], and the continued use of the syndromic approach in the management of cervicitis has been viewed as a temporary solution while awaiting the development of such tests [11].

The majority of women with a cervical infection are asymptomatic [12] and their infection will not be detected by the syndromic approach. As screening with specific diagnostic tests have been out of reach, risk scores based on sociodemographic risk factors, symptoms or signs of infection, urine sticks and microscopy have been explored as screening tools to identify asymptomatic infections among pregnant women. Studies from sub-Saharan countries have shown variable and unconvincing results [9,10,13-16].

It has become clear that vaginal discharge is poorly predictive of cervicitis, and in order to reduce over-treatment, the WHO recommends the incorporation of risk assessments in the syndromic management of cervical infections [5]. In Botswana, the syndromic approach has recently been revised, and lower abdominal pain was included as a second entry symptom in the VDS algorithm [17]. Treatment for *C trachomatis* and *N gonorrhoeae* is reserved for women who present with vaginal discharge or lower abdominal pain *and* have either a positive risk assessment (age less than 21 years or complaints of yellow discharge) or yellow discharge or cervical mucopus on examination. These new recommendations are based on a non-validated study of female STI patients [18]. Risk factors' association with infection is specific to the population group from which they are extracted [5,13], and a validation of the algorithm in the antenatal care is lacking.

There are two parallel strategies to manage reproductive tract infections (RTIs) in pregnancy in Botswana. In addition to the syndromic management of women with symptoms, all antenatal care attendees are clinically screened for RTIs. The antenatal care guidelines recommend a routine speculum examination at the first antenatal visit, to "exclude genital infections, abnormalities and pelvic tumours" [19]. It is not uncommon for abnormal vaginal discharge to be found in women who are not eliciting symptoms. Asymptomatic pregnant women with signs of vaginal discharge will also be provided with syndromic treatment. Clinical screening bypasses the original entry point of the syndromic algorithms: symptoms which lead to health-care seeking, and it is not within the WHO recommendations.

The aim of this study was to determine the prevalence of *C trachomatis* and *N gonorrhoeae* among antenatal care attendees in Botswana, and to assess the validity of the 'vaginal discharge syndrome and lower abdominal pain' algorithm in the diagnosis of cervicitis in pregnancy. We also evaluated the diagnostic accuracy of risk scores based on sociodemographic factors, specific symptoms or signs, or microscopy. The results from Botswana are used to discuss the management of cervicitis in pregnancy in sub-Saharan Africa.

Methods

Participating in this study were 703 pregnant women who visited the 13 main facilities providing antenatal care in Gaborone, Botswana: 12 primary health clinics and one outpatient department. A proportionate sample of attendees was recruited from each location. This proportion corresponded to the percentage of all antenatal care attendees in Gaborone who visited that facility during the previous year. Facilities were visited one-by-one by a medical doctor between October 2000 and February 2001. In the majority of clinics, all attendees were included in the study. In the busiest clinics, only a sample of the attendees was included; the selection of attendees in these clinics was incidental. Approximately one out of every four antenatal care attendees in Gaborone was included in the study during the period of data collection. All participants gave written, informed consent. The only exclusion crite-

rion was the use of antibiotics during the previous two weeks.

A structured interview and information from the patient-held antenatal record were used to obtain data on socio-demographic and behavioural factors, current RTI symptoms, and diagnosis and prescribed treatment for such conditions earlier in the pregnancy. All patients underwent a genital examination; appropriate specimens were collected; and abnormal signs from external and internal genitalia were recorded in detail.

Laboratory analyses

Urine was checked on site with a dipstick; all other specimens were analysed at the National Health Laboratory in Gaborone. Cervical swabs were obtained for ligase chain reaction (LCR) amplification technology for detection of *C trachomatis* and *N gonorrhoeae*. The swabs were placed in LCx® transport media, transported to the laboratory the same day, and stored at -20°C prior to batch processing. The LCx® Assays (Abbott Laboratories, IL) were performed according to the manufacturer's instructions. A case of *C trachomatis* or *N gonorrhoeae* infection was defined as an individual with a positive LCR analysis.

A high vaginal swab for identification of *Trichomonas vaginalis* was placed in Stuart transport media. Before culturing, a wet-mount was made and examined for the presence of motile trichomonads by light microscopy, 100 × magnification. The swab was then agitated into a bottle of Diamond's modified medium. The bottles were incubated with indicators in Oxoid gaspack jars (3.4 litres, with anaerobic system BR 038B). Wet-mounts from the cultures were examined once a day for five days by light microscopy.

Gram-stained vaginal smears were scored for bacterial vaginosis according to Nugent's criteria [20]. Culture of *Candida* species was initiated by direct inoculation of a high vaginal swab on Saboraud plates on site, and Gram-stained smears and wet-mounts from high vaginal swabs were examined for budding yeast cells and pseudohyphae. A cervical smear was gram-stained to count polymorphonuclear leukocytes per high power field (PMN/HPF).

Statistical analyses and risk scores

Data were analysed with the statistical package SPSS Version 11. We performed univariate analyses on all independent variables in our dataset which could be associated with cervical infection. The factors were within four categories: sociodemographic and behavioural factors, symptoms, clinical signs, and microscopy results. The dependent variable "cervicitis" was defined as infection with *C trachomatis* or *N gonorrhoeae*, or both. Factors which in the univariate analysis were associated with infection at a 0.2 level (p-value of odds ratio (OR)) were included in multiple logistic regression analyses. We performed multiple logistic regression analyses on sociodemographic factors, symptoms, clinical signs and laboratory results, separately and combined. Due to the high number of variables, the full analysis of different factors' independent association with cervicitis had to be performed in two steps. First, multiple logistic regression analyses for the four variable categories were performed separately. The analysis was then extended to combining the factors from the different categories which were significantly independently associated with cervical infection in the first step.

Three levels of risk scores were computed and retrospectively applied, and each of them were assessed for their usefulness as a diagnostic tool to manage *N gonorrhoeae* and *C trachomatis* infections in the antenatal care. The first risk score level consists of only sociodemographic factors. At the second risk score level we added findings from the gynaecological examination. At the third level, we also allowed the results from microscopy of vaginal and cervical smears. Microscopy can be done on site, and thus all three risk score levels – the sociodemographic, the clinical and the microscopy score – can theoretically be performed during an antenatal care visit. The weights for each factor used in the risk scores were based on correspondent multiple logistic regression analysis models. The log of the OR for the variables in the model multiplied by 10 and rounded to the nearest whole number were used as weights for the respective factors in the risk scores [9]. The factors included and their respective weights are shown for each risk score in Table 1.

Receiver Operating Characteristic (ROC) curves were used to compare the different risk scores. The ROC curve shows the sensitivity and specificity that correspond to each possible cut-off for the risk score. The validity of different diagnostic strategies (the existing STI management guidelines, diagnosis based on symptoms or signs alone, and diagnosis based on a risk score) was assessed by measuring sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and positive and negative predictive values (PPV and NPV). The LCR-based laboratory diagnosis of cervical infection was used as the reference standard. In the evaluation and comparison of diagnostic strategies, we present two cut-offs for the risk scores, taken at a sensitivity of minimum 0.40 and 0.70.

The study was approved by ethical committees in Botswana and in Norway.

Results

Of the 703 women, 67 (10%) had laboratory-confirmed cervical infection: 51 (8%) were infected with *C trachoma-*

Table 1: Three levels of risk scores: Variables included and their respective weights

Variables included		Sociodemographic score Weight*	Clinical score Weight	Microscopy score Weight
Sociodemographic factors				
Age	<20	21	24	24
	20–29	13	14	14
	30+	0	0	0
Education	Primary school	10	12	11
	Junior secondary school	6	7	6
	Senior secondary or higher	0	0	0
Length of relationship	1 year or less	5	-	-
	Between 1 and 2 years	2	-	-
	2 years and more	0	-	-
Marital status	Unmarried	12	-	-
	Married	0	-	-
Clinical factors				
Amount of discharge	Moderate/profuse	-	2	2
	Scarce	-	0	0
Thin/runny discharge	Yes	-	8	8
	No	-	0	0
Smelly discharge	Yes	-	5	4
	No	-	0	0
Cervix abnormal	Yes	-	3	2
	No	-	0	0
Microscopy results				
White blood cell count in cervical smear	3–4+	-	-	14
	2+	-	-	10
	1+	-	-	7
	No/few	-	-	0
Cut-off at 40% sensitivity		Score >32	Score >28	Score >36
Cut-off at 70% sensitivity		Score >30	Score >21	Score >29

*The log of the OR from the correspondent multiple logistic regression analysis for each of the variables, multiplied by 10 and rounded to the nearest whole number

tis, and 21 (3%) with *N gonorrhoea*. *T vaginalis* was identified in 131 (19%) women and bacterial vaginosis in 268 (38%) women. Candida species were identified by microscopy and/or culture in 416 (59%) of the women. A total of 561 (80%) of the antenatal care attendees had one or more of these five reproductive tract infections.

Subjective symptoms and clinical signs

In spite of the high prevalence of cervical and vaginal infections in this study, few women confirmed symptoms when probed. Complaints of vaginal discharge were elicited from 119 (17%) of the women and lower abdominal pain from 58 (8%). Vaginal discharge was the most common clinical sign; candidalike discharge was found in 81 (12%) and other abnormal discharge was found in 227 (32%) of the women.

Factors associated with C trachomatis *and/or* N gonorrhoeae

Demographic, behavioural, and obstetric factors; symptoms, signs, and simple laboratory tests; and their association with *C trachomatis* and/or *N gonorrhoeae* infection are shown in Table 2. Age was the strongest predictor of cervical infection. The prevalence of infection was highest among teenagers (22%, 95% confidence interval (CI): 13 to 32), whereas two-thirds of the infections were within the largest age group: women 20–29 years. None of the evaluated symptoms predicted cervical infection. Symptoms of vaginal discharge or lower abdominal pain were therefore not included in any of the risk scores. There were 65 (9%) women who reported believing that they had a genital illness, but the prevalence of cervicitis was not significantly higher in this group (OR = 1.6, 95% CI: 0.8 to 3.4). Of clinical findings, vaginal (excluding candida-like) discharge was significantly associated with increased prevalence of cervicitis (OR = 1.8, 95% CI: 1.1 to 3.0). Several discharge characteristics (thin, smelly, foamy and increased amounts) were also significantly associated with cervical infection. Two laboratory results were associated with cervicitis; white blood cells in the cervical smear, and infection with *T vaginalis*.

The factors which were independently associated with cervical infection are shown in Table 3.

Table 2: Univariate analyses on risk factors for cervicitis (*C trachomatis* and/or *N gonorrhoeae*) among 703 antenatal care attendees in Gaborone, Botswana

	No.	Women with cervicitis		Odds ratio	Confidence interval	p-value
		No.	*(%)*		*(95%)*	
Sociodemographic factors						
Age groups						
< 20	76	17	(22)	9.1	3.4–24.1	0.000
20–29	432	44	(10)	3.6	1.5–8.5	0.004
30+	195	6	(3)	1		
Education						
Primary school or less	168	17	(10)	1		
Junior secondary school	310	36	(12)	1.2	0.6–2.2	0.620
Senior secondary or higher	225	14	(6)	0.6	0.3–1.2	0.160
Marital status						
Married	114	2	(2)	1		
Unmarried	589	65	(11)	6.9	1.7–28.7	0.008
Partners last 12 months						
One partner	671	64	(10)	1		
Two or more	32	3	(9)	1.0	0.3–3.3	0.976
Time in relationship						
One year or less	118	19	(16)	2.5	1.4–4.6	0.003
1 to 2 years	137	16	(12)	1.7	0.9–3.2	0.094
>2 years	448	32	(7)	1		
Subjective symptoms						
Vaginal discharge						
No	584	55	(9)	1		
Yes	119	12	(10)	1.1	0.6–2.1	0.822
Lower abdominal pain						
No	650	63	(10)	1		
Yes	53	4	(8)	0.8	0.3–2.2	0.610
Thinks she has an infection						
No	638	58	(9)	1		
Yes	65	9	(14)	1.6	0.8–3.4	0.217
Clinical signs						
Vaginal discharge						
Negative	476	37	(8)	1		
Positive	227	30	(11)	1.8	1.1–3.0	0.023
Candida-like discharge						
Negative	622	61	(10)	1		

Table 2: Univariate analyses on risk factors for cervicitis (*C trachomatis* and/or *N gonorrhoeae*) among 703 antenatal care attendees in Gaborone, Botswana *(Continued)*

Positive	81	5	(6)	0.6	0.2–1.5	0.279
Moderate or profuse discharge						
Negative	447	34	(8)	1		
Positive	256	33	(13)	1.8	1.1–3.0	0.023
Yellow discharge						
Negative	438	38	(9)	1		
Positive	265	29	(11)	1.3	0.8–2.2	0.322
Thin/runny discharge						
Negative	615	48	(8)	1		
Positive	88	19	(22)	3.3	1.8–5.9	0.000
Foamy discharge						
Negative	590			1		
Positive	113	19	(17)	2.3	1.3–4.1	0.005
Smelly discharge						
Negative	659	58	(9)	1		
Positive	44	9	(21)	2.7	1.2–5.8	0.014
Cervical bleeding/erythroplaquia						
Negative	520	45	(9)	1		
Positive	183	22	(12)	1.4	0.8–2.5	0.184
Laboratory analyses						
Urine stix (nitritis/leucocytes)						
Negative	609	59	(10)	1		
Positive	94	8	(9)	0.9	0.4–1.9	0.718
WBC in cervical smear						
None/few	124	5	(4)	1		
1+	267	22	(8)	2.1	0.8–5.8	0.135
2+	171	18	(11)	2.8	1.0–7.8	0.048
3–4+	140	22	(16)	4.4	1.6–12.1	0.004
Candida (microscopy or culture)						
Negative	287	26	(9)	1		
Positive	416	41	(10)	1.1	0.7–1.8	0.724
Trichomoniasis						
Negative	571	41	(7)	1		
Positive	132	26	(20)	3.2	1.9–5.4	0.000
Bacterial vaginosis (BV)						
Negative	435	40	(9)	1		
Positive	268	27	(10)	1.1	0.7–1.9	0.700

Table 3: Univariate and multiple logistic regression analysis of risk factors for cervicitis (*C trachomatis* and/or *N gonorrhoeae*) among 703 antenatal care clients in Gaborone, Botswana

	Total women		Women with cervicitis		Multiple logistic regression	
	No.	(%)	No.	(%)	Odds ratio	p-value
Age groups						
<20	76	(11)	17	(22)	10.5 (3.59–30.72)	0.000
20–29	432	(62)	44	(10)	4.0 (1.60–10.10)	0.003
30+	195	(28)	6	(3)	1	
Education						
Primary school or less	168	(24)	17	(10)	1	
Junior secondary school	310	(44)	36	(12)	0.6 (0.31–1.23)	0.168
Senior secondary or higher	225	(32)	14	(6)	0.4 (0.16–0.80)	0.013
Thin/runny discharge						
No	615	(87)	48	(8)	1	
Yes	88	(13)	19	(22)	2.1 (1.06–4.24)	0.035
WBC in cervical smear						
None/few	124	(18)	5	(4)	1	
1+	267	(38)	22	(8)	2.0 (0.72–5.52)	0.188
2+	171	(24)	18	(11)	2.7 (0.92–7.61)	0.070
3–4+	140	(20)	22	(16)	3.7 (1.31–10.66)	0.014

Syndromic management and screening for cervical infections

The sociodemographic, clinical, and microscopy-based risk scores performed similar in the management of *N gonorrhoeae* and *C trachomatis* infection, as illustrated with their ROC-curves (Figure 1). The diagnostic accuracy of the risk scores did not increase significantly when detailed information from the clinical examination and subsequently the microscopy results were added to the sociodemographic risk factors.

Table 4 presents the evaluated options for the diagnosis of *C trachomatis* and *N gonorrhoeae* in antenatal care in the absence of specific diagnostic tests: the syndromic algorithm, symptoms, signs, and the three risk scores. The VDS algorithm did not identify women with *C trachomatis* and *N gonorrhoeae* in our study population (positive likelihood ratio (LR+) 1.1, 95% CI: 0.6 to 1.9). Symptoms of vaginal discharge or lower abdominal pain in pregnancy proved inappropriate as an entry point to the VDS algorithm, with a LR+ of 0.94 (95% CI: 0.6–1.5). The current practice of clinical screening for signs of vaginal discharge (excluding candida-like discharge) also had low discriminative ability (LR+ 1.5, 95 % CI 1.1–1.9).

All risk scores suffered from the choice between low sensitivity and low specificity. With a cut-off taken at an acceptable sensitivity of minimum 0.7, the risk score based on sociodemographic factors identifies 50 (75%) and misses 17 (25%) of the 67 cervical infections. Per true case treated, six pregnant women would be prescribed multiple antibiotic regimens unnecessarily. With a cut-off at a sensitivity of 0.4, the sociodemographic risk score identifies only 29 (43%) of the cervical infections. The majority of the cervical infections would remain untreated, and although over-treatment is reduced, four pregnant women would still be unnecessary treated with multiple antibiotics per infected women. The more comprehensive clinical and microscopy risk scores show similar results.

Discussion

Pregnant women are usually considered to be a low-risk population, but among antenatal care attendees in Botswana, the burden of reproductive tract infections is very high. The prevalence of cervical infections is 10%, and most of the infected women go undetected through normal antenatal care services. Published studies of STIs among pregnant women in other countries in sub-Saharan Africa show similar trends in the prevalence of cervical infections. In our study, 8% have a *C trachomatis* infection, compared to rates between 6% in Tanzania and 13% in Cape Verde [13,22]. Gonorrhea is found in 3% of the women, compared to rates that range from 2% in Gabon to 8% in South Africa [16,21]. Although difficult to measure, it is likely that complications and sequelae due to these infections among pregnant women and their infants in sub-Saharan Africa are substantial.

Syndromic approach

Elicited symptoms of increased discharge or lower abdominal pain are not predictive of cervical infection in antenatal attendees in Botswana. These symptoms are non-specific; they are common in pregnancy, and their association with cervical infections is even lower among pregnant than among non-pregnant women [23]. The

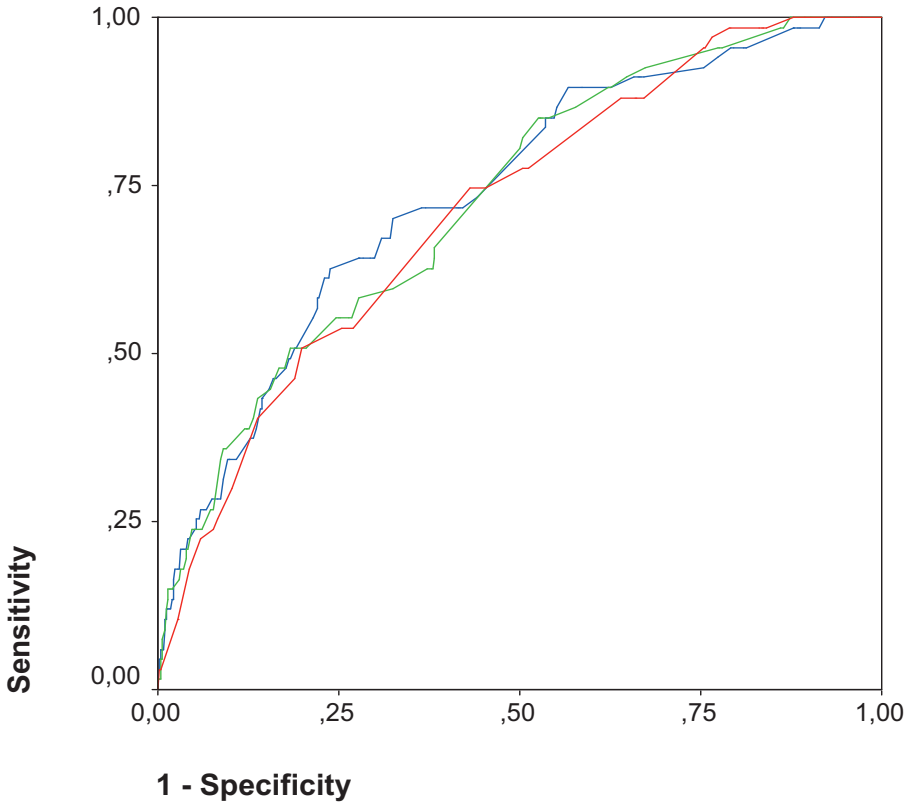

Figure 1
Receiver Operating Characteristics (ROC) curves for three levels of risk scores (sociodemographic, clinical and microscopy risk scores). The risk scores are based on multiple logistic regression analyses and used as a screening tool to identify *N gonorrhoeae* and *C trachomatis*. The risk scores are applied retrospectively on 703 antenatal care attendees in Gaborone, Botswana.

Table 4: Diagnostic strategies to identify infection with *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* in 703 antenatal care attendees in Botswana.

	Positive on assessment		Cervical infection		Sensitivity	Specificity	LR+*	LR-	PPV	NPV
	n	(%)	N	(%)						
Symptoms and signs										
VDS algorithm	104	(15)	11	(11)	0.16	0.85	1.12 (0.63–1.92)	0.98	0.11	0.91
Symptoms alone: VD and/or LAP	155	(22)	14	(9)	0.21	0.78	0.94 (0.57–1.49)	1.02	0.09	0.90
Signs alone: VD (excl. candidiasis)	227	(32)	30	(13)	0.45	0.69	1.45 (1.06–1.89)	0.78	0.13	0.92
Risk scores†, sensitivity minimum 0.7										
Sociodemographic risk score	327	(47)	50	(15)	0.75	0.56	1.71 (1.42–1.99)	0.45	0.15	0.96
Clinical risk score	372	(53)	54	(15)	0.81	0.50	1.61 (1.37–1.83)	0.39	0.15	0.96
Microscopy risk score	273	(39)	51	(19)	0.76	0.65	2.18 (1.80–2.55)	0.37	0.19	0.96
Risk scores, sensitivity minimum 0.4										
Sociodemographic risk score	156	(22)	29	(19)	0.43	0.80	2.17 (1.55–2.91)	0.71	0.19	0.93
Clinical risk score	117	(17)	29	(25)	0.43	0.86	3.13 (2.20–4.30)	0.66	0.25	0.94
Microscopy risk score	116	(17)	29	(25)	0.43	0.86	3.16 (2.22–4.34)	0.66	0.25	0.94

LR+ = positive likelihood ratio; LR- = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value; VDS = vaginal discharge syndrome; LAP = lower abdominal pain; VD = vaginal discharge
* The positive likelihood ratios are calculated with 95% confidence interval.
†Risk factors included in each risk score are described in Table 1

VDS algorithm is used extensively to diagnose cervical infections in antenatal care in Botswana [24], but our results show that this management is no better than random treatment.

To use the genital examination at the first antenatal care visit as a clinical screening tool for cervical infections is also unadvisable. According to the newly revised VDS algorithm in Botswana, symptoms or signs of yellow discharge are risk factors which should lead to treatment for cervical infections. In our study among antenatal care attendees, neither symptoms nor signs of yellow discharge are associated with cervical infection. In pregnancy, symptoms or signs of vaginal discharge in general, yellow discharge, or other specific discharge characteristics should not be used as criteria for treating *C trachomatis* and *N gonorrhoeae*.

Other studies from sub-Saharan Africa conclude that case management with the vaginal discharge syndrome has poor discriminatory ability in the diagnosis of cervicitis [25-27]. Several reviewers [28-30] emphasise that the syndromic approach should not be used as a screening tool for *N gonorrhoeae* and *C trachomatis*. Our study concurs with a substantial body of knowledge indicating that the syndromic approach should be used neither as a case management of symptomatic women nor as a clinical screening tool to identify *C trachomatis* and *N gonorrhoeae* in antenatal care attendees in sub-Saharan Africa.

Screening strategies

Despite extensive analyses, all computed risk scores were of limited value as screening tools in antenatal care attendees. They had poor discriminative ability, even in the study population in which they were computed and adapted to under optimal conditions. As the syndromic approach, the risk scores also resulted in a large number of undetected cervical infections and substantial overtreatment. Additionally, notification and treatment of sexual partners, an essential element of STI management, is difficult to justify when the majority of the identified women do not have an STI [8]. A substantial improvement of the management of cervical infections in antenatal care in developing countries seems impossible without specific diagnostic tests.

The development of simple, rapid tests for *C trachomatis* and *N gonorrhoeae* has been a high priority since the 1990s [9-11]. Major progress has recently been made, and several tests for *C trachomatis* and *N gonorrhoeae* are now on the market [7,32]. The Sexually Transmitted Diseases Diagnostics Initiative at the WHO has begun a programme to field test and systematically evaluate these simple, affordable rapid tests [32,33]. So far, available tests are found to be specific (>90%), but with a variable sensitivity (25–85%) [34-36]. In Botswana, the health system is relatively well functioning, and this country could well serve as an exploratory site for the use of rapid tests for *C trachomatis* and *N gonorrhoeae*. Through the prevention of mother-to-child transmission of HIV programme, all health posts and clinics have lay workers who perform rapid tests for HIV. Simple tests for cervical infections performed by clinicians or lay workers may prove a feasible contribution to the improvement of diagnosis and the reduction of the disease burden of these conditions in this and similar settings.

Consistent with established knowledge on STI epidemiology [6,31], youth is the single factor most strongly associated with *C trachomatis* and/or *N gonorrhoeae* in our study

population. Thus age can be useful as a screening tool in the traditional sense, to minimise the number of standard diagnostic tests by identifying people with a higher-than-average prevalence of infection [29]. If it were decided in Botswana to introduce screening for cervical infections with rapid tests in the antenatal care, selective screening of younger women should be considered.

Conclusion

Although the vaginal discharge syndrome does not discriminate between infected and uninfected women, the algorithm is in extensive use to diagnose and treat *C trachomatis* and *N gonorrhoeae* among antenatal care attendees in Botswana. Unfortunately, risk scores do not appear to improve the management of cervical infections in pregnancy substantially. To diagnose and treat asymptomatic cervical infections, and to reduce the massive overtreatment in the syndromic management, specific diagnostic tests are necessary. Screening for cervical infections in pregnant women is an essential public health measure, and rapid tests will hopefully be available in developing countries within a few years. In the temporary absence of such tests, health authorities in sub-Saharan Africa should consider reallocating their resources to other STI measures rather than diagnosing and treating gonorrhoea and chlamydia inadequately in antenatal care.

Abbreviations

STI, sexually transmitted infection; VDS, vaginal discharge syndrome; PMN/HPF, polymorphonuclear leukocutes per high power field; OR, odds ratio; ROC, receiver operating characteristics; LR+ and LR-, positive and negative likelihood ratios; PPV and NPV, positive and negative predictive value; CI, confidence interval.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MR contributed to the study design, was responsible for data collection and data analysis, and drafted the manuscript. MRa contributed to the study design and to formal and organisational aspects of the study. MV contributed to the study design, and led and performed the majority of the laboratory work. JS and PH supervised the study. All authors read and approved the final manuscript.

Acknowledgements

The project was supported by the Health Sector Agreement between Norway and Botswana. The authors want to thank the Health Research Unit, Ministry of Health, for the valuable contribution to the formal and organisational aspects of the study. We also want to thank the staff at the Government Clinics and at The National Health Laboratory for their co-operation during the field work and Magne Thoresen, University of Oslo, Norway, for statistical review.

References

1. Over M, Piot P: **HIV infection and sexually transmitted diseases.** In *Disease control priorities in developing countries* Edited by: Jamison DT, Mosley WH, Measham AR, Bobadilla JS. Oxford University Press; 1993:455-527.
2. Mullick S, Watson-Jones D, Beksinska M, Mabey D: **Sexually transmitted infections in pregnancy: prevalence, impact on pregnancy outcomes, and approach to treatment in developing countries.** *Sex Transm Infect* 2005, **81:**294-302.
3. Sexton J, Garnett G, Rottingen JA: **Metaanalysis and metaregression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infection.** *Sex Transm Dis* 2005, **32:**351-357.
4. UNAIDS/WHO: *Consultation on STD interventions forpreventing HIV: what is the evidence? Geneva* 2000 [http://www.who.int/hiv/pub/sti/pubevidence/en/].
5. WHO: *Guidelines for the management of sexually transmitted infections. Geneva* 2003 [http://whqlibdoc.who.int/publications/2003/9241546263.pdf].
6. Brabin L: **Clinical management and prevention of sexually transmitted diseases: a review focusing on women.** *Acta Trop* 2000, **75:**53-70.
7. Vuylsteke B: **Current status of syndromic management of sexually transmitted infections in developing countries.** *Sex Transm Infect* 2004, **80:**333-334.
8. Mayaud P, Mabey D: **Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges.** *Sex Transm Infect* 2004, **80:**174-182.
9. Vuylsteke B, Laga M, Alary M, Gerniers MM, Lebughe JP, Nzila N, Behets F, Van Dyck E, Piot P: **Clinical algorithms for the screening of women for gonococcal and chlamydial infection: evaluation of pregnant women and prostitutes in Zaire.** *Clin Infect Dis* 1993, **17:**82-88.
10. Mayaud P, Grosskurth H, Changalucha J, Todd J, West B, Gabone R, Senkoro K, Rusizoka M, Laga M, Hayes R: **Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics.** *Bull World Health Organ* 1995, **73:**621-630.
11. Hylton-Kong T, Brathwaite AR, Del Rosario GR, Kristensen S, Kamara P, Jolly PE, Hook EW, Figueroa JP, Vermund SH: **Marginal validity of syndromic management for reproductive tract infections among pregnant women in Jamaica.** *Int J STD AIDS* 2004, **15:**371-375.
12. Wasserheit JN, Holmes KK: **Reproductive tract infections: Challenges for international health policy, programs, and research.** In *Reproductive tract infections: Global impact and priorities for women's reproductive health* Edited by: Germain A, Holmes KK, Piot P, Wasserheit JN. New York: Plenum Press; 1992:10-13.
13. Mayaud P, Uledi E, Cornelissen J, ka-Gina G, Todd J, Rwakatare M, West B, Kopwe L, Manoko D, Grosskurth H, Hayes R, Mabey D: **Risk scores to detect cervical infections in urban antenatal clinic attenders in Mwanza, Tanzania.** *Sex Transm Infect* 1998:39-46.
14. Mulanga-Kabeya C, Morel E, Patrel D, Delaporte E, Bougoudogo F, Maiga YI, Diawara Z, Ndoye I, Garangue S, Henzel D: **Prevalence and risk assessment for sexually transmitted infections in pregnant women and female sex workers in Mali: is syndromic approach suitable for screening?** *Sex Transm Infect* 1999, **75:**358-359.
15. Schneider H, Coetzee DJ, Fehler HG, Bellingan A, Dangor Y, Radebe F, Ballard RC: **Screening for sexually transmitted diseases in rural South African women.** *Sex Transm Infect* 1998:147-152.
16. Bourgeois A, Henzel D, Dibanga G, Malonga-Mouelet G, Peeters M, Coulaud JP, Fransen L, Delaporte E: **Prospective evaluation of a flow chart using a risk assessment for the diagnosis of STDs in primary healthcare centres in Libreville, Gabon.** *Sex Transm Infect* 1998:128-132.
17. Botswana Ministry of Health: *Management of sexually transmitted infections: Reference manual for health workers. Gaborone* 2005.
18. Bailey G, Ryan C, Rahman M: *Sexually transmitted infections in Botswana: Prevalence of infection and evaluation of syndromic management algorithms. Gaborone* 2004.
19. Botswana Ministry of Health: *Guidelines for antenatal care and the management of obstetric emergencies and prevention of mother-to-child transmission of HIV. Gaborone* 2005.

20. Nugent RP, Krohn MA, Hillier SL: **Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation.** *J Clin Microbiol* 1991, **29:**297-301.
21. Sturm AW, Wilkinson D, Ndovela N, Bowen S, Connolly C: **Pregnant women as a reservoir of undetected sexually transmitted diseases in rural South Africa: implications for disease control.** *Am J Public Health* 1998, **88:**1243-1245.
22. Wessel HF, Herrmann B, Dupret A, Moniz F, Brito C, Bergstrom S: **Genital infections among antenatal care attendees in Cape Verde.** *Afr J Reprod Health* 1998, **2:**32-40.
23. Hudson CP: **Syndromic management for sexually transmitted diseases: back to the drawing board.** *Int J STD AIDS* 1999, **10:**423-434.
24. Romoren M, Rahman M, Sundby J, Hjortdahl P: **Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana.** *Sex Transm Infect* 2004, **80:**395-400.
25. Mayaud P, ka-Gina G, Cornelissen J, Todd J, Kaatano G, West B, Uledi E, Rwakatare M, Kopwe L, Manoko D, Laga M, Grosskurth H, Hayes R, Mabey D: **Validation of a WHO algorithm with risk assessment for the clinical management of vaginal discharge in Mwanza, Tanzania.** *Sex Transm Infect* 1998:77-84.
26. Costello Daly C, Wangel AM, Hoffman IF, Canner JK, Lule GS, Lema VM, Liomba NG, Dallabetta GA: **Validation of the WHO diagnostic algorithm and development of an alternative scoring system for the management of women presenting with vaginal discharge in Malawi.** *Sex Transm Infect* 1998:50-58.
27. Alary M, Baganizi E, Guedeme A, Padonou F, Davo N, Adjovi C, van Dyck E, Germain M, Joly J, Mahony JB: **Evaluation of clinical algorithms for the diagnosis of gonococcal and chlamydial infections among men with urethral discharge or dysuria and women with vaginal discharge in Benin.** *Sex Transm Infect* 1998:44-49.
28. Pettifor A, Walsh J, Wilkins V, Raghunathan P: **How effective is syndromic management of STDs?: A review of current studies.** *Sex Transm Dis* 2000, **27:**371-385.
29. Sloan NL, Winikoff B, Haberland N, Coggins C, Elias C: **Screening and syndromic approaches to identify gonorrhea and chlamydial infection among women.** *Stud Fam Plann* 2000, **31:**55-68.
30. Dallabetta GA, Gerbase AC, Holmes KK: **Problems, solutions, and challenges in syndromic management of sexually transmitted diseases.** *Sex Transm Infect* 1998:1-11.
31. Cates W Jr: **Contraception, unintended pregnancies, and sexually transmitted diseases: why isn't a simple solution possible?** *Am J Epidemiol* 1996, **143:**311-318.
32. Mabey D, Peeling RW: **Rapid diagnostic tests for sexually transmitted infections.** *IPPF Med Bull* 2002, **36:**1-3.
33. **Sexually Transmitted Diseases Diagnostics Initiative (SDI)** [http://www.who.int/std_diagnostics]
34. Vickerman P, Watts C, Peeling RW, Mabey D, Alary M: **Modelling the cost effectiveness of rapid point of care diagnostic tests for the control of HIV and other sexually transmitted infections among female sex workers.** *Sex Transm Infect* 2006, **82:**403-412.
35. Yin Y-P, Peeling RW, Chen X-S, Gong K-L, Zhou H, Gu W-M, Zheng H-P, Wang Z-S, Yong G, Cao W-L, Shi M-Q, Wei W-H, Dai X-Q, Gao X, Chen Q, Mabey D: **Clinic-based evaluation of Clearview Chlamydia MF for detection of Chlamlydia trachomatis in vaginal and cervical specimens from women at high-risk in China.** *Sex Transm Infect* 2006, **82:**33-37.
36. Benzaken AS, Galban EG, Antunes W, Dutra JC, Peeling RW, Mabey D, Salama A: **Diagnosis of gonococcal infection in high risk women using a rapid test.** *Sex Transm Infect* 2006:26-28.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2334/7/27/prepub