ORIGINAL ARTICLE

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

M Romoren, M Rahman, J Sundby, P Hjortdahl

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

See end of article for authors' affiliations

Correspondence to: M Romoren, Institute of General Practice and Community Medicine, University of Oslo, Box 1130 Blindern, N-0318 Oslo, Norway; maria.romoren@medisin.uio.no

Accepted for publication 15 January 2004

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

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

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

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

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

METHOD

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

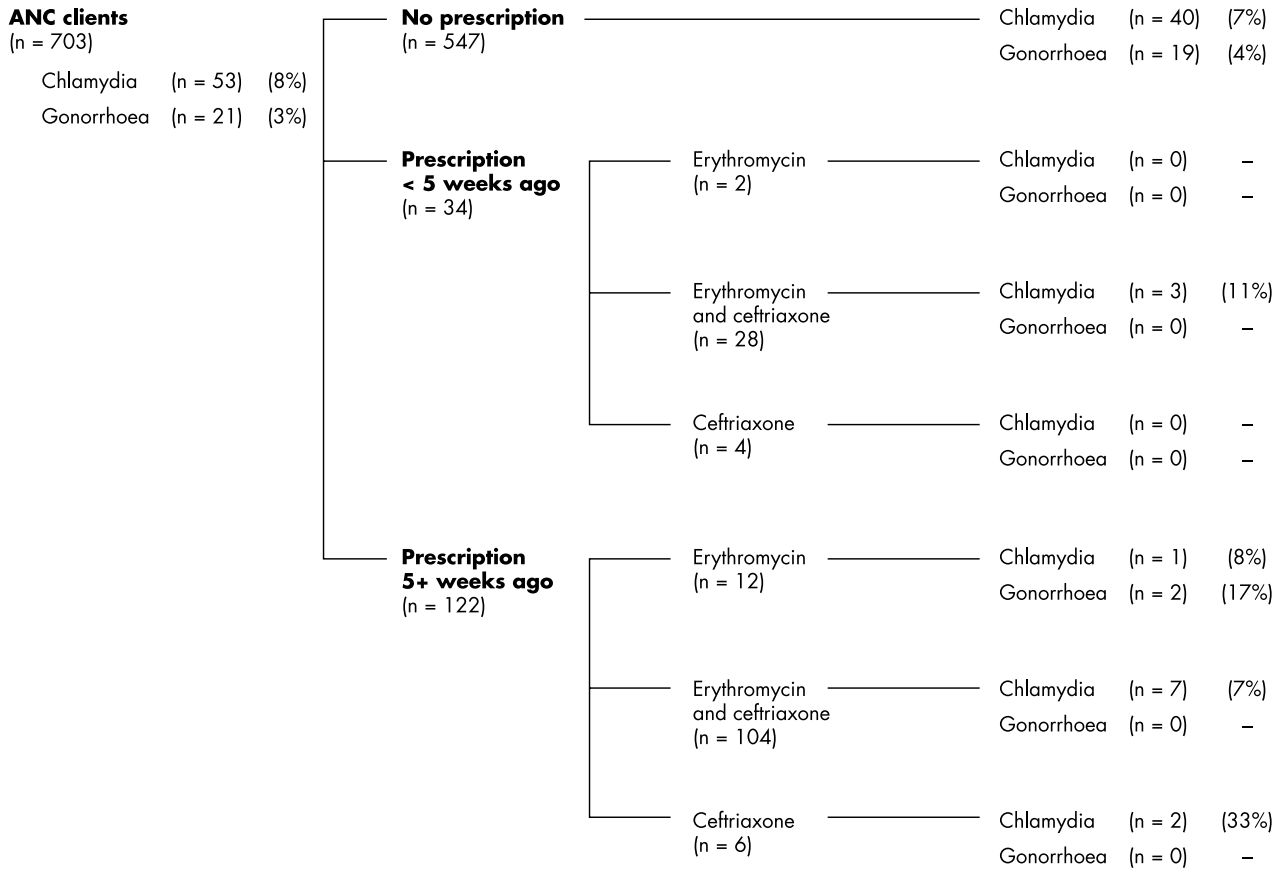

Figure 1 Prescription of erythromycin and ceftriaxone earlier in current pregnancy among 703 antenatal care clients in Gaborone, Botswana, and the distribution of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in this population.

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

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

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

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

RESULTS

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

Re-infection

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

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

Patient compliance

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

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

Improving cure rates

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

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

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

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

Key messages

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

CONCLUSION

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

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

CONTRIBUTORS

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

Authors' affiliations

M Romoren, J Sundby, P Hjortdahl, Institute of General Practice and Community Medicine, University of Oslo, Blindern, Oslo, Norway
M Rahman, AIDS/STI Unit, Ministry of Health, Gaborone, Botswana.

REFERENCES

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