Evaluation of syndromic management guidelines for treatment of sexually transmitted infections in South African women

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ABSTRACT

Objective
To evaluate performance of three different guidelines for the management of vaginal discharge syndrome (VDS) for women living in a rural setting in South Africa.

Methods
We conducted a secondary analysis of data from a cross-sectional study in Mopani District, South Africa. The 2015 and 2008 guidelines of the South African Department of Health (DoH) and the most recent WHO guidelines were evaluated for adequate treatment of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, and *Trichomonas vaginalis* infection.

Results
Of the 489 women included in this analysis, 171 (35%) presented with VDS according to the DoH and 146 (30%) per WHO definition of VDS respectively. Fourty-two (56%) of the women with VDS would be treated adequately for these STI when using the 2015 DoH guideline, whereas 76% (p=0.01) and 64% (p=0.35) would receive adequate treatment with the 2008 DoH and WHO guidelines respectively. Of the symptomatic women who tested negative for all four STI, STI treatment would have been indicated for 36% as per 2015 DoH guideline compared to 69% (p<0.001) respectively 67% (p<0.001) per 2008 DoH and WHO guidelines.

Conclusion
We confirm that a considerable proportion of symptomatic women infected with these common curable STI would receive adequate treatment when using a syndromic management approach, and that significant differences exist between the three guidelines. Furthermore many symptomatic women without these STI receive broad-spectrum antibiotics. Therefore innovative approaches are warranted to improve STI control in settings with syndromic approach.

INTRODUCTION

Sexually transmitted infections (STI) represent a major global public health problem, especially in women. After pregnancy-related causes, STI are the most important cause of quality of life lost in women globally (1). The most recent estimates of the World Health Organization (WHO) show that the vast majority of curable STI occur in the developing world, with an incidence of more than 92 million per year in the African region (2). The bacterial STI prevalence rates in South Africa are relatively high, even compared to other African countries (3,4). It is estimated that one out of four women in South Africa is infected with at least one bacterial STI (3,5). The burden of STI in South Africa is estimated to be 20% higher in women than in men (4). The effects of STI are both direct, through negative impact on reproductive health and quality of life, and indirect, through potential facilitation of the sexual transmission of human immunodeficiency virus (HIV) (6-8). Furthermore, bacterial STI can cause adverse pregnancy outcomes and sequelae in the offspring of infected mothers (9-11).

Detection and treatment of STI are considered a low cost opportunity to improve health in women and comprise an essential component of HIV control programmes in communities where the burden of STI is substantial (7,12). Most Western countries have implemented STI control programmes that vary from case management, based on microbiological diagnosis, to opportunistic screening and treatment in high-risk groups (13). Since availability of laboratory-based testing is often limited in low-resource countries, the WHO recommends syndromic management of STI in individuals living in such areas (14). This means that women presenting with vaginal discharge syndrome (VDS), lower abdominal pain syndrome or genital ulcer disease are treated with a combination of broad-spectrum antibiotics without diagnostic testing. South Africa through the Department of Health (DoH) has implemented similar guidelines to the syndromic approach of the WHO but with some differences (15,16).

The syndromic management approach for women presenting with VDS at healthcare facilities has clear advantages: it is easy to use, inexpensive, and it treats the patient at the first visit for most of the pathogens associated with each syndrome. However, various disadvantages are also widely recognised: the majority of women with a cervical infection are asymptomatic and therefore remain untreated, whereas some symptomatic women are unnecessarily or incorrectly treated with antibiotics (17,18). Several studies revealed a low sensitivity and specificity of the WHO guideline for treatment of STI (19,20). However, limited data are available on the performance of other syndromic management guidelines for VDS in comparison with the WHO guideline.

This study aims to evaluate the most recent guideline (2015) for syndromic management of VDS as defined by the South African DoH (15), and to compare this with the previous (2008) version of this guideline (16) and the WHO (2003) guideline for syndromic management of VDS (14).

METHODS

Study design and population

This is a secondary analysis of data obtained in a cross-sectional study conducted at 25 Primary Healthcare (PHC) facilities in rural Mopani district, Limpopo Province of South Africa. Briefly, all sexually active women (at least one sex act in the previous six months) aged 18 to 49 years visiting PHC facilities were included regardless of the reason for visiting the facility that day. After obtaining informed consent, demographic, sexual behaviour and clinical data were collected through a nurse-administered questionnaire. Clinician-collected vaginal samples were tested for the presence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, and *Trichomonas vaginalis* using real-time polymerase chain reaction as described elsewhere (5,21). Data obtained through the questionnaire and physical examination were combined with laboratory data to evaluate the syndromic management guidelines. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Ref: M110726).

Syndromic management guidelines

The following three guidelines for the management of VDS in women were evaluated: the South African DoH guidelines of 2015 and 2008 and the WHO guideline of 2003 (14-16). These three guidelines differ considerably and are specified in Figure 1. In summary, the different guidelines guide a clinician through the treatment options for a woman presenting with VDS. A combination of metronidazole, azithromycin and ceftriaxone – defined as STI treatment in this study -- is provided to those women who qualify by a combination of demographic characteristics, reporting symptoms, and/or clinical observation by a clinician. Women who do not meet the conditions of the specific guideline are either treated for bacterial vaginosis (metronidazole) and vaginal candidiasis (clotrimazole), for suspected urinary tract infection (UTI), or receive no treatment according to their characteristics and complaints.

The main difference between the three guidelines is the risk assessment. As the prevalence of chlamydia and gonorrhoea is high in our setting the risk assessment mentioned in the WHO protocol is not indicated (5). According to the DoH, STI treatment is not indicated for women above 35 years and without a partner with male urethritis syndrome (2015) or for women with the last sex act more than 3 months ago (2008). These women receive metronidazole and clotrimazole only. Further differences include the different definition of symptoms and signs of VDS between the guidelines and the diagnosis of UTI in the DoH guidelines. A UTI should be excluded by urinalysis or based on complaints. Because of the unavailability of nitrite test strips the physician in this study diagnosed a UTI based on history of dysuria, absence of genital complaints and findings on physical examination.

Data analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc, Chicago, IL). Treatment rates for each STI and for all STI combined were calculated and compared between the different guidelines using the Z-test for population proportions.

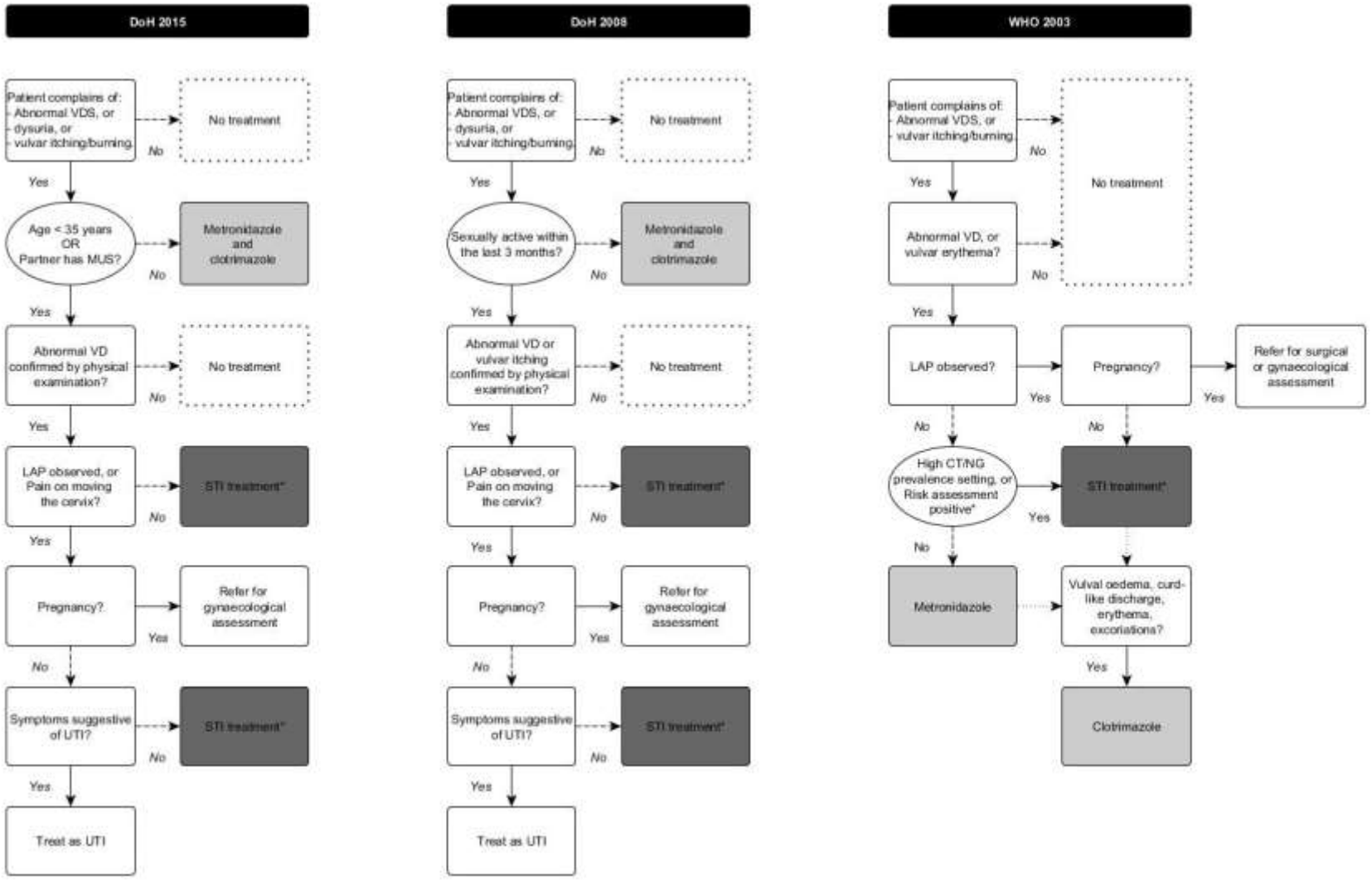

Figure 1. Vaginal discharge syndrome management guidelines of the Department of Health (DoH) and the World Health Organization (WHO) (14-16).

*STI-treatment: A combination of azithromycin, ceftriaxone and metronidazole.

RESULTS

Characteristics of the study population

Among the 489 women included in this analysis, the median age was 31 years (range, 18-49), 146 (30%) reported to be HIV-infected, 71 (15%) were pregnant and 98 (20%) reported a history of VDS. A reported history of VDS or a HIV-positive status were associated with presentation with VDS (p=0.002 and p=0.001, respectively) (Table 1). Two-hundred and seven women (42%) had at least one STI diagnosed by microbiological testing. The prevalence of STI was 17%, 10%, 8.4%, and 20% for *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium* and *T. vaginalis* respectively.

Performance of the guidelines for management of VDS

One-hundred and seventy-one women (35%) presented with abnormal vaginal discharge, dysuria and/or vaginal itching and were therefore classified as symptomatic according to the DoH guidelines. Of these, 75 (44%) were infected with at least one STI, whereas 132 of the 318 (42%) asymptomatic women were infected (p=0.62). As per the WHO guideline, 146 (30%) classified as symptomatic, of which 61 (42%) tested positive for at least one STI. Treatment numbers and percentages for the different guidelines per STI are summarized in Table 2.

As per the 2015 DoH guideline, 42 (56%) of the 75 symptomatic women with an STI would receive adequate treatment, and one (1.3%) would be referred for gynaecological assessment. Figure 2 demonstrates the number of women in every step of the 2015 DoH guideline. Of the 25 women infected with *C. trachomatis*, 13 (52%) qualified for a combination of ceftriaxone, azithromycin and metronidazole and one (4.0%) for referral. Three women (12%) would not have received treatment because they were 35 years or older and did not have a partner with MUS, and eight women (32%) because vaginal discharge was not observed during physical examination. Similarly, of the women infected with *N. gonorrhoeae* and *M. genitalium* respectively, nine (60%) and five (31%) would have received adequate treatment, whereas three (20%) and four (25%) would not have been treated adequately due to older age and partner without MUS, and three (20%) and seven (44%) due to the absence of vaginal discharge on physical examination. No women infected with *N. gonorrhoeae* or *M. genitalium* would have qualified for referral. Of the 42 women infected with *T. vaginalis*, 17 (40%) would receive the combination of ceftriaxone, azithromycin and metronidazole and 10 (24%) the combination of metronidazole and clotrimazole, therefore 27 (64%) would receive adequate treatment for this STI. Fourteen women (33%) would not have been treated as discharge could not be confirmed on examination and one woman (2.4%) would have been referred for gynaecological assessment. Of the 96 women who presented with VDS but tested negative for all STI, 36 (38%) would receive metronidazole and clotrimazole and 35 (36%) the STI treatment.

Using the DoH 2008 guideline 57 (76%) of the 75 women with an STI would have received adequate treatment, which is significantly more compared to the 2015 guideline (56%; p=0.010). The proportions of women correctly treated for *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium*, and *T. vaginalis* would be 68% (p = 0.25), 80% (p = 0.023)

Table 1. Characteristics of women with and without VDS (according to DoH criteria) in this study (n = 489)

Characteristics		Total	Women with VDS	Women without	p-value
Age < 35 years		310 (63)	117 (68)	193 (61)	0.091
Marital status					0.22
	Single	254 (52)	91 (53)	163 (51)	
	Married	191 (39)	59 (35)	132 (42)	
	Widowed	7 (1.4)	3 (1.7)	4 (1.3)	
	Engaged	20 (4.1)	9 (5.3)	11 (3.5)	
	Divorced	16 (3.3)	9 (5.3)	7 (2.2)	
Employed		129 (26)	38 (22)	91 (29)	0.12
Pregnant		71 (15)	22 (13)	49 (16)	0.45
Reported HIV-positive status	HIV-positive	146 (30)	66 (39)	80 (25)*	0.002
HIV-status partner					0.15
	HIV-positive	48 (9.8)	24 (14)	24 (7.7)	
	Tested HIV-negative	113 (23)	37 (22)	76 (24)	
	Reported HIV-negative	93 (19)	31 (18)	62 (20)	
	Unknown	228 (47)	77 (46)	151 (48)	
Use of hormonal contraceptives in the last 6 months		199 (41)	64 (38)	135 (43)	0.29
Condom use at last sex act		184 (38)	68 (40)	116 (36)	0.77
Age of first sexual contact		17 (11-28)	17 (12-26)	17 (11-28)	0.68
Lifetime number of sexual partners		3 (1-30)	4 (1-12)	3 (1-30)	0.076
History of VDS		98 (20)	48 (29)	50 (16)*	0.001
Any STI		207 (42)	75 (44)	132 (42)	0.616
CT		81 (17)	25 (15)	56 (18)	0.396
NG		50 (10)	15 (8.8)	35(11)	0.437
MG		41 (8.4)	16 (9.4)	25 (7.9)	0.569
TV		100 (20)	42 (25)	58 (18)	0.098
Abnormal VDS		119 (24)	119 (70)	0 (0.0)	N/A
Dysuria		94 (19)	94 (55)	0 (0.0)	N/A
Vulval itching		84 (17)	84 (49)	0 (0.0)	N/A

Dichotomic variables: number (percentage). Numeric variables: median (range)
Significant difference ($p<0.05$)

Table 2. Treatment of sexually transmitted infections in symptomatic women using the syndromic management approach.

			CT (N=81)	NG (N=50)	MG (N=41)	TV (N=100)	Any STI (N=207)
DoH 2015	Symptomatic	Total	25 (31)	15 (30)	16 (39)	42 (42)	75 (36)
		Treated	*13 (52)*	*9 (60)*	*5 (31)*	*27 (64)*	*42 (56)*
		Untreated	*11 (44)*	*6 (40)*	*11 (69)*	*14 (33)*	*32 (43)*
		Referred	*1 (4.0)*	*0 (0.0)*	*0 (0.0)*	*1 (2.4)*	*1 (1.3)*
	Asymptomatic	Total	56 (69)	35 (70)	25 (61)	58 (58)	132 (64)
DoH 2008	Symptomatic	Total	25 (31)	15 (30)	16 (39)	42 (42)	75 (36)
		Treated	*17 (68)*	*12 (80)*	*12 (75)*	*34 (81)*	*57 (76)*
		Untreated	*7 (28)*	*3 (20)*	*4 (25)*	*7 (17)*	*17 (23)*
		Referred	*1 (4.0)*	*0 (0.0)*	*0 (0.0)*	*1 (2.4)*	*1 (1.3)*
	Asymptomatic	Total	56 (69)	35 (70)	25 (61)	58 (58)	132 (64)
WHO	Symptomatic	Total	19 (24)	14 (28)	14 (34)	35 (35)	61 (30)
		Treated	*13 (68)*	*9 (64)*	*6 (43)*	*23 (66)*	*39 (64)*
		Untreated	*5 (26)*	*5 (36)*	*8 (57)*	*11 (31)*	*21 (34)*
		Referred	*1 (5.3)*	*0 (0.0)*	*0 (0.0)*	*1 (2.9)*	*1 (1.6)*
	Asymptomatic	Total	62 (77)	36 (72)	27 (66)	65 (65)	146 (71)

Note. CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; STI, sexually transmitted infection; DoH, Department of Health; WHO, World Health Organization.

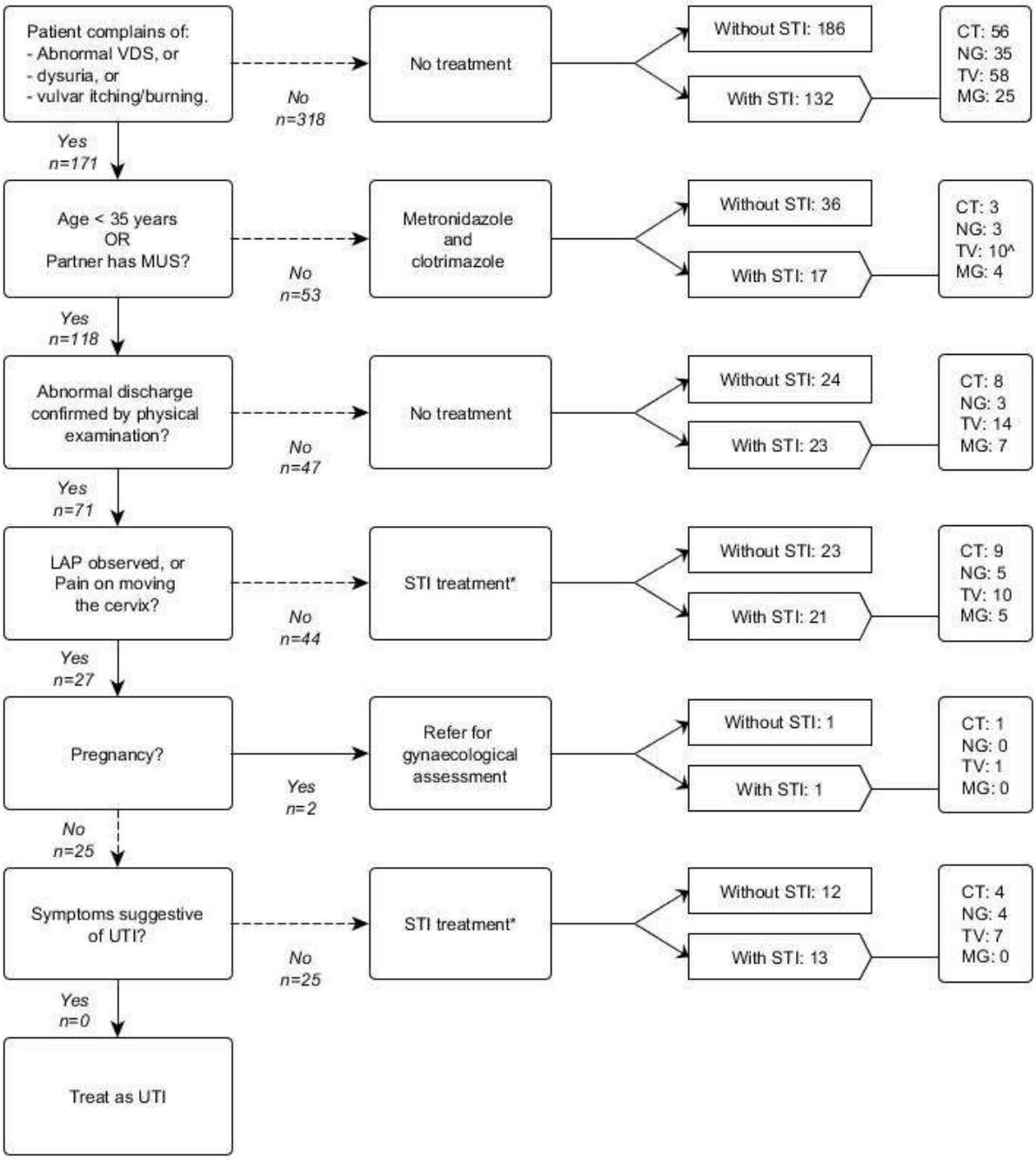

Figure 2. Evaluation of management of sexually transmitted infections in women (n=489) using the 2015 South African Department of Health guidelines for the management of VDS.

*STI-treatment: A combination of azithromycin, ceftriaxone and metronidazole.

^ Of which *T. vaginalis* as only STI: 8

75% (p = 0.013) and 81% (p = 0.087) respectively. No woman with an STI other than *T. vaginalis* would qualify for treatment with metronidazole and clotrimazole only. Of the 96 women with VDS who tested negative for all STI 66 (69%) would receive STI treatment, which is significantly higher than when using the 2015 guideline (36%, p<0.001). Six (6.3%) symptomatic women without any of the tested STI would receive metronidazole and clotrimazole only.

Using the WHO guideline 39 (64%) of the 61 symptomatic women with an STI would have been adequately treated, which is not significantly different from the 2015 DoH (p = 0.35) or the 2008 DoH guideline (p = 0.12). Treatment rates for *C. trachomatis, N. gonorrhoeae, M. genitalium,* and *T. vaginalis* would be 68%, 64%, 43%, and 66% respectively, none of which significantly differ from the treatment rates of the 2015 DoH (p = 0.27, 1.0, 0.51 and 0.90 respectively) and 2008 DoH guideline (p = 0.98, 0.81, 0.074 and 0.13 respectively). Fifty-six women (67%) of the 85 women presenting with VDS without any of the tested STI would receive STI treatment, which is significantly higher than when using the 2015 DoH guideline (p<0.001), but not significantly different compared to the 2008 DoH guideline (p=0.68).

DISCUSSION

This study shows that in this high STI and HIV prevalence setting with syndromic approach to STI management most women of reproductive age with *C. trachomatis, N. gonorrhoeae, M. genitalium*, and/or *T.vaginalis* infection would not receive adequate treatment for these respective STI. The majority of the infected women was asymptomatic and would thus not receive treatment, as reported by several other studies (17,18). Moreover, of the women that present with symptoms, just over half till three-quarters of the women would receive adequate treatment for these four STI using the three syndromic management guidelines.

The main reason for infected women with VDS not to receive adequate treatment is the lack of vaginal discharge and/or vulval irritation on examination, as nearly half of the women without vaginal discharge on examination tested positive for at least one STI. Relatively few women were excluded from STI treatment due to a negative risk assessment (age of 35 years or higher and no partner with MUS in DoH 2015 guideline and last sex act more than 3 months ago in DoH 2008 guideline).

Treatment rates according to the WHO guidelines did not significantly differ from those of the DoH 2015 guideline, however a significantly higher proportion of women without any of the tested STI would receive STI treatment. This could be explained by the age-related step in the DoH 2015 guideline which is missing in the WHO guideline. A higher age is known to reduce the risk for chlamydial infection (5), and this could explain why only a few women with *C. trachomatis* would not receive adequate treatment due to this prerequisite in the 2015 DoH guideline. This result supports the argument that this distinction reduces overtreatment whilst minimally reducing the adequate treatment rate and is therefore considered an useful addition to the guideline.

Significantly more women with an STI would receive adequate treatment under the 2008 DoH guideline as compared to the 2015 guideline. This is partially explained by the lower proportion of women with a negative risk assessment according to the DoH 2008 guideline as compared to the DoH 2015 guideline, which results in a higher proportion of women eligible for STI treatment. Another contributing factor is that, whereas in the 2015 guideline vaginal discharge must be observed during physical examination in order for symptomatic women to receive STI treatment, the 2008 guideline indicates that women without vaginal discharge but with signs of vulval itching are eligible for treatment as well. However, together with the higher treatment rates comes the significantly higher proportion of women without any of the four curable STIs that would receive STI treatment. Therefore the higher treatment rates of the 2008 DoH guideline, compared to the 2015 guideline, presented in this study are merely a result of more women, regardless of infection, receiving STI treatment rather than a better discriminative ability of this guideline.

This study has some limitations. First, possible selection bias of participants may have occurred as we recruited women at PHC facilities regardless of reasons for visiting the facility that day. This might have resulted in an overrepresentation of symptomatic women and should be taken in account when generalizing to the general population. Second, in this study women were actively asked about genital complaints and therefore more women, that would normally not have been consulted for these complaints, could have been classified as symptomatic. It is therefore possible that the actual proportion of women with an asymptomatic STI is even higher. Third, only women who reported to have been sexually active in the last six months were eligible for this study. This could have led to an underestimation of the performance of the 2008 DoH guideline, as it distinguishes between women who have been sexually active within the last three months and women who have not. However, as nearly all women approached to participate in this study reported being sexually active in the last three months, the impact on the results is considered minimal.

This study shows that when using syndromic guidelines for STI management a large proportion of symptomatic women do not receive adequate treatment for these four common curable STI. In order to improve the treatment rates of these women, one could consider to remove vaginal discharge on physical examination as a prerequisite for STI treatment from the 2015 algorithm. However this will simultaneously increase treatment of women without one of these STIs, which may influence the development of antimicrobial resistance among sexually- and non-sexually transmitted bacteria. Compared to the 2008 DoH and the WHO guideline, the most recent (2015) guideline of the DoH reduces antibiotic treatment of women presenting with VDS, and it appears that increasing the algorithm's sensitivity will compromise its specificity.

Furthermore this study confirms that the vast majority of the women with an STI will be left untreated because of the absence of any complaints. Using the syndromic management approach only will therefore always result in high undertreatment rates and

low sensitivities, irrespective of the algorithm. In order to improve the undertreatment rates, alternatives or additives to the syndromic management should be explored.

Some studies have evaluated the addition of a risk assessment to the syndromic approach on its performance. Fonck and colleagues showed that the addition of a risk score would improve the performance of the algorithm in Kenya in 2000 (19). However, the improvement would be small and the new algorithm would still not reach acceptable levels of sensitivity and specificity. Another study, conducted in Botswana in 2007, demonstrated no significant improvement in the management of chlamydia and gonorrhoea in pregnant women (18).

There are no studies conducted to evaluate mass treatment of STI on the prevalence in the general population. Periodic presumptive treatment in pregnant women or high-risk groups such as female sex workers has shown to reduce the prevalence of bacterial STI (22,23), although research shows conflicting results on pregnancy outcomes (24). Furthermore, long-term (cost) effectiveness, induction of antimicrobial resistance, and potential risk compensation are point of concerns.

A significant improvement in STI management in resource poor settings appears to be difficult without the introduction of diagnostic tests. The use of accurate diagnostic (*e.g.* point-of-care) tests will not only contribute to diagnosis and treatment of the most common STI in (asymptomatic) women, but can also decrease treatment with unnecessary use of broad-spectrum antibiotics of women without an STI who present with VDS of other origin (25,26). This is essential as unnecessary use of antibiotics could eventually lead to a decrease of antimicrobial susceptibility of these STI (and possibly other infectious diseases), adding to the global rise of resistance as one observes for *N. gonorrhoeae* nowadays (27,28). Furthermore, the use of diagnostic tests could justify and strengthen the partner notification system, which is considered to be an essential part of STI management (25,29). Finally, it will give insight into the epidemiology and characteristics of the causative organisms and the option to monitor and conduct surveillance of these infectious diseases. We therefore conclude that in this rural population with a high burden of STI that are left untreated under the current syndromic management approach, (targeted) introduction of diagnostic tests is crucial for reducing the burden of infection. Despite the higher cost associated with diagnostic tests compared to the syndromic management approach, data from modelling and feasibility studies suggest that diagnostic testing, especially in high prevalence populations such as sex workers and pregnant women, may be a cost-effective and feasible strategy (29-32). Further research to explore the feasibility, performance and cost-effectiveness of such an approach in routine healthcare programmes in low resource settings is warranted.

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Potential conflict of interest
Prof. dr. S.A. Morré (SAM), fulltime employee of the VU University Medical Center Amsterdam, has been involved in the technical development of the PRESTO-Plus CT-NG-TV assay (Developed by Microbiome, Amsterdam, NL) (SAM is co-founder and co-director of Microbiome), a spin-in company of the VU University Medical Center, Amsterdam, the Netherlands. None of the other authors report a potential conflict of interest.

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