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Preface

"Improving public health control of sexually transmitted diseases in Botswana" is one of the institutional collaboration projects financed by the Health Sector Agreement between Norway and Botswana. The project has two main components; an epidemiological study and an economic evaluation. In 2000 and 2001, the National Health Laboratory in Gaborone, the AIDS/STD Unit and the Health Research Unit in the Ministry of Health in Botswana and the University of Oslo, Norway, conducted a cross-sectional study on sexually transmitted infections (STIs) among pregnant women in Gaborone. One of the aims of the study was to collect data for the cost-effectiveness analysis presented in this report.

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Abstract

Objectives: Chlamydia is the most common bacterial sexually transmitted infection worldwide and a major cause of morbidity – particularly among women and neonates. We compared costs and health consequences of using point-of-care (POC) tests with current syndromic management among antenatal care attendees in sub-Saharan Africa. We also compared erythromycin with azithromycin treatment and universal with age-based chlamydia management.

Methods: A decision analytic model was developed to compare diagnostic and treatment strategies, using Botswana as a case. Model input was based upon 1) a study of pregnant women in Botswana, 2) literature reviews and 3) expert opinion. We expressed the study outcome in terms of costs (US$), cases cured, magnitude of overtreatment and successful partner treatment.

Results: Azithromycin was less costly and more effective than was erythromycin. Compared to syndromic management, testing all attendees on their first visit with a 75% sensitive POC test increased the number of cases cured from 1 500 to 3 500 in a population of 100 000 women, 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 specific POC tests provided the advantage of substantial reductions in overtreatment with antibiotics and improved partner management.

Conclusions: Using POC tests to diagnose chlamydia during antenatal care in sub-Saharan Africa entails greater health benefits than syndromic management does – and at acceptable costs – especially when restricted to younger women. Changes in diagnostic strategy and treatment regimens may improve people's health and even reduce health care budgets.

Introduction

There has long been a consensus that simple, affordable and preferably on-site tests are needed to improve the management of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in the developing world.[1] Major progress has recently been made, and several tests are now on the market. We have conducted an economic evaluation to compare testing symptomatic and asymptomatic attendees using rapid point-of-care tests with the existing syndromic management of chlamydia. The setting for our analysis is the first antenatal care visit of pregnant women in Botswana. The antenatal care program in this country is well functioning and highly attended. 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 sexually transmitted infections such as gonorrhoea and trichomoniasis.

SEXUALLY TRANSMITTED INFECTIONS IN THE DEVELOPING WORLD

Sexually transmitted infections (STIs) are highly prevalent in the developing world. An estimated 340 million new curable STIs occur annually worldwide, of which almost half are chlamydia and gonorrhoea infections.[2] Sub-Saharan Africa has the highest worldwide prevalence of these two infections, which are major causes of morbidity, particularly in women.[3] In females, a cervical infection with *N gonorrhoeae* or *C trachomatis* can cause acute symptoms with increased discharge, dysuria and lower abdominal pain, or be asymptomatic. The infection can progress to pelvic inflammatory disease, which in turn may cause chronic pelvic pain, 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.[4]

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 ulcerative and non-ulcerative STIs can enhance HIV transmission.[5, 6] Consequently, UNAIDS and WHO have recommended that high priority be given to the development of STI control programmes, one of the most important interventions for curbing the spread of AIDS.[7, 8] 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.

CHLAMYDIA AND GONORRHOEA IN THE CURRENT STI MANAGEMENT

Due to the complications associated with maternal, foetal, and infant morbidity and mortality, it should be part of the mandate of the antenatal care programs to diagnose and treat chlamydia and gonorrhoea. However, diagnosis and treatment of STIs in the developing world is usually limited to the 'syndromic approach'. In the early 1990s, the World Health Organization developed syndromic management guidelines for symptomatic STI patients for countries without laboratory support. With the use of flowcharts, presenting symptoms and clinical signs are classified into defined STI syndromes such as genital ulcer or genital discharge syndrome. The patients are treated with standardized drug regimens including at least two antibiotics - to cover the possible causes of their syndrome.[9] The vaginal discharge syndrome 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.[4, 10-12] The low sensitivity hampers the possibility of preventing reproductive complications and sequelae and of interrupting onward transmission. The majority of women with a cervical infection are asymptomatic and will not be identified and treated with a syndromic approach.[13] Evidence from the Rakai, Uganda study on STI control for AIDS

prevention has shown that relying on treatment of only those with symptoms reaches less than 8% of the infected population.[14]

The low specificity 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. A study from Zimbabwe indicates that about two thirds of patient with signs interpreted at clinic level as an STI are not infected and should not have been treated.[15] A high level of overdiagnosis undermines partner notification as most patients do not have an STI and their partners should neither be notified nor treated. Again, overtreatment of partners is costly to the health care system and the individual, and women may unnecessary be at risk of stigma and violence from their sexual partners when they refer them for treatment.[16, 17]

In Botswana, women complaining of symptoms of vaginal discharge or lower abdominal pain are managed with the vaginal discharge algorithm according to national syndromic approach guidelines.[18] 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. The syndromic approach is based exclusively on symptoms and clinical criteria, and the strategy 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. A national evaluation of the quality of the STI management in Botswana indicated that only a minority (17%) of the patients were assessed and managed according to the guidelines.[19] The lack of access to specific diagnostic tests and the uncertainties of the syndromic approach may discourage health workers from following the guidelines, resulting in inadequate history-taking and examination, insufficient or unnecessary prescriptions and partner notification without commitment.

The literature discusses alternative approaches to chlamydia and gonorrhoea in developing countries, such as risk assessment, clinical screening and mass treatment.[20, 21] The two former methods have low sensitivity and specificity; the latter is linked to development of antibiotic resistance and high drug wastage. The development of simple point-of-care tests for *C trachomatis* and *N gonorrhoeae* has been a high priority since the 1990s.[20, 22, 23] 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.[23]

INTRODUCING TESTS TO DIAGNOSE CHLAMYDIA

The use of nucleic acid amplification tests (NAATs), the best diagnostic tool for *C trachomatis* infections, has long been a natural and established routine in the developed world. The tests are widely used both for testing symptomatic patients and screening for infections in selected populations, but they are costly and have been beyond reach for laboratories in resource poor settings.

STI control programmes which take into account the prevalence of asymptomatic infections are also needed in developing countries.[7, 22, 24] Major progress in the development of point-of-care tests has recently been made, and several tests are now on the market.[11, 25] The sensitivity and specificity of these tests will necessarily be lower than for the advanced, laboratory-based diagnostic tests. The Sexually Transmitted Diseases Diagnostics Initiative at the WHO has started a programme to evaluate simple, affordable point-of-care tests, and several are currently being field tested.[25] (http://www.who.int/std_diagnostics). So far, test evaluations have shown variable sensitivities (25-85%), but high specificity (>90%).[26] A recent study found that a commercially available test which

is widely used in China had a sensitivity of 50%. More tests are in development, and most likely, more sensitive tests will be available within a few years.

A rapid test with a sensitivity of 65% can lead to a greater proportion of infected patients treated compared to NAATs with sensitivity of 90% when the return rate for test results and treatment is low.[27] Mathematical models show that rapid tests with a sensitivity of 70% have the potential to reduce the prevalence of chlamydia and gonorrhoea in sex workers and avert HIV infections in their clients. Encouraging data on an improved rapid test for ocular chlamydial infection have recently been published.[28] The evaluated test had a sensitivity of 84% and a specificity of 99% using PCR as the reference standard.

POINT-OF-CARE TESTS IN ANTENATAL CARE IN BOTSWANA

Botswana is one of the Sub-Saharan countries with high prevalence rates of HIV and STIs. In 2005, 33% of the antenatal care attendees were HIV infected.[29] STIs are a major public health problem: during the last decade, between 100 000 and 200 000 STI-related outpatient consultations were registered every year.[30, 31] Among pregnant women in the capital of Botswana, Gaborone, 8% were found to have chlamydia, while 3% had gonorrhoeae.[32]

To explore diagnostic tests as an alternative or addition to the current STI management is consistent with the health policy in Botswana.[33] Although resources are limited, Botswana is one of the few African countries classified as “Upper Middle Income”.[34] Point-of-care tests for chlamydia can prove to be cost saving in a wider perspective, but health authorties may be discouraged by the direct cost of purchasing and using the tests. This is why using Botswana to evaluate the existing STI management and explore the costs and benefits of laboratory analysis in diagnosing STIs is favourable. STI and HIV prevalences are high, creating an obvious need to

improve the diagnosis and treatment of chlamydia,[35] and there is a realistic economic possibility to introduce this service. A research project on point-of-care tests in Botswana can be used as a model, providing likely short or long term benefits for other countries in the region.

Among different relevant patient groups we have chosen antenatal care attendees to explore the costs and effects of introducing point-of-care tests because among pregnant women there is the added possibility of preventing the adverse obstetric outcomes related to these infections during pregnancy. There is also 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 already incorporated into the antenatal routine. At the women's first antenatal visit, blood is drawn for Hb, blood group, RH-factor, syphilis and HIV tests. The samples are either tested on-site or transported to a laboratory.

In addition to the syndromic management of symptomatic pregnant women, all antenatal care attendees in Botswana are clinically screened for reproductive tract infections. The antenatal care guidelines recommend a routine speculum examination at the first antenatal visit, to "exclude genital infections, abnormalities and pelvic tumours".[36]. It is not uncommon for abnormal vaginal discharge to be found in women not eliciting symptoms. As the nurses will not ignore pathological findings, asymptomatic women with signs of vaginal discharge are provided with syndromic treatment. This management bypasses the original entry point of the syndromic algorithms: symptoms which lead to health-care seeking. Specimens for the 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, an introduction of point-of-care tests for chlamydia will not lead to any change in the number or content of the routine antenatal care visits.

In the process of implementing the prevention of mother-to-child-transmission (PMTCT) programme, and subsequently the antiretroviral treatment programme, 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. To utilize clinicians or lay counselors to perform simple rapid tests for chlamydia could provide an opportunity to reduce the disease burden of this infection.

Improved diagnosis of chlamydia in pregnancy is arguably an equitable health investment. In most countries in Sub-Saharan Africa, the antenatal care coverage is above 70%.[37] In Botswana, at least 95% of pregnant women attend antenatal clinics at least once during their pregnancy.[38]. Investing in a service that aims to cover all reproductive women and subsequently their partners and their children promotes a high degree of fairness in resource distribution.

AGE AS A RISK FACTOR FOR CHLAMYDIA

Youth is the single factor most strongly associated with *C trachomatis* infection among pregnant women in Botswana [35], which is consistent with established knowledge on STI epidemiology.[10, 39] The patients' age is already used in the diagnosis of chlamydia in the syndromic management: the risk assessment incorporated in the vaginal discharge syndrome is considered positive if the patient is under 21 years. 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.[40] Chlamydia screening programs in other countries select people for testing based on their age, and we have evaluated whether this is a recommendable option in Botswana.

TREATMENT OPTIONS FOR CHLAMYDIA IN PREGNANCY

Efficacy, tolerance, compliance, and cost are factors to consider when preparing guidelines for antibiotic treatment of chlamydial infection. In the national guidelines in Botswana, doxycycline 100 mg tablets twice daily for seven days is the drug of choice for both males and females. In pregnancy, erythromycin 500 mg tablets four times daily for seven days is recommended. Antenatal care attendees in Botswana diagnosed with the syndromic approach are prescribed multiple drug regimens that require many tablets to be administered correctly, which may reduce compliance. The erythromycin regimen is complex in itself, and compared to other treatment alternatives, erythromycin has a significantly higher level of gastrointestinal side effects, which frequently discourages patients from complying with the regimen and thereby reduces the cure rate.[41, 42] This may be especially problematic in women who experience pregnancy nausea.

Several drugs can cure chlamydia infections, but if poor compliance is suspected, directly observed single-dose therapy should be considered.[43] The oral administration of 1 g of azitromycin has a similar or higher efficacy and similar or fewer side effects than the week-long regimens, and has become the drug of choice in most of the developed world.[44, 45] Clinical experience and research data suggest that azitromycin is effective and safe for the foetus[42] The azithromycin regimen is less costly than erythromycin. We have evaluated the changes in costs and effectiveness of a shift from the erythromycin regimen to azithromycin for the treatment of chlamydia infections in antenatal care attendees in Botswana. As doxycycline is a cheap drug with acceptable cure rates, we modelled doxycycline treatment to partners.

PARTNER NOTIFICATION AND TREATMENT

The management and treatment of sexual partners of patients with treatable sexually transmitted diseases is essential to prevent reinfection of the index patient, cure infected partners, break the chain of transmission, and prevent complications[16] The evidence for the effectiveness of strategies for partner notification has been reviewed, but only 2 of 11 studies included were from developing countries.[46] The probability of reinfection is lowest if patient and partner are treated at the same time and avoid sexual intercourse during the following week. Botswana, as most low-income countries, uses a patient-based partner notification strategy: the index patients are told to inform their own contacts and refer them for treatment.

With respect to treatment of partners, one can distinguish between epidemiological treatment, where all partners are empirically treated, and test-based treatment, where all partners are tested and those with a positive test are treated. The syndromic management relies on epidemiological treatment, and we also modelled epidemiological treatment for the point-of-care test strategy.

ECONOMIC EVALUATIONS

The health challenges facing sub-Saharan Africa are immense, and the discrepancy between needs and resource availability is striking. The HIV/AIDS pandemic represents the highest burden of disease, in particular among young children and adults in reproductive age. In Botswana, the life expectancy has fallen drastically the last decade; according to the WHO to 40 years.[47] The morbidity related to HIV is a great challenge for the health care system, which itself is struggling with the loss of manpower. Given the limited availability of resources, it is necessary to ask questions about their most efficient use.[48] Is this particular expenditure of health resources worthwhile, given the alternative uses to which they might be put? Budgets are insufficient to meet all health care needs, and decision makers need to choose which interventions should be publicly funded. Economic

evaluations could prove helpful in prioritizing between the ranges of competing health interventions in resource-poor settings.

In all societies – from the richest to the poorest – there is a gap between what health care could achieve with respect to reduced mortality and morbidity, and what in reality is achieved. The reason is simply that societies have limited resources in terms of skilled manpower, equipment, buildings, pharmaceuticals, *etc.* Rationing of resources is therefore inevitable. In market-based health care systems, this is achieved by means of charging a market price for health care services such that there is a balance between supply and demand. This mechanism removes queuing and the impression that rationing is going on. Priority setting is achieved by the consumers' willingness to pay. This willingness is captured by the prices, and the prices send signals to suppliers about what products are valued by the consumers. Most societies, however, have chosen to abolish free-market health care and introduced public insurance systems or other means such that people are not denied health care for economic reasons. Such health care systems tend to result in more equitable distribution of health care services, but will inevitably result in queuing because demand is not constrained sufficiently by user charges. While priority setting is achieved by the "the invisible market hand" in competitive markets, priorities are set by politicians or managers in public systems. Economic evaluation is a means to mimic the market mechanism by estimating benefits and resource use of different policy options.

A full economic evaluation can be defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences".[49] Economic evaluation is a tool for making decisions that will maximise for example health benefit. The basic tasks of any economic evaluation are therefore to identify, measure, value and compare costs and consequences of the alternatives being considered in an incremental analysis, which means that the difference in costs is

compared with the difference in consequences[49]Full economic evaluations are often classified into three different approaches: Cost-Benefit Analysis (CBA), Cost-Effectiveness Analysis (CEA) and Cost-Utility Analysis (CUA). In short, these methods are primary distinguished according to how the consequences are being measured.

This evaluation of *C trachomatis* infection policies is a cost-effectiveness analysis (CEA), an analysis in which the health benefit is measured in natural units such as life year gained, hip fracture avoided, *etc*. In our case we use cured cases of chlamydia as the measure of benefit. The CEA (along with CUA) are dependent on comparisons to an external standard to assess whether a specific programme is worthwhile or not, because the goal for the decision-maker is to maximize the benefits within a given budget. The most comprehensive use of cost-effectiveness ratio is to analyse the incremental cost-effectiveness ration (ICER), which is the ratio between the difference in cost and the difference in benefits between two interventions.

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

The cost analysis in a CEA is dependent on which perspective is chosen for the analysis. Analysis performed from a societal perspective is often preferred, which means that all costs and health consequences should be captured irrespective of who pays or who benefits. The costs included in such a perspective are all relevant resources consumed by implementing the relevant health care programme, and can be divided into the following cost items: health sector costs; costs on other (public) sectors; patient/family (time) costs and productivity losses. After identifying the relevant costs, the cost analysis consists of measuring the quantities of resources used and valuing them by assigning unit costs or prices. The final cost of the health care programme is then measured in monetary units. Due to lack of information on costs outside the health care sector, this analysis adopted a health care provider's perspective.

Economic decision analysis is a systematic approach to decision making under uncertainty. The process is designed to help decision makers think clearly about the many elements of complex decisions, as in our case the range of possible consequences of introducing, or not introducing point-of-care tests to diagnose chlamydia. The aim of a decision analysis is to synthesize currently available evidence regarding the effectiveness and costs of alternative health care strategies. The method is suited to incorporating into the decision-making process both what is known about a problem and also what is uncertain. In some instances the method will illuminate where better data are needed before a health-care decision can be made.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

Genital chlamydia is the most common bacterial STI in Europe and the United States, and numerous cost-effectiveness analyses on screening for chlamydia in this setting have been published. In brief, screening with specific tests is shown to be cost-effective above a certain prevalence level in these countries. Studies that have included the management of partners have shown that effective partner referral is essential for a cost-effective screening program.

The results from these analyses are not easily transferable to resource poor settings for a number of reasons. Disease patterns in general, the prevalences of STIs and HIV and the occurrence of complications are different, as is the health care systems and people's beliefs and behaviors. More specifically, existing cost evaluations analyze the use of laboratory tests with high sensitivity and specificity which are too resource demanding for developing countries. There are only a few economic evaluations of chlamydia screening among pregnant women, and no published studies on chlamydia screening among pregnant women in developing countries. In conclusion, there is an obvious lack of economic evaluation to support the choice of strategy to manage *C trachomatis*

infections during antenatal care, particularly with regard to developing countries. The results from existing cost evaluations and important review articles are summarized below.

From static to dynamic modelling

The majority of published cost-effectiveness analyses are based on static models, commonly a decision analysis model. The static models of chlamydia screening focus on the disease and the disease progression in infected individuals. The effect measured will be number of infections detected and cured and complications avoided in these individuals. The models are referred to as 'static' because they assume a constant force of infection.

In 2000, the first dynamic models of chlamydia screening were published.[50, 51] *C trachomatis* is a sexually transmitted microbe, and transmission 'dynamic' models of chlamydia screening (such as the stochastic network simulation model and the state transmission simulation model) focus on the occurrence and spread of the infection in the population. The use of dynamic models has been advocated in the evaluation of large-scale screening programs, as these models incorporate transmission dynamics, re-infection and the change of disease prevalence over time. Programs targeting smaller groups such as pregnant women have been specifically mentioned as an exception, as they are less likely to lower the chlamydia prevalence.[52] Thus, there is a role for both static and dynamic models in the evaluation of *C trachomatis* screening programs.[53]

Dynamic models require much more detailed data about the sexual behaviour and the infectious disease than static models, such as duration of partnerships, frequency of sexual intercourse and transmission probability per sexual contact. The uncertainties regarding the additional data needed for a dynamic model can be substantial. The main advantage of a dynamic model is that it incorporates the effects of changes in disease prevalence over time. Welte *et al.*

compare a static and a dynamic cost evaluation of opportunistic chlamydia screening in the Netherlands.[54] The static model estimated a cost-effectiveness of US$700 per major outcome averted, whereas the dynamic model rendered net savings. The models also differed in results regarding screening older women. The diverging outcomes of the model analyses were mainly caused by the transmission chains considered in the models and assumptions about the screening program's influence on chlamydia prevalence and force of infection. A dynamic model accounts for the direct effects on the cured persons and the indirect protection effects on other persons. The static model mainly focuses on the savings resulting from prevented sequelae in the screened woman. As it assumes a constant prevalence, the model overestimates the cost-effectiveness ratio of an effective screening program that reduces the chlamydia prevalence.

Cost-effectiveness of partner pharmacotherapy

Some years ago, the risk for reinfection due to failed partner referral was included in the commonly used decision analysis.[52] Postma *et al*. found that within the broader framework of the screening program, partner pharmacotherapy was a cost-saving activity; primarily due to prevention of reinfection in women who have been cured through the screening.[55]

Studies on cost-effectiveness of screening for chlamydia in pregnancy

Screening sexually active women for chlamydia will result in averted costs of managing acute and long-term complications. For pregnant women, potential benefits of averted vertical transmission and post partum infections are relevant for every case of infection detected. We have identified two published cost evaluations of chlamydia screening specific for pregnant women (Appendix 1). Both

papers present static cost-effective decision models of chlamydia screening in pregnancy in which major outcomes averted is used as outcomes.

A Dutch study concludes that screening with advanced laboratory methods for asymptomatic *C trachomatis* infection in pregnant Dutch women renders net savings at a minimum prevalence rate of 4% or more.[52] Nettleman and Bell have analyzed culture and direct antigen testing of pregnant women assuming different prevalences of infection and deriving probabilities of major outcomes averted from published literature. They conclude that screening all pregnant women is not cost-effective, but the excess cost was modest when direct antigen tests were used.[56]

Two papers present analyses that use a study population of pregnant women, but due to the use of short term outcomes (cost per infection detected), they are not strictly defined to case finding in pregnancy. Rours *et al*. discuss testing strategies with advanced technology and Hueston and Lenhart discuss different treatment regimen. [57, 58] We have identified no published economic evaluations of chlamydia infection in pregnancy that use dynamic models, none which include partner treatment and none conducted in resource poor settings.

Economic evaluations for developing countries

There is an obvious lack of cost evaluations of strategies to diagnose and treat sexually transmitted diseases other than HIV in developing countries. The papers identified by searches in Medline and EMBASE examine costs and benefits of the syndromic management, mass treatment, or management of STI patients in pharmacies (Appendix 2). One recent publication estimates the incremental cost-effectiveness of using point-of-care tests compared to syndromic management of chlamydia and gonorrhoea among female sex workers in Benin.[26] It was assumed in the model that cervical infections increase the risk of HIV transmission 2-8 times. POC tests for chlamydia and gonorrhoea

with higher sensitivity than the syndromic approach could thus result in more cervical infections treated and reduce HIV transmission. The conclusion from this specific population was that such tests can be a cost effective strategy; averting HIV infections and decreasing the degree of inappropriate treatment of cervical infections.

In general, diagnosing and treating STIs in developing countries have been considered cost-effective.[59] The fact that bacterial and viral STIs can enhance HIV transmission is believed to increase the cost-effectiveness of STI management in countries with a substantial HIV prevalence. STI management has compared favorably with other interventions, for example highly active anti-retroviral therapy (HAART).[60] Gilson *et al*. reported that improved management of STIs in rural Tanzania reduced HIV transmission by 40% at an estimated cost of $10 per disability adjusted life year (DALY) saved.[61]

Reviews of economic evaluations of chlamydia screening

The most recent systematic review of screening for *C trachomatis* identified 713 papers, and included 57 formal economic evaluations and two cost studies - none from developing countries.[62] The authors conclude that three main methodological issues threaten the validity of the economic evaluations. Firstly, most evaluations, also of large-scale screening programs, used a static and not dynamic modeling approach that the reviewers consider inappropriate for the study of infectious diseases. Secondly, restricted outcomes such as cost per case detected should not be used as a basis for policy recommendations. Thirdly, most studies did not acknowledge or investigate the uncertainty associated with probability estimates for the long-term sequelae associated with chlamydia infection.

A review from 2002 assessed cost effectiveness of screening asymptomatic sexually active women less than 30 years of age in a primary care setting.[63] None of the evaluated studies were

from developing countries. The models showed screening to be cost effective at prevalences of 3-10% and cost saving at prevalences as low as 1% if age was used as a selection factor and DNA based tests were used in urine samples. The authors emphasize that the assumptions used in the models have been difficult to confirm and there is a need for more data, particularly on the risk of complications in women with asymptomatic lower tract infection.

Another review of economic evaluations of chlamydia screening programs in developing countries concluded that studies show considerable variability with regard to end points (cost per case, per cured patient, per PID or major outcome averted), as well as the probabilities used for progression of disease, the considered sequelae and costing (e.g. cost per PID).[52] Most of the included studies identified were static models of screening among non-pregnant females seeking health care. All studies showed that chlamydia prevalence is one of the most important determinants of the cost-effectiveness ratio, and several studies showed that effective partner referral is essential for a cost-effective screening program. It was noted by the authors that no quality of life changes associated with chlamydia screening programs have been considered in the evaluations, and that not all chlamydia-associated diseases are taken into account (e.g. stillbirth, preterm delivery and low birth weight).

We also identified a review of literature on the epidemiology of chlamydia infection, its health consequences, and the benefits, problems and cost-effectiveness associated with chlamydia screening with advanced laboratory tests among young women in the United States.[64] The authors report that the reviewed economic studies conclude that universal screening is more cost-beneficial than selective screening when the disease prevalence is above 2 to 10%.

CHALLENGES WITH THE ECONOMIC EVALUATION IN THIS STUDY

The benefits of a health service can be classified as in the box below:

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
c) The value of less personal pain and loss

Major challenges in performing a cost-effectiveness analysis of the management of STIs in developing countries lie in the estimated effectiveness. Some of the complications caused by *C trachomatis* are immediate, whilst the majority occur after a long time and will be difficult to measure. In addition, complications such as pelvic inflammatory disease, extrauterine pregnancy, premature labour and the neonatal infections can occur both because of and independent of chlamydia. In Botswana, as in most developing countries, estimates of the occurrence of these conditions are largely unavailable. If any information exists, the proportion of the conditions that may be attributed to chlamydia is unknown.

To compare the cost effectiveness of chlamydia management strategies with other health interventions, the effectiveness has to be measured in a value such as quality adjusted life years. The difficulty with estimating the chlamydia-associated diseases makes it impossible to consider quality of life changes associated with chlamydia management programs.

The costs to the health services in sub-Saharan Africa of a given complication of STIs are also nearly impossible to estimate. In Botswana, the public health sector operates with overall lump sums, for example salaries or drug use in primary health care. 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 have never been calculated.

We selected a static model to evaluate the introduction of point-of-care tests in antenatal care. A dynamic model requires much more detailed data about the sexual behaviour and the natural history of *C trachomatis* infections. The exact patterns of sexual behaviour in a population are virtually impossible to assess. What is the nature of the formation and termination of steady and casual partnerships? What is the spread of infection in partnerships? In our study, the majority of the pregnant women stated when interviewed that they had one partner during the last 12 months. On the other hand, the prevalences of sexually transmitted infections were high (chlamydia 8%, gonorrhoea 3%, trichomoniasis 19% and syphilis 5%). In this setting we question whether a dynamic model would perform better than a static model, as the additional data needed would be either unreliable estimates or "educated guesses".

AIMS AND HYPOTHESIS

The aim of this economic evaluation was to compare the costs and health consequences in sub-Saharan Africa of testing asymptomatic and symptomatic women with a POC test versus syndromic management of chlamydia in antenatal care. Two treatment alternatives in pregnancy were evaluated: erythromycin and azithromycin, while we modelled doxycycline to partners. Three alternative strategies were evaluated: managing all women, selective management of women under 30, and selective management of women less than 20 years.

Methods

We evaluated the cost and the effectiveness of syndromic approach and point-of-care tests in diagnosing and treating chlamydia infections in antenatal care. In a static decision model comparing the two strategies, we incorporated the evaluation of three management strategies: managing all

women, selective management of women under 30, and selective management of women less than 20 years. Two treatment options were evaluated, the current erythromycin regimen and azithromycin provided directly observed. Core issues in the economic evaluation are summarized in Table 1.

THE DECISION ANALYTIC MODEL

A decision tree incorporating the two strategies for the diagnosis and treatment of chlamydia among antenatal care attendees was conducted in TreeAge Pro Suite 2006. The decision tree is a branching structure in which nodes symbolise voluntary decisions and events which have multiple possible outcomes and are not under the decision maker's control. The node's branches represent the alternatives or outcomes associated with that event (Figure 1). We modelled all main event pathways that had distinct resource implications or outcome values associated with them. The probabilities of the different outcomes, the resource consequences and the health consequences associated with the diagnostic strategies were estimated.

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 have not included further transmission from the male partner. We are aware that multiple partnerships are common in Botswan.[37] This and 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 is underestimated.

Information to feed the decision tree was based on our cross-sectional study among 703 antenatal care attendees who visited 13 primary health care clinics in Gaborone, the capital of Botswana, between October 2000 and February 2001 and/or literature reviews and/or expert opinions. The

study is described in Appendix 3, the literature reviews are described in Appendix 4.

The literature reviews for the costs and probabilities consisted of extensive searches in Medline, Embase, The Cochrane Library, text books, reports and other relavant sources, including local literature searches. The reviews do not formally qualify for categorization as systematic; it was practically impossible to do formal reviews 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: Three participants are medical doctors and representatives from Department of HIV/AIDS Prevention and Care in the Ministry of Health, including one former and one current leader of the STI management in Botswana. These two have supervised nurses and run workshops in syndromic management nationwide, providing them with a unique knowledge of the challenges of the syndromic approach from the nurses' perspective and experience. Three participants are Norwegian medical doctors with extensive experience with research in the field of STIs and reproductive health in sub-Saharan Africa. 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 key structure of the decision tree is shown as one main tree and three partner subtrees (Figure 1). The first step in the model represents the choice of chlamydia management for the women coming for their first antenatal care consultation. The structure of the decision tree is identical for the two strategies, but the probabilities of the events are different. If we use the syndromic management as an example, the next node in the model is the probability of having symptoms or signs which results in a diagnosis or not. Symptoms and signs are not specific of *C trachomatis* infection, and the next nodes in the decision tree represent the probability of infection among the women who have (true positive) and the women who have not (false negative) been syndromically diagnosed with

chlamydia. All these probabilities are based on data from our epidemiological study on the prevalence of selected STIs among pregnant women in Gaborone. The following nodes include the probability of being prescribed correct treatment, the patient being compliant with the treatment regimen and the treatment being effective.

Partner notification and treatment is shown in the partner subtrees. Some partners are, while others are not, infected. The partners may or may not be notified and attend the clinic, they may or may not be prescribed correct treatment and they may or may not be compliant. Infected partners may be symptomatic or not, and symptomatic males may or may not seek care independent of their female partner, which may or may not be effective. Partner subtree A illustrates that for the women with *C trachomatis* infection who are correctly diagnosed and treated, it is important that the partner is treated to avoid reinfection. If partners are not cured, the female may be reinfected. As illustrated in partner subtree C, the situation is reversed when the infected female is not cured: infected partners who are treated adequately may be reinfected by their female partner. Partner subtree B illustrates partner notification of uninfected partners.

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 tests than with syndromic management. When a pregnant woman is diagnosed with vaginal discharge syndrome, she may have candida, bacterial vaginosis, trichomoniasis, chlamydia or gonorrhoeae, or physiologically increased discharge or abdominal pain which is common in 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

may not be 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 (Table 1). The possibility that this is not the case is 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.

The analysis evaluate testing for *C trachomatis* only, assuming that tests for *N gonorrhoeae* infection, trichomoniasis, bacterial vaginosis and candida remains unavailable in the routine care. This implies that attendees with symptoms or signs of vaginal discharge or lower abdominal pain must be managed with syndromic approach algorithms for other conditions in addition to an adequate response to the chlamydia test. Asymptomatic attendees testing positive for chlamydia need treatment for this infection only.

HEALTH OUTCOMES ASSOCIATED WITH TREATING CHLAMYDIA

We sought information in Botswana on the prevalence of chlamydia related complications and the resources spent to treat these complications. Local experts such as medical doctors and nurses, health statisticians, health economists and officers in the ministry were interviewed, and health statistics on patient morbidity and mortality and national health accounts and health budgets was collected. The

effects of chlamydia on morbidity and mortality in Botswana have never been measured. We have not been able to identify any statistics or research which could have demonstrated the benefits of diagnosing and treating chlamydia (such as reduced number of complications and reduced infection transmission). We also conducted literature reviews on the complications of chlamydia in pregnant women and their related costs in other developing countries (Appendix 5).

Ideally, we should have measured the prevented complications in chlamydia infected women and their offspring, and the resulting cost savings to the health system, with the different strategies. After extensive literature searches, interviews with experts and collection of health statistics, we conclude that we lack knowledge on consequences and long term complications of *C trachomatis* infection in Botswana and similar settings. The comparison of point-of-care tests and syndromic approach in the management of chlamydia is therefore restricted to measuring health outcome, or effectiveness, as the number of infections successfully treated and cured with each strategy. Discounting was not performed, as the time perspective was less than one year.

MODEL INPUT PARAMETERS: THE FEMALE DECISION TREE

All parameters have been given a base case value, with which the base case analysis is run. All probabilities also have upper and lower values, as the values could not be determined exactly. The range either represents the range between different studies on the topic (azitromycin cure rates), a 95% confidence interval (CI) (sensitivity and specificity of syndromic approach) or a reasonable, subjective bound of uncertainty decided by the expert panel (probability of partner notification in the syndromic approach). The model input variables; the values and the basis for the ranges are shown in the embedded Table A1.

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 (embedded Table A1 and A2). Based on this knowledge, we modelled different management strategies: to include all women, selective management of women under 30, and selective management of women less than 20 years. Chlamydia incidence is not included in the model. As prevalences may differ in other settings or 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 3-31% represents the range of prevalences found in other studies among antenatal care attendees in sub-Saharan Africa.[4]

Table A1: Age specific prevalence of chlamydia 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)

Table A2: Chlamydia prevalence in age groups suitable for selective management; from the study among 703 antenatal care attendees in Gaborone, Botswana

Age	N (%)	% Prevalence (95% Confidence interval)
<20	76 (10.6)	15.8 (9.3-25.6)
<30	508 (72.3)	9.3 (7.0-12.1)
Total	703 (100)	7.5 (5.8-9.7)

Sensitivity and specificity of the point-of-care test

Several POC tests for *C trachomatis* are commercially available. The evaluated specificity of the tests is consistently found to be high, whereas the sensitivity has not yet been firmly determined (Table B). The specificity of the test was therefore set at 98.5% (97.0-100%).

The sensitivity has varied widely across tests and the population being tested, ranging from 25 to 85% [65]. The evaluations have also differed with respect to reference standard used. A recent

publication presents an evaluation of an antigen detection assay widely used in China, finding a sensitivity of 50% [67]. As higher sensitivities are more ideal, more tests are in development. Recently, data on a rapid test with 83.6% sensitivity for ocular *C trachomatis* infections was published [28]. 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 50-85%. Tests with sensitivities lower than 50% were not considered, as tests with lower sensitivity would detect fewer infections than the syndromic approach.

Table B: 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 [67]
Chlamydia optical immunoassay	Female STI clients	73.8%	100%	Pate *et al*. 1998 [68]
Chlamydia optical immunoassay	"Female clients"	31.6%	98.9%	Widjaja *et al*. 1999 [69]
Chlamydia optical immunoassay	Female STI clients	64.2%	99.1%	Swain *et al*. 2004 [70]
Direct fluorescent antibody test	Female STI clients	73.6%	99.9%	Swain *et al*. 2004 [70]
IgA Rapid Sero Test (ELISA)	Pregnant women	69.6%	97.2%	Witkin *et al*. 1997 [71]

Sensitivity and specificity of syndromic management

The sensitivity and specificity of the syndromic approach were based on our study data for new antenatal care attendees (Appendix 3). 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 attendees are clinically screened for STIs, and women with signs of cervical or yellow vaginal discharge will also be provided treatment. 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 clinically diagnosed with chlamydia, 140 (85%, 95% CI 79-90%) had been prescribed erythromycin. This is consistent with other studies from sub-Saharan Africa (see box below).

The probability of prescription of the recommended drug is likely to be higher if the specific point-of-care test is positive. The nurse will know 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 the low rates of prescription in accordance with the treatment guidelines in syndromic approach are caused by the uncertainty in the diagnosis and the complexity of the treatment regimens. The nurses report 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 prescription [52, 55]. A Medline search yielded no studies on health workers' prescription of treatment for chlamydia specifically (see Appendix 4). The expert panel assumed that if a specific point-of-care test for chlamydia is positive, it is realistic to assume a 93% (85-100%) probability of prescription of treatment. The nurses may forget the prescription or prescribe ineffective drugs, it is likely that it happens in about one in 15 test positive cases.

In a 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 who were observed prescribed treatment for chlamydia to 92 (93%) of the clients [Boonstra et al. 2003]. This prescription rate is likely to be higher than in an antenatal care population. The probability of a chlamydia is higher, and with the lower abdominal pain syndrome, only drugs for chlamydia and gonorrhoea is recommended. Buve *et al* estimate (2001) in their report from Tanzania that 80% of the STI clients were prescribed adequate drugs.

Compliance and drug effectiveness

When the correct drug has been prescribed, patient compliance, drug efficacy and treatment of infected partners are the main factors necessary for successful cure of chlamydia. It is generally accepted that the drugs recommended for chlamydia are nearly 100% effective when taken as recommended, and we have therefore used a combined probability for compliance and drug efficacy. The risk of reinfection is captured in a separate variable.

Compliance and drug effectiveness 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 effectiveness with **azitromycin**

- 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)

The probability of cure with different treatment strategies is based on original studies and reviews, Appendix 6. We use a 0.95 probability of compliance and drug effectiveness for the single-dose treatment with azitromycin, independent of diagnostic strategy [72]. The base case value and the uncertainty bounds are based on available original studies from developed as well as developing countries, and on review papers. The literature consistently shows that the compliance and drug effectiveness for the single dose treatment is very high, and to ensure high 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 [73, 74]. In original studies and reviews of cure rates with erythromycin where the chlamydia diagnosis is based on a specific test, the probabilities of cure were 0.86 (0.72-0.95). The expert panel believe that the cure rates for attendees diagnosed with a point-of-care test are likely to be similar, but assigned large uncertainty bounds (0.50-0.95).

The 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 an 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, compared to women who had not. Low compliance was a core factor in explaining why the prescribing of erythromycin did not necessarily lead to a cure for *C trachomatis*. The attendees who in the study setting are syndromically diagnosed with a cervical infection have an insignificantly higher prevalence of chlamydia compared to those who have not been diagnosed. The expert panel also notes that their common clinical experience is a high level of non-adherence to erythromycin among women diagnosed with vaginal discharge syndrome.

There are few papers published in Medline on patient compliance to STI drugs in developing countries (see Appendix 4). Only clinical cure rates can be measured in the syndromic management of STIs: As it is unknown which infection or condition the patient is suffering from, information on drug efficacy or reinfection rates is unachievable.

MODEL INPUT PARAMETERS: THE PARTNER SUB-TREE

Probability of partner being infected and probability of reinfection

The of chlamydia transmission rates 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 C). The Medline search and the studies are described in Appendix 4. 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 [75]. 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 RTIs are very high in the area, most likely increasing the susceptibility and infectiousness of genital infections. In our study, 21 (3%) were infected with *N gonorrhoea*, *T vaginalis* was identified in 131 (19%) women, bacterial vaginosis in 268 (38%) women and *Candida* species were identified by microscopy and/or culture in 416 (59%) of the women. Noteworthy, this is only a selection of conditions and not including any of the infections causing genital ulcer.

We have not modelled possible chlamydia infections in partners of uninfected women. In addition, we assumed that none of the male partners who are effectively treated reinfect their female partner before they themselves are cured.

Table C: 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%	[75]
2. STI clinic, UK. 97 M and 93 F index cases, half of their partners were tested	75%	75%	[76]
3. STI clinic, UK.404 chlamydia-infected ♀ reported 632 sexual contacts and 147 (23%) were tested	44%	-	[77]
4. Australian study, primary health care and specialist clinics. 87 M/F index cases w/chlamydia	52%	52%	[78]

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 [79]. 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 [14]. In a work-site-based study from Tanzania, 89% of men with chlamydia reported no symptoms [80]. In a study among young incarcerated minority males in the US, 10% of men with chlamydia had symptoms [81]. Two population based studies on urethritis in men from Tanzania showed that 35% of men with chlamydia and/or gonorrhoea were symptomatic [79]. As gonorrhoea is more often 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 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. We have plausible estimations for overall partner attendance, but there are no data for and it is difficult to estimate partner attendance in detail for subgroups of antenatal care attendees (see Box below). We have therefore modelled a mean value for the probability of partner notification and attendance to a health facility for all partners of the diagnosed females.

Factors which may influence partner notification and/or attendance

- If the antenatal care is prescribed 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)

The success of partner notification 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 use health statistics data from Botswana on partner notification within the syndromic approach. These data are in line with studies from other sub-Saharan countries on partner notification and attendance. There were 0.085 male STI contacts registered per female STI client in Botswana in 2002, demonstrating that partner notification is very poor [82]. 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 [83, 84]. 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 emphasize that the number of partners who will be notified by the women and subsequently attend a health facility is low.

The lower bound of partner notification and attendance with the POC test strategy represents the current partner attendance, whereas we used data from studies in developed countries as a basis

for the upper bound (Table D). Medline searches and the studies identified are described in Appendix 4. 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. 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% (0.0.09-0.65%).

Table D Partner notification and attendance to health facility:

Studies used as a basis for the modelled probability	Partners		Reference
	Notified	Attend	
Syndromic management/African countries			
Male partners per female STI client in Botswana		8.5%	[82]
Female STI clients in Uganda. A study to improve partner notification.		22%	[16]
Female STI clients in Uganda	4%		[14]
STI clients in South Africa		<20%	[85]
Diagnostic test/western countries			
STI clients in the Netherlands. Optimal conditions.		60-82%	[86]
STI clients in the UK. Optimal conditions.		<65%	[87]
Modelled probability of partner attendance			
Syndromic approach strategy		8.5% (5-15%)	
Diagnostic test strategy		50.0% (35-65%)	

Probability of symptomatic males seeking other care and being cured

Symptomatic males may seek care independently of their pregnant partner, and they may subsequently be adequately managed or not. Data on health care seeking among symptomatic males is scarce. Buve *et al*. has reported from Tanzania that 51% of males and females with genital discharge or genital ulcer sought care [79]. Importantly, 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, of the male respondents who ever had STI symptoms, 85% 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 [37]. However, the number of symptomatic episodes among these males is not reported. In conclusion, data to estimate other health care seeking among symptomatic partners are very uncertain. The expert panel based their estimates on a) available studies, b) their common clinical experience (for example that many patients don't seek health care before their symptoms are severe), c) knowledge of and literature on the wide use of alternative and traditional medicine in the population, and on discussions with nurses in the primary health care. Based on the limited data and on expert opinions, we estimate 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.

The cure rates among these symptomatic males who seek 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: 63% were diagnosed correctly, 73% were prescribed correct treatment and 84% were compliant [79]. In an observational study from primary health care in Botswana, adequate history taking and clinical examination among male STI clients was found in 54% and 57% of the cases [83]. Of the males who - often on scanty evidence – were diagnosed with urethral discharge syndrome, 91% received an appropriate prescription. Compliance was not measured in this study, and the authors note that the 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 expert panel agreed that this is a parameter with a large degree of uncertainty, and estimated that 50% (30-70%) of the symptomatic males who seek care independently are cured for

their chlamydia infection.. They based their estimate on a) the limited data available, b) their knowledge of and experience from primary health care in Botswana and other sub-Saharan countries and c) on discussions with nurses in the primary health care and other resource persons. In the model 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

The 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. In the first study among 33 males with urethral discharge, 70% were prescribed ceftriaxone for gonorrhoea and 76% were prescribed doxycycline for chlamydia [84]. In the second study, all 32 males with urethral discharge syndrome were prescribed ceftriaxone and doxycycline [83]. We have not identified studies on quality of prescription to partners, and we therefore assumed that the probability of correct prescription will be within the range of the identified studies of index patients (0.85, 0.76-1.00).

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 point-of-care test is positive than with the syndromic approach. Cost-effectiveness analyses of chlamydia screening from developed countries are all operating with 100% correct prescription. We base the upper bound of the probability of correct prescription with the test strategy on studies these cost evaluations [55]. The expert panel assumed that if a point-of-care test for chlamydia is positive, it is realistic with a 93% (85-100%) probability of prescription of treatment. The nurses may forget

the prescription or prescribe ineffective drugs, but it is likely that correct drug is prescribed to 14 of 15 partners of test positive attendees.

Probability of compliance and drug effectiveness among male partners

In Botswana, the standard treatment for chlamydia in males is doxycycline 100 mg tablets twice daily in one week. We have also modelled directly observed treatment with 1g azitromycin, which may be considered to improve compliance to the treatment.

It has been shown that full compliance to doxycycline may not be necessary to obtain a cure. We have not found useful data on compliance from developing countries, and we did not identify any studies on compliance and cure rates in partners. The probabilities used for the syndromic management strategy represents the experts opinion of the local conditions. The panel assumed that with the doxycycline regimen, partners of patients with a positive chlamydia test will be more compliant than partners of patients diagnosed with vaginal discharge syndrome. They 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 of compliance to and effectiveness of doxycycline with the point-of-care strategy is identical to the estimate of the current level, whereas the upper bound is based on original studies and reviews from developing 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.

RESOURCE CONSEQUENCES AND COST MEASURES

Diagnosis and treatment of chlamydia in pregnancy takes place within the framework of the antenatal care services and the STI management program. 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}). Currently available point-of-care tests cost from US$ 0.85-7.00 [11, 26]. We evaluated direct test costs from US$0.5-4.0, as cheaper tests may be available in the near future. We did not include costs of training needs for the staff undertaking the test. Introducing the use of POC tests to diagnose chlamydia in pregnancy will benefit from two existing programmes: the antenatal care programme and the STI management programme. At the women's first antenatal visit, they undergo a clinical examination , urine is checked with a dip-stick, and blood is drawn for Hb, blood group, RH-factor, syphilis and HIV test. Taking a specimen and performing the POC test can relatively easily be incorporated in this routine. Additionally, the syndromic approach has been the established management of STIs in sub-Saharan Africa for decades, and requires frequent training and supervision of health personnel. A shift in the diagnostic strategy of chlamydia in antenatal care fits well within the ongoing activities of the national STI management programmes.

In the base case analysis, we used drug and salary costs from Botswana, while upper and lower ranges for the costs were estimated and evaluated in the sensitivity analyses to ensure relevance to countries with different personnel costs. Drug costs for erythromycin and doxycycline were calculated on the basis of accounting data from the Technical Support Services, Ministry of Health. The cost of azithromycin and upper and lower prices for the treatment regimens were collected from the International Drug Price Indicator Guide (102). The cost of testing and dispensing

were based on government salaries of health personnel, and registration and estimates of time used on procedures at the clinics. We used a salary range of +-50% to estimate the extent to which the expenditures for health personnel affected the results. The intention with this uncertainty range is to ensure relevance of the analysis in countries other than Botswana, and to cover the uncertainty regarding the time spent to perform the procedures. Costs from Botswana were obtained in 2006 Botswana Pula (BWP) and converted to US dollars using average currency exchange rates for 2006 (BWP1 = USD0.18). Details of the modeled costs are shown in Table 3.

We assumed 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 programmes, as expenses related to the building (e.g. power, rates), and costs associated with administration, transport, maintenance, cleaning etc. Intangible costs such as work time and leisure time forgone for care-givers and patients are not estimated. The attendees are routinely coming to the clinic, and the individuals' costs (travel costs and expenditure on goods and services) will not be affected by the STI management strategy.

SENSITIVITY ANALYSIS

To test the robustness of model results, we undertook a range of sensitivity analyses. We first explored the consequences of parameter uncertainties in one-way sensitivity analyses, where one parameter at a time was varied up and down within the pre-specified uncertainty bounds while maintaining the others at their base-case values (Table 1-2). In these analyses, testing all new antenatal care attendees with a 50-85% sensitive POC test was compared to syndromic management in the same population, with azithromycin as treatment for *C trachomatis* infections in pregnancy. We also performed probabilistic sensitivity analyses using Monte Carlo simulation, allowing the effects of joint uncertainty across all the parameters of the model to be considered [62]. Universal

testing of antenatal care attendees, first with a 50% and then a 75% sensitive POC test, was compared to syndromic management, using azithromycin as the drug of choice. We adopted beta distributions for the probabilities to constrain the values between zero and one, and gamma distributions for the costs because of their skewness. The probabilities in the two strategies were linked to account for interdependencies.The model was run 10 000 times.

Results

Health outcome and costs

Choice of antibiotics

In an antenatal care population of 100 000 attendees with a 7.5% chlamydia prevalence, syndromic management and treatment with erythromycin would entail a total cost of $54 400 and result in 800 cases of chlamydia cured ($66 per cured case) (Table 3). Replacing erythromycin with azithromycin would entail a total cost of $31 400 and result in 1 500 cases cured ($21 per cured case). In all scenarios, single-dose treatment with azithromycin implied lower cost and greater effectiveness than did treatment with erythromycin (Table 3). Therefore in the next sections we compare POC testing with the syndromic approach and universal versus age-based selective management using only the azithromycin treatment.

POC tests versus the syndromic approach

Testing all attendees with a 50% sensitive POC test priced at $0.85 would cost $106 800 and result in 2 400 *C trachomatis* infections cured per 100 000 women ($87 per additional case cured) (Table 3). With increasing test sensitivity, the number of cases cured would increase further, while the cost of the programme would remain virtually unchanged, reducing the incremental cost per cured case.

Universal or selective management

Restricting syndromic management or testing for chlamydia to teenage attendees would entail the lowest cost per case cured: $10 with the syndromic approach, $22 with a 50% sensitive POC test, and $15 with a 75% sensitive POC test (Table 3). Selective compared to universal syndromic management implies lower programme costs but results in fewer infections cured – as fewer women are included – and the same applies to the use of POC tests (Table 3). Reserving chlamydia treatment to teenagers would reduce the programme costs of syndromic management by 80%, but also reduce the number of cases cured by about 60%. Using a 75% sensitive POC test among teenagers, however, would be as effective as the syndromic management of chlamydia among all attendees, and the programme cost would be reduced from $31 400 to $22 425 (Table 3).

Overtreatment and partner management

In a population of 100 000 pregnant women, syndromic management and azithromycin treatment would result in 1 500 cured cases, although 29 900 individuals would be treated unnecessarily (Table 4). The treatment costs would be $31 400, 90% of which represents treatment of uninfected individuals. Introducing the testing of all attendees with a 50% or 75% sensitive POC test would result in 2 400 or 3 500 cured infections and 1 790 or 1 870 individuals unnecessarily treated. Furthermore, drug costs wasted on uninfected individuals would be reduced by 95%. Selectively testing attendees less than 20 years of age with a 50% or 75%sensitive test would imply 980 or 1 460 cases of chlamydia cured and 290 or 310 individuals unnecessarily treated, reducing drug wastage to 1% of the current level.

With syndromic management, 140 of the estimated 6 000 infected partners would be successfully treated (Table 5). Using a 50% or 75% POC test would increase this number to 570 or 850, which also would reduce reinfection rates. The majority of attendees diagnosed with syndromic approach are uninfected, and increasing partner attendance from the current 8.5% to 50% would result in 1 200 more cases cured per 100 000 attendees – while 11 700 additional uninfected partners would be unnecessarily treated. Increasing partner attendance to 50% when using 50% or 75% sensitive POC tests would result in 1 300 or 2 100 more cases cured, while 700 or 900 additional partners would be treated unnecessarily.

Model uncertainty

In the one-way sensitivity analyses, the cost of the POC test had its greatest impact on the incremental cost per case cured of introducing POC tests (Figure 2). High chlamydia prevalences result in the lowest incremental cost per additional case cured; decreasing from $91.80 in populations with 3% prevalence to $11.00 in populations with 31% prevalence (Table 6). The probability of a partner being notified and attend health care with the POC-test strategy was also an importanat factor; the incremental cost per additional case cured ranged from $69.90 with poor attendance to $18.10 with optimal performance. For the remaining model parameters, realistic changes in values made little difference to the results.

As for the probabilistic sensitivity analyses, using POC tests was more effective and more costly than was the syndromic approach in practically all model iterations. The incremental number of infections cured with a 50% or 75% sensitive POC tests varied from -250 to 4 100 or from 500 to 7 200 per 100 000 women screened. The additional cost ranged from $ 58 700 to $94 700 or from $ 60 800 to $96 200. In Botswana, health authorities currently pay about $66 per cured infection with

C trachomatis. Adopting this willingness-to-pay threshold, replacing syndromic management with POC tests of all attendees had a 29% probability of being cost-effective with a 50% sensitive test and 94% with a 75% sensitive test (Figure 3).

Discussion

The results of this study indicate that there may be substantial benefits in changing current diagnostic and treatment strategies for chlamydia in antenatal care in sub-Saharan Africa. The prevailing syndromic management of all attendees appears to be the least effective; it incurs high costs per case cured and entails considerable overtreatment.

The study is limited by uncertainties in several of the model parameters. There is a paucity of high-quality studies providing data relevant for sub-Saharan Africa, and many probabilities are based partly on expert advice. For the POC-test strategy, the level of correct prescription, patient compliance and partner notification have a high degree of uncertainty, and were provided with broad uncertainty ranges. The sensitivity analyses show that partner notification with POC tests is important for the effectiveness of the strategy, also indicating the potential impact of strategies to improve partner notification. The cost of the POC test, which was the largest source of variation in the results, will be known by authorities who consider implementating a POC-test strategy.

Large evidence gaps and conflicting evidence exist regarding chlamydia-related complications and their economic consequences.[89, 90] Because of this lack of knowledge, especially for developing countries, cured infections was used as the effect measure; thus important health benefits of case detection and treatment are not captured in this analysis. 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 allocation

should be highly relevant to health policy makers. If successful chlamydia treatment reduces complications such as neonatal infections and post-partum infections, or reduces HIV transmission, [5, 6] it would strengthen the conclusions of this study.[52]

To our knowledge, no studies in resource-poor settings have explored the costs and health consequences of chlamydia management strategies in pregnancy. One study has estimated the incremental cost-effectiveness of using POC tests for chlamydia and gonorrhoea among sex workers in Benin. Compared to syndromic management, such tests were cost-effective; averting HIV infections and decreasing inappropriate treatment.[26] Reviews of economic evaluations, mainly from developed countries, indicate that chlamydia screening is cost-effective, depending on prevalence; azithromycin is cost-effective; and partner notification is essential.[52, 62] The studies showed considerable variability with regard to probabilities used, complications and costing considered, and were hampered by methodological problems. The reviews point out the need for more data, particularly on the risk of complications.

We used a static model to evaluate the chlamydia management of antenatal care attendees, a relatively small, non-core group within the total population. Static models assume constant infection prevalence, even when strategies result in fewer or more infections being cured. In contrast, dynamic models incorporate the impact of changes in strategy on infection prevalence. In recent years, the use of dynamic models has been advocated.[62, 23] However, chlamydia programmes targeting pregnant women are less likely to lower prevalence, and have been specifically mentioned as an example in which static models may be the preferred option.[54]

Botswana was used as the case for this analysis, but the model should be applicable to other sub-Saharan countries. In the majority of countries in the region, 70% or more of pregnant women attend antenatal care at least once,[54] providing a convenient framework for diagnosis, treatment

and follow-up. Botswana is classified as “upper-middle income”, but the cost estimates will nevertheless be applicable to less wealthy settings with lower labour costs. The cost drivers in the model are POC tests and drugs purchased in international markets, and these prices will be relatively similar across countries. The sensitivity analysis indicates how higher or lower parameter values would change the results. To the extent that model data differ from those of other countries, the analysis can be revised on the basis of local data.

Improving maternal and perinatal conditions and combating HIV/AIDS received substantial attention in the Millennium Declaration.[91, 92] 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.[93] Treatment of STIs is a strategy area that has already been prioritized in sub-Saharan Africa.[94] 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.

First, single-dose treatment with azithromycin should be preferred, providing lower costs and higher efficacy than does the week-long erythromycin regimen. Azithromycin is safe in pregnancy, with fewer side effects and less interaction with other drugs.[42] Second, POC tests are necessary to improve effectiveness and reduce excessive overtreatment with the current management. In Botswana, the direct cost of introducing POC tests in antenatal care would increase the total health expenditure by 0.006%, an investment which may be more than offset by the reduced cost of the medical consequences of infection. Third, targeted partner notification is a good argument for introducing specific POC tests. Managing sexual partners of STI patients is essential to prevent reinfection, cure partners, break the chain of transmission and prevent complications;[12] 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.[12, 17] If POC tests are introduced, however, patient-delivered medication or information for partners should be considered.[66] Finally, the use of POC tests entails lowest incremental cost per case cured in populations with high prevalence. Adoption of age-restricted chlamydia treatment will entail lower programme 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 programmes in sub-Saharan Africa. Before recommending the routine use of POC tests in developing countries, carefully designed studies of their effectiveness are needed, and modelling studies can be used to help design and interpret them.

Conclusion

The results of this study indicate that sub-Saharan countries can substantially improve the management of chlamydia in antenatal care. Changes in diagnostic and treatment strategies may improve maternal and infant health as well as resource use.

Key messages

- The use of single-dose azithromycin for the treatment of chlamydia in pregnancy was more effective and less costly than is the use of erythromycin.
- Moderately sensitive but highly specific POC tests may substantially improve case detection and treatment, and dramatically reduce the massive overtreatment that exists with syndromic approach.

- The use of POC tests will entail lowest incremental cost per case cured in high-prevalence settings, and their effectiveness will increase with optimal partner notification.
- Testing all teenagers with a 75% sensitive POC test was equally effective and less costly than the current syndromic management strategy was.

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Competing interests

All authors: none declared. As the corresponding author, Maria Romoren states having full access to all the data in the study and the final responsibility to submit for publication.

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Contributors

M Romoren and I S Kristiansen designed the decision analytic model. Data collection was undertaken by M Romoren, F Hussein and T W Steen; the epidemiological study in Gaborone was planned and conducted by M Romoren, M Velauthapillai, J Sundby and P Hjortdahl. Data were analysed by M Romoren, and interpreted by M Romoren and I S Kristiansen. The manuscript was written by M Romoren, and all authors have proved the final version.

Table 1 Core issues in the economic evaluation

Research question	In the management of chlamydia infection among antenatal care attendees, what are the incremental costs and health benefits of a) Replacing syndromic management with point-of-care tests? b) Replacing erythromycin with azithromycin treatment c) Replacing universal management with an age-based selective management strategy?
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
Sensitivity analyses	One-way and probabilistic sensitivity analyses

Table 1 Model probabilities

Parameter	Probability		Source
	Base-case value	Lower and upper bounds	
Probabilities common to both strategies			
Chlamydia trachomatis prevalence			
Prevalence among all antenatal care attendees	0.075	0.06-0.10	A
Prevalence among attendees < 30 years	0.093	0.07-0.12	A
Prevalence among attendees < 20 years	0.158	0.09-0.26	A
Chlamydia trachomatis transmission rate	0.80	0.50-0.96	Ref w1-w4, B
Infected male with symptomatic infection	0.15	0.10-0.20	Ref w10-w12, B
Symptomatic male seeking care independently	0.50	0.30-0.70	Ref w12, w13, B
Symptomatic male cured independently	0.50	0.30-0.70	Ref w12, w13, B
Variables in the syndromic approach strategy			
Syndromic approach sensitivity	0.49	0.36-0.62	A
Syndromic approach specificity	0.65	0.61-0.69	A
Prescription of treatment to diagnosed attendee	0.85	0.79-0.90	Ref 14, A
Female compliant to erythromycin and drug effectiveness	0.50	0.30-0.70	Ref 14, w14, w15, A, B
Female compliant to azithromycin and drug effectiveness	0.95	0.88-1.00	Ref w14-w17
Male partner notified and attended clinic	0.09	0.06-0.11	Ref w11, w12, w18-w21
Prescription of treatment to attending partner	0.85	0.76-1.00	Ref w22, w23, B
Male compliant to doxycycline and drug effectiveness	0.80	0.60-1.00	Ref w15, w16, B
Variables in the point-of-care strategy			
Point–of-care test sensitivity	0.75	0.50-0.85	Ref 9, 10, 17, w5, w24
Point-of-care test specificity	0.985	0.97-1.00	Ref 9, 10, 17, w24
Prescription of treatment to diagnosed attendee	0.93	0.85-1.00	Ref 14, 22, 23, A, B
Female compliant to erythromycin and drug effectiveness	0.86	0.50-0.95	Ref 14, w14, w15, A, B
Female compliant to azithromycin and drug effectiveness	0.95	0.88-1.00	Ref w14-w17
Male partner notified and attends clinic	0.25	0.09-0.65	Ref w11, w12, w18-w21, w25, w26, B
Prescription of treatment to attending partner	0.93	0.85-1.00	Ref 22, 23, w22, w23, w27, B
Male compliant to doxycycline and drug effectiveness	0.90	0.80-1.00	Ref w15, w16, B

A = Data from the original study among antenatal care attendees in Botswana; B = expert judgment. Further supporting evidence is presented in the technical report.

Table 2 Model costs (2006 US$)

Resources used	Base-case value	Lower and upper bounds	Unit	Source
Personnel costs				
Pharmacy technician	4.95	2.48-7.43	$/hour	Ref w6, w7
Lay worker	1.98	0.99-2.97	$/hour	Ref w6, w7
Dispensing (3 minutes x $C_{pharmacy\ technician}$)	0.25	0.12-0.37	$/episode	A
Testing (5 minutes x $C_{lay\ worker}$)	0.17	0.08-0.25	$/episode	A
Unit costs				
Erythromycin	1.49	0.37-6.6	$/drug regimen	Ref w8, w9
Azithromycin	0.74	0.43-1.65	$/drug regimen	Ref w9
Doxycycline	0.25	0.11-1.56	$/drug regimen	Ref w8, w9
POC test	0.85	0.50-4.00	$/test	Ref 7, 18
Treatment (cost of drug + cost of dispensing)*				
Erythromycin treatment	1.74	0.49-6.97	$/episode	
Azithromycin treatment	0.98	0.55-2.02	$/episode	
Doxycycline treatment	0.50	0.23-1.93	$/episode	
Testing with POC test (cost of test + cost of testing)†	1.02	0.58-4.25	$/episode	

A = Data from the original study among antenatal care attendees in Botswana, C = Cost, POC = point-of-care
*Modelled costs for the syndromic management strategy and the POC-test strategy
† Modelled additional costs for the POC-test strategy

Table 3: Testing all women with point-of-care (POC) tests compared to syndromic approach (SA) – according to treatment regimen, universal- or age-based management and test sensitivity. Expected and incremental costs and effects per 1 000 attendees included in the programme, and total programme costs and effects in a population of 100 000 antenatal care attendees.*

Strategy		Cost (US$)	Incremental cost (US$)	Effectiveness (cured cases)			Incremental effectiveness (cured cases)	Cost per cured case (US$)	Incremental cost per cured case (US$)	Total programme costs (US$)	Total programme effectiveness (cured cases)
				♀	♂	Total					
Erythromycin											
Including all	**SA**	544		7	2	8		66		54 400	800
	POC 0.50	1 104	560	15	6	22	13	51	42	110 400	2 200
	POC 0.65	1 124	579	20	8	28	20	40	29	112 400	2 800
	POC 0.75	1 137	592	23	9	32	24	35	25	113 700	3 200
	POC 0.85	1 150	605	26	10	36	28	32	22	115 000	3 600
Including <30	**SA**	548		8	2	10		54		40 600	700
	POC 0.50	1 119	571	19	8	27	17	42	35	82 800	2 000
	POC 0.65	1 143	595	25	10	35	24	33	24	84 600	2 600
	POC 0.75	1 159	611	29	11	40	30	29	21	85 800	3 000
	POC 0.85	1 176	627	32	13	45	35	26	18	87 000	3 300
Including <20	**SA**	562		14	4	17		32		11 000	300
	POC 0.50	1 174	612	32	13	45	28	26	22	22 900	900
	POC 0.65	1 215	653	42	17	59	41	21	16	23 700	1 200
	POC 0.75	1 242	680	49	19	68	50	18	14	24 200	1 300
	POC 0.85	1 269	707	55	22	77	59	17	12	24 700	1 500
Azithromycin											
Including all	**SA**	314		12	3	15		21		31 400	1 500
	POC 0.50	1 068	754	17	7	24	9	45	87	106 800	2 400
	POC 0.65	1 080	766	22	9	31	16	35	49	108 000	3 100
	POC 0.75	1 088	773	25	10	35	20	31	38	108 800	3 500
	POC 0.85	1 095	781	29	11	40	25	27	31	109 500	4 000
Including <30	**SA**	316		15	3	19		17		23 400	1 400
	POC 0.50	1 077	761	21	8	29	11	37	71	79 700	2 100
	POC 0.65	1 092	775	27	11	38	19	29	40	80 800	2 800
	POC 0.75	1 101	785	32	12	44	25	25	31	81 500	3 300
	POC 0.85	1 111	794	36	14	49	31	22	26	82 200	3 600
Including <20	**SA**	324		26	5	32		10		6 300	600
	POC 0.50	1 110	785	36	14	50	18	22	43	21 600	1 000
	POC 0.65	1 130	810	46	18	65	33	18	25	22 000	1 300
	POC 0.75	1 150	830	54	21	75	43	15	19	22 400	1 500
	POC 0.85	1 170	840	61	23	84	53	14	16	22 800	1 600

*Assuming that 19.5% of the attendees are less than 20 years of age and 74.0% are less than 30, and a *C trachomatis* prevalence of 15.8% among attendees less than 20 years of age and 9.3% among attendees less than 30 and 7.5% in the general population

Table 4: The number of female and male cases cured, the number of patients overtreated, total costs, drug costs* and costs of drug wastage†. Testing all women with a 50% or 75% sensitive point-of-care (POC) test compared to syndromic approach in a population of 100 000 antenatal care attendees‡.

Strategy	Cases cured (n)	Overtreatment (n)	Cost (US$)	Drug costs (US$)	Drug wastage		
					(US$)	% of drug costs	% of total costs
Syndromic approach	1 500	29 910	31 400	31 400	28 240	90%	90%
Using POC tests (50% sensitivity)	2 400	1 790	106 800	5 300	1 520	29%	1%
Using POC tests (75% sensitivity)	3 500	1 870	108 800	7 200	1 560	22%	1%

*Azithromycin treatment of pregnant women, doxycycline treatment of partners
†Cost of drug wastage = monetary cost of treating uninfected antenatal care attendees or uninfected partners
‡Assuming a *C trachomatis* prevalence of 7.5% in the general population

Table 5: Expected number of antenatal care attendees and their partners diagnosed, treated* and cured. Testing all women with a 50% or 75% sensitive point-of-care test compared to syndromic approach in a population of 100 000 antenatal care attendees†.

Strategy	Women diagnosed with chlamydia (n)		Women prescribed treatment (n)		Women initially cured (n)	Women re-infected		Women cured (n)	Partners notified and attended			Partners treated			Partners cured (n)
									♀ True positive (n)		♀ False positive (n)	♀ True positive (n)		♀ False positive (n)	
	True pos	False pos	True pos	False pos		n	(%)		Partner CT+	Partner CT-	Partner CT-	Partner CT+	Partner CT-	Partner CT-	
Syndromic approach	3 680	32 380	3 120	27 520	2 970	1 720	(58)	1 240	250	62	2 750	210	50	2 340	140
POC (50% test sensitivity)	3 750	1 390	3 490	1 290	3 313	1 620	(49)	1 700	750	190	350	700	170	320	570
POC (75% test sensitivity)	5 630	1 390	5 230	1 290	4 970	2 430	(49)	2 540	1130	280	350	1 050	260	320	850

CT+, *C trachomatis* infected; CT-, *C trachomatis* uninfected; SA, Syndromic approach; POC, Using point-of-care tests
*Azithromycin treatment to pregnant women, doxycycline treatment to partners
† Assuming a *C trachomatis* prevalence of 7.5% in the general population

Table 6 Sensitivity analysis: cost per additional case cured with a POC test compared to syndromic approach under different assumptions about model parameters*

Variable	Parameter range		Cost (US$) per additional case cured with POC-test strategy†	
	Lower bound	Upper bound	Lower bound	Upper bound
Probabilities common for both strategies				
Chlamydia trachomatis prevalence	0.03	0.31	91.80	11.00
Chlamydia trachomatis transmission probability	0.50	0.96	41.50	35.40
Compliance to azithromycin and drug effectiveness	0.88	1.00	40.90	36.40
Infected male with symptomatic infection	0.10	0.20	37.90	38.40
Symptomatic male seeking care independently	0.30	0.70	37.80	38.40
Symptomatic male cured independently	0.30	0.70	37.80	38.40
Probabilities in the syndromic approach strategy				
Syndromic approach sensitivity	0.36	0.62	32.40	46.50
Syndromic approach specificity	0.61	0.69	36.50	39.70
Prescription of treatment to test positive attendee	0.79	0.90	37.30	38.90
Male partner notified and attends clinic	0.06	0.11	37.00	39.30
Prescription of treatment to attending partner	0.76	1.00	36.1	40.70
Male compliant to doxycycline and drug effectiveness	0.60	1.00	37.20	39.10
Probabilities in the point-of-care strategy				
Point-of-care test sensitivity	0.50	0.85	86.80	31.30
Point-of-care test specificity	0.97	1.00	38.80	37.40
Prescription of treatment to test positive attendee	0.85	1.00	44.00	34.20
Male partner notified and attends clinic	0.09	0.65	69.90	18.10
Prescription of treatment to attending partner	0.85	1.00	38.90	37.70
Male compliant to doxycycline and drug effectiveness	0.80	1.00	41.60	35.20
Costs ($/unit)				
Cost of point-of-care test	0.50	4.00	20.90	193.40
Cost of treatment with azithromycin	0.43	1.65	41.80	27.30
Cost of treatment with doxycycline	0.11	1.56	37.50	38.20
Cost of testing	0.08	0.25	34.00	42.20
Cost of dispensing	0.12	0.37	39.70	36.60

*Chlamydia management of all antenatal care attendees. First-line treatment regimens: Azithromycin to pregnant women, doxycycline to males.
†Base-case results: The syndromic approach costs $21.00 per case cured; using POC tests costs $30.90 per case cured, and the incremental cost of testing all women with a POC test is $38.10 per additional case cured.

Figure legends

Figure 1 Key structure of the decision tree and its branches

Figure 2 Tornado diagram summarizing one-way sensitivity analyses in which testing all women with a POC test is compared with syndromic management of chlamydia among 100 000 antenatal care attendees.

Figure 3 Cost-effectiveness acceptability curves for testing all women with a POC test compared to syndromic management. The vertical line represents the current willingness to pay in Botswana (US$66).

Appendix 1

MEDLINE AND EMBASE SEARCHES FOR COST EVALUATIONS OF CHLAMYDIA SCREENING IN PREGNANCY

MEDLINE IN PROCESS 27.6.06

1. Chlamydia trachomatis.mp.(89)
2. pregnancy.mp. (3825)
3. cost effectiveness.mp. (618)
4. economic evaluation.mp. (113)
5. 1 and 2 and 3 (0)
6. 1 and 2 and 4 (0)
7. mp=title, original title, abstract, name of substance word

MEDLINE 27.6.06

1. Chlamydia trachomatis.mp. or exp Chlamydia trachomatis/ (9401)
2. pregnancy.mp. or exp Pregnancy/ (563782)
3. cost effectiveness.mp. or exp Cost-Benefit Analysis/ (44788)
4. 1 and 2 and 3 (46)

46 papers from 1987 to 2005 were identified and all abstracts read. 6 papers, of which four in English, presented cost evaluations of chlamydia testing among pregnant women.

- Rours et al. Use of pooled urine samples and automated DNA isolation to achieve improved sensitivity and cost-effectiveness of large-scale testing for Chlamydia trachomatis in pregnant women. Journal of clinical microbiology, Vol. 43, 2005.
  The authors compare costs per chlamydial infection detected with individual and pooled urine samples using different nucleic acid amplification test strategies. The urines are collected from pregnant women, but due to the temporary effectiveness measures the analysis is not specific for this patient group.
- Postma et al. [Screening for asymptomatic Chlamydia trachomatis infection in pregnancy; cost-effectiveness favourable at a minimum prevalence rate of 3% or more.] Ned Tijdschr Geneeskd, Vol 144, 2000.
  The paper is in Dutch. The authors present a pharmaco-economic model analysis of screening for chlamydia in pregnancy. The test used in the model was a ligase chain reaction test, infection was treated with erythromycin or amoxicillin, and the cost of major complications averted (neonatal pneumonia and conjunctivitis, pelvic inflammatory disease, extrauterine pregnancy, infertility, chronic pelvic pain) was calculated. As far as I can understand, the source for the outcomes averted is another cost-effectiveness analysis.
- Postma et al. Socio-economic aspects of extended STD screening in pregnancy. AIDS Care, Vol 12, 2000.
- Hueston and Lenhart. A decision analysis to guide antibiotic selection for Chlamydia infection during pregnancy. Archives of family medicine, Vol. 6, 1997.
  A decision analysis model to determine the cost of treatment and treatment failure rates of different drug treatment strategies. Treatment with amoxicillin, followed by azitromycin for non-responders was the most cost-effective strategy. The study population was pregnant women, but due to the temporary effectiveness measures the analysis is not specific for pregnancy.
- Ottesen et al. [Chlamydia trachomatis in pregnant women in the country of Vestjaelland. Prevalence, prevention of perinatal transmission and cost-effectiveness of screening.] Ugeskrift for Laeger, Vol 158, 1996.

The paper is in Danish. This is a paper on prevalence of chlamydia among pregnant women in Vestjaelland. Of 339 women, 10 had chlamydia. All were treated with erythromycin, and among the 7 children who were tested, none had chlamydia. The authors provide a simple cost calculation of chlamydia testing in pregnancy, but not a formal cost evaluation.

- Nettleman and Bell. Cost-effectiveness of prenatal testing for Chlamydia trachomatis. Am J Obstet Gynecol, Vol 164, 1991.
  Nettleman and Bell analyse culture and direct antigen testing of pregnant women assuming different prevalences of infection. Probabilities of major outcomes averted were derived from published literature (1979-87). Available abstracts of these papers were collected. The authors conclude that screening all pregnant women is not cost-effective, but the excess cost was modest when direct antigen tests were used.
  Probability conjunctivitis 0.25
  Probability pneumonia 0.15, of which 75% receive outpatient therapy and 25% are hospitalized
  Probability post-partum endometritis/salpingitis 0.1, of whom 0.07 result in ectopic pregnancy
  Probability partner infected 1.0
  Probability epididymitis 0.04

EMBASE (1980 to 2006 week 30) 2.8.06

1. Chlamydia trachomatis.mp. or exp Chlamydia Trachomatis/ (9365)
2. exp "COST OF REPRODUCTION"/ or exp "HOSPITAL COST"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST UTILITY ANALYSIS"/ or exp "HOSPITAL RUNNING COST"/ or exp "DRUG COST"/ or exp "COST BENEFIT ANALYSIS"/ or exp "COST MINIMIZATION ANALYSIS"/ or exp "COST"/ or cost.mp. or exp "HEALTH CARE COST"/ (196953)
3. exp PREGNANCY/ or pregnancy.mp. (211574)
4. 1 and 2 and 3 (96)

Among the 96 identified papers, titles and relevant abstracts were read. The search yielded no papers not identified through Medline.

Appendix 2

LITERATURE SEARCHES FOR COST EVALUATIONS OF CHLAMYDIA SCREENING IN DEVELOPING COUNTRIES

MEDLINE IN PROCESS 7.8.06

1. Chlamydia trachomatis.mp. [mp=original title, abstract, name of substance word] (103)
2. Cost effectiveness.mp. [mp=original title, abstract, name of substance word] (596)
3. Cost.mp. [mp=title, original title, abstract, name of substance word] (4591)
4. 1 and 2 (3) None from developing countries
5. 1 and 3 (3) None from developing countries

MEDLINE 1 (1966-July week 4 2006)

1. exp Chlamydia trachomatis/ (7905)
2. exp "Costs and Cost Analysis"/ (126280)
3. exp Developing Countries/ (47278)
4. exp AFRICA/ (116999)
5. combine 1 and 2 (138)
6. combine 3 and 5 (0)
7. combine 4 and 5 (1)

Mayaud P. Grosskurth H. Changalucha J. Todd J. West B. Gabone R. Senkoro K. Rusizoka M. Laga M. Hayes R. et al. Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics. [Journal Article. Multicenter Study] *Bulletin of the World Health Organization. 73(5):621-30, 1995.*

MEDLINE 2 (1966-July week 4 2006)

1. Chlamydia trachomatis.mp. or *Chlamydia trachomatis (9495)
2. cost.mp. or *"Costs and Cost Analysis"/ (182891)
3. *Africa, Western/ or *Africa, Northern/ or *South Africa/ or *Africa, Eastern/ or africa.mp. or *Africa, Central/ or *"Africa South of the Sahara"/ or *Africa/ (57992)
4. developing countries.mp. or *Developing Countries/ (55890)
5. 1 and 2 and 3 (7) None were economic analyses
6. 1 and 2 and 4 (12)

EMBASE (1980-2004 week 25)

1. exp Chlamydia Trachomatis/ (7546)
2. exp "COST OF REPRODUCTION"/ or exp "HOSPITAL COST"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST UTILITY ANALYSIS"/ or exp "ENERGY COST"/ or exp "HOSPITAL RUNNING COST"/ or exp "COST CONTROL"/ or exp "DRUG COST"/ or exp "COST BENEFIT ANALYSIS"/ or exp "COST MINIMIZATION ANALYSIS"/ or exp "COST"/ or exp "HEALTH CARE COST"/ or exp "COST OF ILLNESS"/ (122117)
3. exp Developing Country/ (13917)
4. combine 1 and 2 (232)
5. combine 3 and 4 (5)

- Damasus-Awatai G. Freeman-Wang T. Human papilloma virus and cervical screening. [Journal: Review] *Current Opinion in Obstetrics & Gynecology. Vol. 15(6)(pp 473-477), 2003*
- Chen MY. Donovan B. Screening for genital **Chlamydia trachomatis** infection: Are men the forgotten reservoir?. [Journal: Editorial] . *Vol. (124-125)(pp 124-125).*

- Frick KD. Mecaskey JW. Resource allocation to prevent trachomatous low vision among older individuals in rural areas of less developed countries. [Journal: Review] *Documenta Ophthalmologica. Vol. 105(1)(pp 1-21), 2002*
- Frick KD. Colchero MA. **Cost-effectiveness** of alternative strategies to prevent trachomatous blindness. [Journal: Review] *Expert Review of Pharmacoeconomics & Outcomes Research. Vol. 2(3)(pp 219-228), 2002*
- Van der Veen F. Fransen L. **Drug**s for STD management in **developing** countries: Choice, procurement, **cost**, and financing. [Journal: Article] *Sexually Transmitted Infections. Vol. 74(SUPPL. 1)(pp S166-S174), 1998*

EMBASE (1980-2004 week 25)

1. exp Chlamydia Trachomatis/ (7546)
2. exp "COST OF REPRODUCTION"/ or exp "HOSPITAL COST"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST UTILITY ANALYSIS"/ or exp "ENERGY COST"/ or exp "HOSPITAL RUNNING COST"/ or exp "COST CONTROL"/ or exp "DRUG COST"/ or exp "COST BENEFIT ANALYSIS"/ or exp "COST MINIMIZATION ANALYSIS"/ or exp "COST"/ or exp "HEALTH CARE COST"/ or exp "COST OF ILLNESS"/ (122117)
3. exp AFRICA/ (42518)
4. combine 1 and 2 (232)
5. combine 3 and 4 (4)

- Pepin J. Mabey D. Sexually transmitted infections in **Africa**: Single dose treatment is now affordable. [Journal: Editorial] *Sexually Transmitted Infections. Vol. 79(6)(pp 432-434), 2003.*
- MacLachlan EW. Baganizi E. Bougoudogo F. Castle S. Mint-Youbba Z. Gorbach P. Parker K. Ryan CA. The feasibility of integrated STI prevalence and behaviour surveys in developing countries. [Journal: Article] *Sexually Transmitted Infections. Vol. 78(3)(pp 187-189), 2002*
- Mukenge-Tshibaka L. Alary M. Lowndes CM. Van Dyck E. Guedou A. Geraldo N. Anagonou S. Lafia E. Joly JR. Syndromic versus laboratory-based diagnosis of cervical infections among female sex workers in Benin: Implications of nonattendance for return visits. [Journal: Article] *Sexually Transmitted Diseases. Vol. 29(6)(pp 324-330), 2002*
- El-Shourbagy M. Abd-El-Maeboud K. Diab KM. El-Ghannam A. Nabegh L. Ammar S. Genital **Chlamydia trachomatis** infection in Egyptian women: Incidence among different clinical risk groups. [Journal: Article] *Journal of Obstetrics & Gynaecology Research. Vol. 22(5)(pp 467-472), 1996.*

EMBASE 2.8.06 (1980 to 2006 week 30)

1. Chlamydia trachomatis.mp. or exp Chlamydia Trachomatis/ (9365)
2. exp "COST OF REPRODUCTION"/ or exp "HOSPITAL COST"/ or exp "COST EFFECTIVENESS ANALYSIS"/ or exp "COST UTILITY ANALYSIS"/ or exp "HOSPITAL RUNNING COST"/ or exp "DRUG COST"/ or exp "COST BENEFIT ANALYSIS"/ or exp "COST MINIMIZATION ANALYSIS"/ or exp "COST"/ or cost.mp. or exp "HEALTH CARE COST"/ (196953)
3. developing countries.mp. or exp Developing Country/ (23427)
4. exp AFRICA/ or africa.mp. (59484)
5. 1 and 2 and 3 (20) All abstracts read, none were relevant.
6. 1 and 2 and 4 (14) All abstracts read, none were relevant.

Appendix 3

IMPROVING PUBLIC HEALTH CONTROL OF STIS IN BOTSWANA: METHODS OF THE EPIDEMIOLOGICAL STUDY

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 criterion 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 sociodemographic 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. Symptoms and signs of a reproductive tract infection were classified into defined syndromes following the national STI guidelines and were treated accordingly. Women

diagnosed with the vaginal discharge syndrome were treated for chlamydia, gonorrhoea, trichomoniasis, bacterial vaginosis and vulvovaginal candidiasis in accordance with the treatment guidelines.

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^{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* infection was defined as an individual with a positive LCR analysis, used as the reference standard when evaluating the syndromic approach.

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 x 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).

Data were analysed using the statistical package SPSS, Version 11. To evaluate the clinical diagnosis of chlamydia, univariate logistic regression analyses were used to assess the association between genital symptoms and signs and the laboratory-verified diagnosis. Socio-demographic risk factors and genital symptoms and signs which in univariate analysis were associated at a 0.2 level (p-value of odds ratios (OR)), were included in multivariate logistic regression analysis. The validities of the vaginal discharge algorithm were assessed by measuring sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and positive and negative predictive values (PPV and NPV), using the laboratory diagnosis of *C trachomatis* infection as the reference standard.

Appendix 4

MEDLINE SEARCHES FOR THE VARIABLES IN THE DECISION TREE

Nurses' adherence to prescription guidelines

Medline in process 20.6.06

1. Chlamydia trachomatis
2. Prescription
3. 1+2

No papers found

Medline 20.6.06

1. Chlamydia trachomatis.mp. or exp Chlamydia trachomatis/ 9381
2. prescription.mp. or exp Prescriptions, Drug/ 34 299
3. 1+2

7 papers identified. Titles and abstracts read, none were studies or reviews on drug prescription.

Compliance to prescribed treatment

Medline in process 13.6.06

1. Sexually transmitted diseases
2. Compliance
3. 1+2

No papers found

Medline 13.6.06

1. Sexually transmitted diseases.mp. or exp Sexually Transmitted Diseases/
2. Erythromycin.mp. or Erythromycin/
3. Compliance.mp. or *Compliance/ or *Patient Compliance/
4. 1+2+3

26 papers identified. Titles and abstracts read and if relevant, full text obtained.

Concordant infection

Medline in process 10.5.06

1. Chlamydia trachomatis
2. Sexual partners
3. 1 + 2

One paper identified, not on the topic of concurrent infections.

Medline 10.5.06

1. Chlamydia trachomatis
2. Sexual partners
3. 1 + 2

132 papers published from 2001-2006 identified. Titles and abstracts read and if relevant, full text obtained.

1. Quinn et al. report a study of 494 couples attending an STI clinic in the USA, 53 couples were concordantly infected with chlamydia, while in 48 couples one of the partners were infected. 78

females had chlamydia, of whom 53 (68%) of the male partners were infected (*95% CI 57-77% MR*). 76 males had chlamydia, of whom 53 (70% (*95% CI 59-79% MR*).) of the female partners were infected. Approximately 90% were steady partners, and the participants reported median 6 intercourses the last 30 days. The number of episodes of intercourse did not correlate with infection status.

2. Markos reports a concordance of chlamydia trachomatis between sexual partners of 0.75. The study was conducted in an STI clinic, UK. 97 males and 93 females were chlamydia positive, half of their partners were tested.
3. Manavi et al report that 404 women in their UK study were infected with chlamydia based on PCR. The women, who had sought care in an STI clinic, reported 632 contacts. 155 (23%) males attended the clinic and 147 were tested. Of these men, 64 (44%) had a chlamydia infection.
4. Mak et al report from their Australian study that 126 index cases had gonorrhea and 87 had chlamydia. 53% and 52% of the sexual contacts of the respective index cases who came to the health facility had a concordant infection.
5. In a Japanese study (Okazaki et al), the infection rate of chlamydia in 149 sexual partners with pregnant wives with c trachomatis diagnosed by antibody or antigen test. Antibody-positive rate was 60% (90/149 cases) and antigen positive rates was 7% (11/149). Noteworthy, the detected concordance seems to be dependent of the diagnostic test used.

Partner notification with syndromic approach

Medline 4.5.06

1. *Sexually Transmitted Diseases/ 8943
2. partner notification.mp. or exp Contact Tracing/ 1926
3. 1 and 2 232
4. exp Africa, Western/ or exp Africa, Northern/ or South Africa/ or exp Africa, Eastern/ or africa.mp. or exp Africa, Central/ or exp "Africa South of the Sahara"/ or exp Africa/ or exp Africa, Southern/ 120 871
5. 3 and 4 36

Abstracts on relevant papers obtained and read

1. A Cochrane review on partner referral strategies report the following: Only two studies were conducted in developing countries, one unpublished and one unrepresentative [Mathews et al. 2001]. All studies identified had some risk of bias, and none had pregnant women as index patients. In the unpublished study from South Africa reports with patient referral and contact cards that the STI clients reported mean 1.04 partners, while 0.18 partners were reported treated by the index patient. The other trial among patients with NGU resulted in 0.18 partners receiving treatment with the patient referral strategy.
2. A trial among STI clients from Uganda compared the efficacy of patient delivered partner medication with patient referral [Nuwaha et al. 2001]. STIs were diagnosed and managed according to the syndromic approach, and all patients were given IEC regarding the importance of partner treatment (5-10 min). Index patients were either given contact slips to pass to their sexual partners or medication to take to the partners. Index patients were asked to return to the clinic within 2 weeks and asked if they referred their partners/if the partner took the medication. In the medication group, 93 female patients reported 103 partners, and 86 (83%) partners were reported to have taken the medication. In the patient referral group, 94 female patients reported 104 partners, and 23 (22%) of these were referred. These results are from an optimal study setting, and may represent the highest partner treatment rates achievable.
3. Paxton et al report from Uganda that 4% of symptomatic women *notified* their partners (how many partners who sought care after being notified is not known) [Paxton et al. 1998].
4. A study in South Africa evaluated the effect of a video based health education strategy to improve partner notification [Mathews et al.]. The rate of contact cards returned *per index patient* in the control phase was 0.2, and increased to 0.27 in the intervention phase.

Partner notification with diagnostic testing (in pregnancy)

Medline 4.5.06

1.	*Chlamydia trachomatis/ or *Chlamydia/	5 913
2.	contact tracing.mp. or *Contact Tracing/ or*Sexual Partners/ or partner treatment.mp	3 477
3.	Pregnancy/	520 794
4.	1 and 2	101
5.	3 and 4	17

Abstracts on relevant papers obtained and read

1. According to the Cochrane review on partner referral strategies, contract referral is more effective than patient referral. In a study by Cleveland et al, partners attending the clinic increased from 0.31 to 0.62 per patient [Mathews et al. 2001].
2. In a study from Amsterdam, 60% of all male contacts of female STI clients were referred; 81.5% of the steady partners. The contact tracing strategy included a thorough interview and follow up by a public health nurse [van de Laar et al. 1997].
3. In a study from general practice in the UK, 65% of participants receiving practice nurse led partner notification had at least one partner treated [Low et al. 2006].

Appendix 5

LITERATURE REVIEWS: COMPLICATIONS OF CHLAMYDIA

We performed a (semi-) systematic literature review to get an overview of studies and other published material (and identify explicit knowledge on) the complications of *C trachomatis*-infection in pregnant and non-pregnant women in developing countries. The prevalence of *C trachomatis* and its complications in developing countries is likely to have other epidemiological characteristics than in the developed world. Unfortunately, due to lack of research and partly also lack of knowledge, opportune diagnosis and little technological resources, information from developing countries is virtually non-existing. We therefore also conducted literature searches on pregnancy-related complications among women in without restricting the search to developing countries.

The searches were performed in the largest biomedical literature bases: MEDLINE, EMBASE and The Cochrane Library. To limit the search, we selected the following main key words: *Chlamydia trachomatis* and *complications*. We also did a search for pregnancy related complications: *Chlamydia trachomatis* and *premature labour* or *premature infant* or *pregnancy complications.* We subsequently limited our searches by including *developing countries* as a key word. We also tried to vary the key words to avoid missing relevant literature (for example changing "developing countries" to "Africa" or "third world"). Abstracts of papers and reports identified as relevant in the searches were read, and we got access to and read papers and reports which we found having relevance to the described aim of the literature review. We also identified, collected and read papers, reports and books referred to in the originally identified

material (the snowball strategy). The content of the material collected is described in detail below.

All complications - developing countries

EMBASE (1980-2004 week 23)

KEY WORDS
Chlamydia trachomatis
Complications
Developing countries

1. exp Chlamydia Trachomatis, Subject Heading (7540)
2. exp NEUROLOGICAL COMPLICATION/ or exp UTERINE COMPLICATION/ or exp INFECTIOUS COMPLICATION/ or exp PEROPERATIVE COMPLICATION/ or exp POSTTRAUMATIC COMPLICATION/ or complications.mp. or exp INFECTION COMPLICATION/ or exp POSTOPERATIVE COMPLICATION/ or exp COMPLICATION/ or exp LABOR COMPLICATION/ or exp ANESTHESIA COMPLICATION/ or exp PREGNANCY COMPLICATION/ or exp LUNG COMPLICATION/ (359846)
3. developing countries.mp. or exp Developing Country/ (18749)
4. combine 1 and 2 and 3 (8)
5. of 8 abstracts read, we found two possibly relevant papers:

Update on the impact of Chlamydia trachomatis infection on male fertility. *Journal: Review. Gonzales et al., Andrologica. Vol. 36(1)(pp1-23), 2004*
This review has a focus on male infertility in the developed world. The authors describe several complications of *C trachomatis* also in women, with references (from the developed world):

- The incidence of the infection in women having spontaneous abortions is about 21% compared with 9% in the control group. When at least one partner of the couple is infected, the spontaneous abortion rate risis to 59% (Virgil et al, 2002)
- In a recent meta-analysis including 23 studies with a total of 2729 patients, the discriminative capacity of chlamydial antibody titres in the diagnosis of any tubal pathology was comparable with that of HSG in the diagnosis of tubal occlusion (Mol et al, 1997)
- Chlamydial infections are also acquired by the newborn during delivery and account for 25-50% of conjunctivitis and 10-20% of pneumonia in these children (Fenton, 2000)
- Routine screening of asymptomatic women for chlamydial infection and treating those identified as infected has been shown to reduce the incidence of PID (Scholes et al, 1996)
- There is some evidence that C trachomatis may contribute to pregnancy complications other than ectopic pregnancy, such as premature rupture of membranes, premature birth and low birth weight or stillbirth (Gravett et al, 1986)

Genital infections and reproductive health: Infertility and morbidity of mother and child in developing countries. *Bergstrom, Scandinavian Journal of Infectious Diseases, 1990*.
Abstract: Gonorrhea and chlamydia infection give few maternal problems during pregnancy but may be more important as a cause of puerperal endometritis-myometritis, which constitutes one of the leading causes of maternal death in many developing countries. The fetal/neonatal infant morbidity is affected by gonorrhea and chlamydia infection.

COCHRANE LIBRARY (7th of June 2004)

1. MeSH Chlamydia trachomatis (233)
2. MeSH Female genital diseases and pregnancy complications (9992)
3. Developing countries (309)
4. 1 and 2 and 3 (0)
5. 1 and 3 (1)

Diagnosis of ophthalmia neonatorum, *Winceslaus J, Goh BT, Dunlop EM, Mantell J, Woodland RM, Forsey T, Treharne JD, British Medical Journal Clinical Research Ed. 1987.*
Ninety consecutively seen babies with eye discharge in the first three weeks of life were examined. Four babies had "sticky eyes" with no evidence of ophthalmia and had uniformly negative cultures and test results for antichlamydial antibody; these babies were excluded. Of the 86 babies with ophthalmia neonatorum, Neisseria gonorrhoeae was isolated from eight, Chlamydia trachomatis from 44, other bacteria alone from 20, and 14 had negative cultures. Three babies with negative cultures had longstanding conjunctivitis and had been treated with chloramphenicol eye ointment; all had antichlamydial IgM antibodies, indicating that the conjunctivitis was chlamydial. Hence the total number of babies whose conjunctivitis was chlamydial was 47. The result of the Gram stained conjunctival smear correlated well with that of culture and final assessment by the microimmunofluorescence test, enabling an immediate presumptive diagnosis to be made of gonococcal, chlamydial, or bacterial conjunctivitis. Prompt and effective treatment of babies was started. Explanation to the mother and contact tracing were carried out when the confirmatory cultures and antibody tests were completed.

MEDLINE (1966-4th week of May 2004)

1. exp Chlamydia trachomatis/ (6997)
2. exp Developing Countries/ (42300)
3. exp PREGNANCY COMPLICATIONS, INFECTIOUS/ or exp PREGNANCY COMPLICATIONS/ or exp PREGNANCY COMPLICATIONS, NEOPLASTIC/ or exp POSTOPERATIVE COMPLICATIONS/ or exp PREGNANCY COMPLICATIONS, PARASITIC/ or exp LABOR COMPLICATIONS/ or exp PREGNANCY COMPLICATIONS, CARDIOVASCULAR/ or exp INTRAOPERATIVE COMPLICATIONS/ or exp PREGNANCY COMPLICATIONS, HEMATOLOGIC/ (481085)
4. 1 and 2 and 3 (1)

Frequency of Chlamydia trachomatis in pregnant women. *[Journal Article] Kirmani N. Hafiz S. Jafarey SN. JPMA - Journal of the Pakistan Medical Association. 44(3):73-4, 1994 Mar.*
Not relevant.

Preterm birth and low birth weight - developing countries

MEDLINE (1966-4th week of May 2004)

1. exp Chlamydia trachomatis/ (6997)
2. exp Labor, Premature/ or exp Pregnancy Outcome/ or exp Infant, Premature/ (49133)
3. 1 and 2 (90)
4. exp AFRICA/ (102054)
5. exp Developing Countries/ (42300)
6. 3 and 5 (0)
7. 3 and 4 (2)

1. el-Shourbagy M. Abd-el-Maeboud K. Diab KM. el-Ghannam A. Nabegh L. Ammar S. Genital **Chlamydia trachomatis** infection in Egyptian women: incidence among different clinical risk groups. [Journal Article] *Journal of Obstetrics & Gynaecology Research. 22(5):467-72, 1996 Oct.*
UI: 8987330

2. Donders GG. Desmyter J. De Wet DH. Van Assche FA. The association of gonorrhoea and syphilis with **premature** birth and low birthweight. [Journal Article] *Genitourinary Medicine. 69(2):98-101, 1993 Apr.*

Preterm birth and low birth weight - all countries

MEDLINE (1966-4th week of May 2004)

8. exp Chlamydia trachomatis/ (6997)
9. exp Labor, Premature/ or exp Pregnancy Outcome/ or exp Infant, Premature/ (49133)
10. 1 and 2 (90)
11. Limited to 11 full texts and 3 abstracts

Of 90 papers identified, we decided to limit our further reading to papers published in 1997 or later. This was due to the fact that we had read Andrews et al: The preterm prediction study, published in 2000, who summarizes findings from earlier years as "non conclusive" (see summary of the paper).

Of the 31 titles, we chose to read 11 full texts and three abstracts which were thought to be relevant.

Full text papers

1. **Effect of treatment for Chlamydia trachomatis during pregnancy.** *Rastogi et al, International Journal of Gynecology and Obstetrics 2002*. 15 patients were chlamydia

positive and successfully treated for CT (group 1). 26 patients were CT positive and not treated (group 2). 127 patients were CT negative (group 3). Results: The main duration of premature deliveries were lower in group 2 compared with group 1 (33.1 vs 35.5 weeks). Stillbirths were significantly higher in group 2 than group 3 (11.5% vs 4.7%). Weaknesses: few cases and no multiple regression to adjust for confounders. *Conclusion: Can not be used in our model.*

2. **Immunological aspects of genital chlamydia infections.** *Witkin, Best Practice & Clinical Obstetrics and Gynaecology 2002*. *Not relevant.*

3. **Influence of infection with Chlamdyia trachomatis on pregnancy outcome, infant health and life-long sequelae in infected offspring.** *Mårdh, Best Practice & Clinical Obstetrics and Gynaecology 2002*. Mårdh describes all possible complications with thorough literature references, although the quality of these studies is unknown there are no estimates on the prevalence of these complications.
   -Early spontaneous abortion (Indian study; women more likely to have chlamydial antigen detected in endometrial curettage samples than controls)
   -Late spontaneous abortion, recurrent spontaneous abortion
   -Studies have postulated an association between C trachomatis infection and both PROM and premature birth. Gravett et al (1986) found in a case-control study that chlamydia in mothers was associated with premature birth at <37 weeks (OR 4.4). A correlation has been demonstrated between adverse pregnancy outcome and anitchlamlydial serum IgM (but not IgG) antibodies, on the one hand, and adverse pregnancy ooutcome on the other (13 of 67 IgM+ and 8 of 99 IgM-). The authors assumed that women with a recent and probably acute ongoing chlamydial infection were at risk of preterm delivery. Statistical correlation between genital chlamydial infection in mothers has generally been performed late in pregnancy and often not adjusted for other known aetiological factors for prematurity, including infectious agents other than C trachomatis.

4. **The role of infection in preterm labour and delivery.** *Romero et al, Paediatric and Perinatal Epidemiology 2001.* The paper gives thorough theoretical background on the issue, with references. Re chlamydia: The role of C trachomatis as an intrauterine pathogen has not been clearly elucidated. This microorganism is an important course of cervicitis and has been recently isolated from amniotic fluid (ref). A case of congenital pneumonia caused by C trachomatis suggests that this micro-organism may be capable of causing ascending intra-amniotic infection (ref). The uncertainty about the role of C trachomatis in the aetiology of microbial invasion and intrauterine infection may be related to difficulties in isolating the micro-organisms from amniotic fluid with standard culture techniques. The use of PCR to detect specific sequences for this micro-organism should help resolve this question.

5. **Chlamydia trachomatis infection and the risk of perinatal mortality in Hungary.** *Nyari et al, Journal of Perinatal Medicine 2001.* Epidemiological study of C trachomatis infection among pregnant women admitted to the hospital before labor: 6156 women, prevalence of infection 5.9%. Bivariate analysis showed a slight, but significant difference between the rate of premature uterine activity that occurred in the infected group than in the non-infected (8.1 vs. 5.3). PROM occurred in 21% of the infected and 19.9 on the non-infected. Perinatal mortality occurred in 148 (2.4%) of all pregnancies. Multiple regression showed a higher risk of perinatal mortality among C trachomatis-infected women (OR 1.9), low birth weight (OR 1.7), no pervious delivery (OR 1.9) and

high rate of unemployment (1.5), adjusted for age, demographic and social status, C trachomatis infection, previous pregnancy, previous delivery, low birth weight, PROM, and intrauterine distress or growth retardation –but not adjusted for any other microbial infections.

6. **Chlamydia trachomatis seropositivity is associated both with stillbirth and early preterm delivery.** *Gencay et al, APMIS 2000.* A case "control" study which finds and association between C trachomatis antibodies and both stillbirth and preterm delivery, however not controlling for any confounding factors. The authors conclude that C trachomatis is an important agent associated with stillbirth and preterm delivery, making screening for genital chlamydial infection highly relevant especially when viewing the therapeutic possibilities. In mothers with stillbirth, the observed high IgG seropositivity rate indicates a past or persistent infection, whereas in extreme preterm delivery cases, the involvement of acute infection was suggested

	IgG	IgM	Tot
72 consecutive stillbirths	20(28%)	1(1%)	24(33)
48 preterm deliveries between week 23 and 29	6(13%)	4(8%)	9(19)
96 consecutive liveborn deliveries	10(10%)	0 -	10(10)

7. **The preterm prediction study: Association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth.** *Andrews et al, Am J Obst Gyn 2000.*
   This is a retrospective case-control study within The Preterm Prediction Study where 2929 pregnant women were evaluated longitudinally to determine risk factors for spontaneous preterm birth. This study consist of 117 case patients with a spontaneous preterm birth at <37 weeks with corresponding matched control subjects.
   After adjustment for risk factors for spontaneous preterm birth, women with C trachomatis infection at 24 weeks gestation were 2 times as likely as uninfected women to have a spontaneous preterm birth at <37 weeks gestation and 3 times as likely to have a spontaneous preterm birth at <35 weeks gestation. Whether universal screening and treatment for C trachomatis infection with a sensitive NAAT method for detection would significantly reduce spontaneous preterm delivery remains an unanswered question.

8. **A murine model for the study of Chlamydia trachomatis genital infections during pregnancy.** *Pal et al, Infection and immunity, May 1999.* In our murine model, we have shown that C trachomatis inoculated intra-vaginally on day 5 of gestation in mice infects the endometrium and the membranes of the yolk sac, resulting in early termination of pregnancy. This is not surprising since chlamydial endometritis commonly occurs during a genital infection and the ability of C trachomatis to infect amniotic cells has been demonstrated in vitro. Most likely, fetal membranes were affected following infection of the endometrium. It is possible that the direct damage to the fetal membranes resulting from the infection, in combination with endotoxin activity is a significant factor in the premature termination of pregnancy.

9. Maternal IgM at mid-trimester and preterm delivery. Numazaki et al, The Lancet 1999. A letter reporting a study with 178 pregnant women of which IgM was detected in ten at 10-22 weeks of gestation. None of these had any complications during pregnancy or labor. Contrarily, they report that the numbers of perinatal complications including preterm delivery were significantly higher in IgG and IgA antibody positive pregnant women at 30 weeks of gestation than in seronegative pregnant women. *Insufficient information to evaluate the quality of the referred study.*

10. **Chlamydia trachomatis: impact on human reproduction.** *Paavonen nad Eggert-Kruse, Human Reproduction Update 1999.* The paper gives thorough theoretical background on the issue, with references. Chlamydial PID is the most common preventable cause of infertility and adverse pregnancy outcome. Based on the available evidence, approximately 20% of women with chlamydial lower genital tract infection will develop PID, approximately 4% will develop chronic pelvic pain, 3% infertility and 2% adverse pregnancy outcome. However, these estimates are based on relatively weak evidence. Chlamydial infection fills the general prerequisites for disease prevention by screening, i.e. chlamydial infections are highly prevalent, usually asymptomatic, are associated with significant morbidity, can be reliably diagnosed, and are treatable. Screening programs for C trachomatis will be of paramount importance in the prevention of long-term sequelae. The cost of screening is only a fraction of the health care cost incurred due to complications resulting from undiagnosed and untreated chlamydial infections. Current strategies to control C trachomatis still largely depend on clinic-based screening of symptomatic patients, and have not been successful. The development of highly sensitive and specific nucleic acid amplification tests for the diagnosis of chlamydial infections has been an important advance in the ability to conduct population-based screening programs to prevent complications.

    The proportion of tubal factor infertility among all infertility ranges from less than 40% in developed countries to up to 85% in developing countries (WHO 1987). After a single episode of PID, the relative risk for tubal factor infertility is approximately 10%, and each repeat episode doubles the risk. Studies have demonstrated a strong link between serum antibodies to C trachomatis and tubal factor infertility or ectopic pregnancy. Ectopic pregnancy is the main cause of maternal mortality in the first trimester of pregnancy in developing countries. In addition to infertility and ectopic pregnancy, other morbidity is also associated with history of PID, such as chronic pelivc pain caused by extraluminal scarring. Chronic pelvic pain following PID occurs in between 24% and 75% of women. There is some evidence that C trachomatis may also contribute to pregnancy complications other than ectopic pregnancy, including premature rupture of membranes, preterm birth, low birth weight and stillbirth. Early pregnancy loss ore recurrent pregnancy loss may be induced by asymptomatic C trachomatis infection.

11. **The frequency and the role of Chlamydia trachomatis infection in premature labor.** *Kovacs et al, International Journal of Gynecology & Obstetrics 1998.* A prospective multi center study in Hungary of 6161 pregnant women of whom 362 (5.75%) were C trachomatis positive. An association between low birth weight or premature labor and C trachomatis, was not found. The perinatal mortality rate was significantly higher in the C trachomatis positive patients (3.6 vs. 2.0%). Neonatal morbidity, measured as referrals to perinatal intensive care unit was significantly higher among children of C trachomatis positive mothers (17.1 vs. 6.3%). In newborns of C trachomatis positive mothers, congenital pneumonia developed in 21.8% in the non-treated and only 8.6 in the treated group ($p<0.001$).

    Some of the C trachomatis positive women were treated ("in three of seven centers"): it is unclear how many as well as the effect of this treatment. The analysis did not control for any confounding factors.

Abstracts

1. **Chlamydia trachomatis infection among pregnant women: prevalence and prenatal importance.** *Paul et al, National Medical Journal of India, 1999.* This is *a small epidemiological study* of 94 pregnant women between 26 and 30 gestational week and 172 women presenting in spontaneous labor. There was no association found between infection with C trachomatis and low birth weight or prematurity. This study is of suboptimal quality.

2. **Chlamydia trachomatis infection in pregnancy: risk factor for an adverse outcome**. *Rastogi et al, British Journal of Biomedical Science 1999*. This is *a small epidemiological study* of 122 pregnant women who were tested (culture) for C trachomatis, and of whom adverse effects of pregnancy were recorded in 87 of them. 26 (21%) women were infected with C trachomatis. The authors report an increased risk of stillbirth (17 vs. 6%), prematurity (27 vs. 18) and low birth weight (27 vs. 23) in the infected women.

3. **Comparison of pregnancy outcome between treated and untreated women with chlamydial cervicitis**. *Rivlin et al, Journal of the Mississippi State Medical Association*. Of 81 pregnant women with chlamydia, 58 were treated and 23 were not treated. The two groups were similar with regards to abortion, preterm rupture of membranes, preterm delivery, chorioamnionitis, endometritis, and neonatal and infant complications. *The study is interesting, but small and substandard*.

Review of C trachomatis-related complications in other literature

Reproductive tract infections: Global impact and priorities for women's reproductive health. *Germain et al, Plenum press, New York, 1992*. Research on the economic consequences of STDs is still very limited. Only one study has attempted to quantify the economic cost of RTIs and their complications and sequelae in developing countries: M. Over and P. Piot concluded that STDs, excluding HIV infection, account for 5 percent of the total discounted healthy life years lost in Sub-Saharan Africa. Few data are available on the complications and sequelae of RTIs (adverse outcomes of pregnancy, maternal mortality, cervical cancer, ectopic pregnancy, infertility, and chronic pelvic pain).

Complications and sequelae occur more often in developing countries than in developed countries because of cultural barriers to seeking care, restricted access to health care, insufficient diagnostic facilities, and antibiotic resistance patterns, among other factors. The cost of treating these complications and sequelae are almost certainly much greater than the cost of treating the infection itself. While no quantitative data are readily available, hospital admission records from gynecology wards suggest that the opportunity costs of these preventable complications are substantial. Programs to reduce the incidence of RTIs in the female population and to administer early treatment of RTIs will substantially reduce the development of complications and sequelae, and have a major impact on the costs of RTIs.

The preterm prediction study: Association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. *Andrews et al, Am J Obst Gyn 2000.* Although abundant evidence is now available to link certain genital tract infections with spontaneous preterm birth, investigations of the association between C trachomatis infection of

the female genital tract during pregnancy and subsequent spontaneous preterm birth have produced mixed results. Some reports have linked the presence of maternal chlamydia infection with low birth weight, premature birth, premature rupture of membranes, and even an increased risk of perinatal death (ref). However, such an association with adverse pregnancy outcomes is not a universal finding (ref). Most available studies have used insensitive screening tests to diagnose C trachomatis infection of the genital tract and also have methodological shortcomings, including a limited ability to control for potential confounding variables (ref). The CDC has recommended that screening and treatment of genital tract C trachomatis infection be considered for pregnant women with certain risk factors to prevent neonatal sequelae resulting from vertical transmission of this organism. Because of the conflicting data regarding the association of C trachomatis infection with preterm birth and in the absence of data that treatment of this infection will prevent preterm birth, however, no recommendations has been made for a screening and treatment program expressly to prevent preterm birth.

Disease control priorities in developing countries, chapter 20: HIV infection and sexually transmitted diseases. *Over and Piot, Oxford Medical Publications, 1992.*Two parameters important in estimating the burden of STDs are the prevalence of infection and the rate of complications and sequelae. The degree of health-seeking behaviour and the quality of health services and STD control programs directly control the latter and, by reducing transmission, indirectly control the former. The morbidity of STIs occurs mostly between the ages of fifteen and forty-five years – not only the sexually most active period in life but also the most economically and demographically productive age.

Studies in Sweden have shown that 8 to 10 percent of women with gonococcal or chlamydial infection develop pelvic inflammatory disease. The annual incidence rate of PID among urban women in Sub-Saharan Africa can be estimated at 1 to 3 percent between the ages of fifteen and forty-five, with incidence rates of 0.4 to 1.2 percent, and 0.4 to 1.5 percent for gonococcal and chlamydial PID, respectively (assuming that 20 to 40 percent of cases of PID are du to N gonorrhoeae and 20 to 50 percent to C trachomatis. Half of these cases occur during the puerperal period. The annual mortality rate due to PID in this age group could then be 0.1 to 0.5 per 1000 (assuming 1 percent fatality rate).

The annual incidence of bilateral tubal occlusion leading to infertility is estimated at 0.3 to 1.5 percent in urban women in Sub-Saharan Africa, with gonococci and chlamydia each being responsible for 20 to 40 percent of cases (assuming a 15 to 40 percent risk of tubal occlusion after one episode of PID).

The annual incidence of ectopic pregnancy in urban Africa resulting from PID is estimated at 0.01 to 0,04 percent, with an annual mortality rate of 0.001 to 0.005 percent for women between 15 and 45.

Finally, maternal mortality due to gonococcal and chlamydial infection (post partum infectious complications) may be as high as 0,04 to 0.2 percent annually in Sub-Saharan Africa (with a maternal mortality rate of 0.5 to 1 percent and a 10 to 20 percent incidence of postpartum infections). In general, the overall mortality from STDs is not well defined. It is often a hidden mortality and morbidity because of a long latency period between the acute infection and the complication or sequelae leading to death.

In neonates, conjunctivitis and respiratory disease are the main causes of morbidity due to N gonorrhoeae and C trachomatis infection in the mother. The incidence depends on the prevalence of these infections in the pregnant women. Disablement from gonococcal neonatal infection is due to keratitis and blindness, while, disablement from chlamydial infection results mainly from chronic respiratory disease.

Per capita annual disease burden of chlamydia in Sub-Saharan Africa

Discounted disability-adjusted life-days lost: 8.6 (high prevalence)/0.8 (low prevalence

Discounted productive disability-adjusted life-days lost: 5.8 (high prevalence)/0.5 (low prevalence

Burden of chlamydia in high-prevalence (incidence 9.5) urban areas

Discounted disability-adjusted life-days lost: 4.8 –or saved: 1.3

Discounted DALYs saved per case prevented or cured when epidemics independent

1. Static benefit 1.05.
2. Dynamic benefit, core: 43.0, non-core: 4.4
3. Total benefit core 44.1, non-core 5.5

Discounted DALYs saved per case prevented or cured when chlamydia increases HIV transmission

…and so on.

Sexually Transmitted Diseases Treatment Guidelines 2002*, CDC*: A test for C trachomatis should be performed at the first prenatal visit. Women aged <25 years and those at increased risk for chlamydia (i.e. new or more than one sex partner) also should be tested during the third trimester to prevent maternal postnatal complications and infection in the infant. Screening during the first trimester might enable prevention of adverse effects of chlamydia during pregnancy. However, evidence for preventing adverse effects during pregnancy is lacking. If screening is performed only during first trimester, a longer period exists for acquiring infection before delivery.

Chlamydia trachomatis: impact on human reproduction. *Paavonen nad Eggert-Kruse, Human Reproduction Update 1999.* Chlamydial PID is the most common preventable cause of infertility and adverse pregnancy outcome. Based on the available evidence, approximately 20% of women with chlmayidal lower genital tract infection will develop PID, approximately 4% will develop chronic pelvic pain, 3% infertility and 2% adverse pregnancy outcome. Hwoever, these estimates are based on relatively weak evidence. Chlamydial infection fills the general prerequisites for disease prevention by screening, i.e. chlamydial infections are highly prevalent, usually asymptomatic, are associated with significant morbidity, can be reliably diagnosed, and are treatable. Screening programmes for C trachomatis will be of paramount importance in the prevention of long-term sequelae. The cost of screening is only a fracion of the health care cost incurred due to complications resulting from undiagnosed and untreated chlamydial infections. Current strategies to control C trachomatis still largely depend on clinic-based screening of symptomatic patients, and have not been successful. The development of highly sensitive and specific nucleic acid amplification tests for the diagnosis of chlamydial infections has been an important advance in the ability to conduct population-based screening programmes to prevent complications.

Genital Chlamydial Infections. *Peipert, N Engl J Med 2003.* C trachomatis is an important causal agent in pelvic inflammatory disease, with sequelae including infertility, ectopic pregnancy, and chronic pelvic pain (ref.). Up to two thirds of cases of tubal-factor infertility and one third of cases of ectopic pregnancy may be attributable to C trachomatis infection (ref). Chlamydial infection during pregnancy is associated with a number of adverse outcomes of pregnancy including preterm labour, premature rupture of membranes, low birth weight, neonatal death, and postpartum endometritis (ref). Chlamydial infection during pregnancy may be transmitted to the infant during delivery (ref). An infant born to a mother with active infection has a risk of acquiring infection at any anatomical site of 50 to 70 percent. Approximately 30 to 50 percent of infants born to chlamydia-positive mothers will have conjunctivitis, and at least 50 percent of infants with chlamydial conjunctivitis will also have nasopharyngeal infection. Chlamydial pneumonia develops in about 30 percent of infants with nasopharyngeal infection (ref).

There is good evidence that screening women who are at risk for C trachomatis infection can prevent reproductive sequelae by reducing the rate of pelvic inflammatory disease (ref). The strongest evidence supporting screening in women comes from a large randomized trial of screening and treatment at a health maintenance organization in Seattle (ref) among at-risk asymptomatic women 18-34 years of age. By the end of the follow-up period, there were 9 verified cases of PID in the screened group and 33 cases in the usual-care group. Long term adverse effects were not addressed. Two ecologic studies in Sweden showed that the rates of both ectopic pregnancies and PID were reduced in communities after screening for chlamydial infection was adopted (ref). Although data from randomized trials of screening for chlamydial infection during pregnancy are lacking, there is some evidence that screening high-risk women for C trachomatis during pregnancy can reduce the rate of adverse outcomes of pregnancy. Two observational studies showed associations between the treatment of chlamydial infection during pregnancy and improved outcomes of pregnancy, including lower rates of premature rupture of the membranes, low birth weight, births of infants who were small for their gestational age, and neonatal death (ref).

Mass antimicrobial treatment in pregnancy. *Temmerman et al, J of Reprod med.* Maternal genital infection is one of the causes of preterm birth that may be most susceptible to intervention. Sexually transmitted diseases, especially syphilis, gonorrhea and chlamydia, are endemic in many developing countries and play an important role in perinatal morbidity and mortality (ref STD, Holmes et al.). Two case-control studies from Nairobi reported a significant association between maternal gonococcal infection and prematurity (ref). In addition, high rates of opthalmia neonatorum and postpartum upper genital tract infections were observed; they were significantly associated with gonococcal and chlamydial infections (ref).

Chlamydia in Pregnancy: A randomized trial of Azitromycin and erythromycin. *Adair et al, Obstetrics & Gynecology.* Chlamydia infection during pregnancy can cause adverse effects on both the gravida and the neonatate, including spontaneous abortion, fetal death, premature rupture of membranes, preterm delivery and postpartum endometritis (ref.). Neonatal vertical acquisition may result in conjunctivitis and pneumonia. Transmission to the neonatate can occur in more than 70% of the cases (ref.)

TRIALS

Improved pregnancy outcome following successful treatment of chlamydial infection. *Cohen et al. JAMA 1990.* Pregnancy outcomes of 224 women successfully treated with erythromycin were compared with those of 79 chlamydia-positive women who failed to respond to treatment, and 244 chlamydia-free control women. The frequency of premature rupture of membranes, premature contractions and small-for-gestational age infants were significantly lower in the successfully treated patients when compared with those of the chlamydia positive patients, but not significantly different compared to the control patients.

Prematurity and perinatal mortality in pregnancies complicated by maternal chlamydia trachomatis infections. Martin et al, JAMA 1982. Prospective study of morbidity associated with C trachomatis infection during pregnancy. 18 of 268 women were C trachomatis positive. Stillbirth or neonatal death occurred ten times more often among C trachomatis positive women than among unifected controls matched for age, marital status, socioeconomic status, and race.

Cervical Chlamydia trachomatis and mycoplasmal infections in preganancy. Epidemiology and outcomes. *Harrison et al, JAMA 1983*. Prospective study of chlamydia and mycoplasma in pregnancy. CT in 8%, MH in 23.5%. The cervical infections did not predict low birth weighet, abortion, stillbirth, prematurity, or premature rupture of membranes. Only MH predicted

endometritis/fever after vaginal delivery (RR 7.3). IgM seropositive CT had more low-birth-weight infants and more premature rupture of membranes than IgM negative or CT culture negative women. Thus, only certain subgroups of infected women may experience adverse pregnancy outcomes.

Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome. *Gravett et al, JAMA 1986.* Prospective study of pregnancy outcome among 534 pregnant women. BV in 19% and CT in 9%. Neonatates born to women with BV had lower mean birth weight, and BV was significantly associated with PROM (OR 2), preterm labour (OR 2), amniotic fluid infection (OR 2.7), but not with birth weight <2.5 kg. Cervical infection with CT was independently associated with preterm premature rupture of the membranes, preterm labor and low birth weight (OR 1.5, CI 0.8-2.0).

The preterm prediction study: Association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. *Andrews et al, Am J Obst Gyn 2000.* This is a retrospective case-control study within The Preterm Prediction Study where 2929 pregnant women were evaluated longitudinally to determine risk factors for spontaneous preterm birth. This study consist of 117 case patients with a spontaneous preterm birth at <37 weeks with corresponding matched control subjects.

After adjustment for risk factors for spontaneous preterm birth, women with C trachomatis infection at 24 weeks gestation were 2 times as likely as uninfected women to have a spontaneous preterm birth at <37 weeks gestation and 3 times as likely to have a spontaneous preterm birth at <35 weeks gestation. **Whether universal screening and treatment for C trachomatis infection with a sensitive NAAT method for detection would significantly reduce spontaneous preterm delivery remains an unanswered question.**

A murine model for the study of Chlamydia trachomatis genital infections during pregnancy. *Pal et al, Infection and immunity, May 1999.* Infant mortality in the US has recently increased. These high infant mortality rates are mainly due to high rates of premature birth and associated low birth weight. Determinants that affect low birth weight include genetic, social, environmental and behavioral factors. Infections of the genital tract are considered to account for up to 40% of preterm births. Organisms that have been associated with this problem include, among others, C trachomatis, N gonorrhoeae, M hominis, Gardnerella vaginalis, Streptococcus agalactiae, T vaginalis and U urealyticum.

Several studies over the last two decades have attempted to determine the impact that a C trachomatis genital infection has on pregnancy outcome. Some of these studies found maternal and fetal morbidity and mortality associated with both acute and past chlamydial infections, while others did not confirm these data (ref). Most likely, depending on the infecting inoculum, time of gestation, and susceptibility of the host, a variety of clinical manifestations ranging from asymptomatic infection to termination of pregnancy may occur.

In our murine model, we have shown that C trachomatis inoculated intravaginally on day 5 of gestation in mice infects the endometrium and the membranes of the yolk sac, resulting in early termination of pregnancy. This is not surprising since chlamydial endometritis commonly occurs during a genital infection and the ability of C trachomatis to infect amniotic cells has been demonstrated in vitro. Most likely, fetal membranes were affected following infection of the endometrium. It is possible that the direct damage to the fetal membranes resulting from the infection, in combination with endotoxin activity is a significant factor in the premature termination of pregnancy.

Conclusion: spontaneous abortion, preterm birth and low birth weight

We have little specific knowledge on what extent infection with *C trachomatis* has on pregnancy outcome, especially in developing countries. This is a very demanding research question, and weaknesses in methodology include imperfect sensitivity or specificity of tests and lack of control for confounding factors. Differences between studies may be caused by differences in test method, focus on acute or chronic infection or gestational time when infection is identified.

Evidence lacking:
-The prevalence of abortion, preterm birth and low birth weight in the population
-The extent which *C trachomatis* infection increases the risk of spontaneous abortion and preterm birth, or the proportion of these conditions which are caused by *C trachomatis*
-The extent to which diagnosis and treatment of *C trachomatis* in pregnancy can prevent these complications

Appendix 6

PROBABILITY OF CURE WITH DIFFERENT DRUG REGIMENS TO TREAT CHLAMYDIA

Source	**Patient group**	**Correct prescription**	**Azitromycin**		**Erythromycin‡**		**Doxycycline**	
			Compliant	Effectiveness	Compliant	Effectiveness	Compliant	Effectiveness
Postma [55] CE	Female index Male partners	100% 100%	90% 90%	95% 95%		95% 95%	- -	- -
Welte [52] CE-R	Unspecified		100%	95%			80%	95%
Roberts [62] CE-R	Unspecified	100%	100%				75-87%	
Romoren [32] OD	Pregnant women				"low"			
Guaschino [97] 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 [103] M	Pregnant women				Clinical cure 95%			
Adimora [45] 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 [50] CE	Unspecified	100%	Treatment success rate 90% (80-100%), re-infections included (AB unspecified)					
de Vries [104] CE	Male and female	100%	90%	95%	Based on the same operational research as Postma			
Adair [105] OD	Pregnant women	NA	NA	97.5%	(53.5%)	95.3%		
Rustomjee [72] OD	Female index	NA	100%	100%				
Miller [96] 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.

A treatment failure may be due to non-compliance, microbiological cure failure or re-infection

Studies, primarily from developing countries, have measured compliance and partner notification in randomized, controlled trials [72, 105, 106]. Yet 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.

There are few papers published on Medline on patient compliance to STI drugs in developing countries. Only clinical cure rates can be measured in the syndromic management of STIs: As it is unknown which infection or condition the patient is suffering from, information on drug efficacy or reinfection rates is unachievable. 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 [79].

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