

# Validation of national algorithms for the diagnosis of sexually transmitted diseases in Brazil: results from a multicentre study

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**Objective:** To validate STD flow charts for the management of genital discharge and genital ulcer currently recommended by the National STD Control Programme in Brazil.

**Methods:** A study was conducted in five Brazilian STD clinics from January to June 1995. After an interview, a clinical examination was performed by a physician, who recorded a presumptive diagnosis, based on his/her clinical experience. This diagnosis was compared with a gold standard laboratory diagnosis in order to calculate sensitivity, specificity, and positive predictive value of the clinical diagnosis. The validity of the simulated national flow charts was assessed using the same method.

**Results:** A total of 607 men and 348 women participated in the study. Gonorrhoea was the aetiology most frequently detected in men with urethral discharge. The sensitivity of the clinical diagnosis was far lower than the sensitivity of the national flow chart, using the syndromic approach, for both gonococcal and chlamydial urethritis. Adding a simple laboratory test (Gram stain) to the national flow chart increased the specificity and positive predictive value for gonorrhoea. Among the women with vaginal discharge, a cervical infection was detected in 17%, a vaginal infection in 74%, and mixed infection in 9%. The sensitivity of the diagnosis for cervical infection increased from 16% (clinical aetiological approach) to 54% (when adding a syndromic approach) and to 68% when adding a risk assessment, as in the national flow charts. The cure or improved rate of genital ulcers was 96% after 1 week.

**Conclusions:** The results of the study will help to convince policy makers and those involved in training healthcare workers in Brazil of the public health advantages of the syndromic approach, as an essential part of STD/HIV control activities.

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## Introduction

The control of sexually transmitted diseases (STDs) is now recognised as a key strategy in the prevention of HIV infection. Lowering the incidence and duration of infectiousness of STDs will not only have an impact on the incidence of complications, but has the potential to slow down the spread of HIV. In Mwanza, Tanzania, the incidence of HIV was reduced by 42% by strengthening STD case management in the health services, through the introduction of a syndromic approach, regular supervision, and the availability of STD drugs.<sup>1</sup>

Since 1993, the National AIDS/STD Control Programme in Brazil has recommended a syndromic approach for the management of patients attending with STD symptoms. National algorithms for the management of STDs were designed by consensus building, because data on aetiology of syndromes were not available in Brazil. In addition, a nationwide training programme was set up to train healthcare providers in syndromic management. However, a recent evaluation of the quality of STD care in Rio de Janeiro and Santos (São Paulo) showed a very low level of acceptance of the syndromic

approach, with only 50% of the male and 3% of the female STD patients receiving a syndromic treatment.<sup>2</sup> The study results also indicated that most healthcare workers continued to use a clinical aetiological diagnosis for STD, because they overestimated the predictive value of clinical signs.

This study was set up to validate the currently recommended algorithms and, through its results, to increase the acceptance of the syndromic approach. The specific objectives were (1) to identify the most common aetiologies of genital discharge in patients attending with STD symptoms; (2) to calculate the sensitivity, specificity, and predictive value of a clinical presumptive diagnosis and of the national flow charts, with regard to the urethral discharge and the vaginal discharge syndromes; and (3) to assess the clinical cure rate of a syndromic treatment for genital ulcers.

## Materials and methods

### STUDY DESIGN

The study was conducted in five urban public STD centres in different geographic areas in

Brazil (Manaus, Recife, Belo Horizonte, São Paulo, and Porto Alegre). These centres were dermatovenerology clinics or sections of large public clinics and STD patients mainly attended the centres. From January to June, 1995, consecutive men and women, attending the centres with a genital ulcer syndrome or with complaints of genital discharge, were invited to participate in the study. Patients who were 12 years or younger and patients who had been treated for the current STD in another healthcare facility were excluded.

Written informed consent was obtained from all participants. Sociodemographic data, sexual and medical history were recorded by a nurse during a face to face interview, using a structured questionnaire. A physician performed a genital examination, including speculum examination for female patients, and recorded a presumptive diagnosis, based on his/her clinical experience. Genital samples (urethral and vaginal smears, cervical swabs, swabs from the ulcers) and blood was collected for laboratory examination by the same physician. After health education and counselling, a syndromic treatment was given, independent of the presumptive (aetiological) diagnosis.

#### LABORATORY PROCEDURES

During the examination a potassium hydroxide test was performed (considered positive when a fishy amine odour was released from vaginal fluid when it was mixed with 10% KOH so-

lution) and the vaginal pH was measured using a pH paper (Analyticalb 7-14, Farmitalia, Carlo Erba, Milan, Italy).

*Trichomonas vaginalis* was identified through a microscopic examination of a wet mount preparation in both men and women with genital discharge. A Gram stained vaginal smear for detection of candida spp and leucocytes and Gram stained urethral smears for the detection of Gram negative diplococci and leucocytes were done. Urethral and cervical smears were cultured for *Neisseria gonorrhoeae* by inoculation on modified Thayer-Martin medium, followed by incubation in a candle extinction jar at 35°C for 24-48 hours. Isolates were identified on typical colonial morphology, oxidase positive reaction, and Gram stain. *Chlamydia trachomatis* antigens were detected in cervical and urethral specimens by a direct immunofluorescence test (Chlamydia Direct IF Identification) (Biomerieux, Mency l'Etoile, France). All sera were screened by a Venereal Disease Research Laboratory test (VDRL) (Boehring, Marburg, Germany), and considered positive when the titre was  $\geq 1/4$ . Reagent samples were confirmed by a fluorescent treponemal antibodies absorption test (FTA-Abs) (Biomerieux, Mency l'Etoile, France).

Wet mount, Gram stains, culture for *N gonorrhoeae*, and syphilis tests were performed in the laboratory of the STD clinic by an experienced laboratory technician. Slides for the detection of *C trachomatis*, all Gram stained slides, and remaining sera were transported to the reference laboratory in São Paulo (Laboratory of the Faculty of Public Health of the University of São Paulo), where the chlamydia tests were performed and all other material retested for confirmation purposes.

#### VALIDATION OF ALGORITHMS

The clinical diagnosis was validated by comparing the result of the physicians' presumptive diagnosis with a gold standard laboratory diagnosis in order to determine sensitivity, specificity, and positive predictive value (PPV). The outcome of the national algorithms including a syndromic approach and/or risk factors was simulated using data from interviews and/or clinical examinations (flow charts see figs 1-3). The outcome of the national flow charts for situations where simple laboratory tests are possible were simulated using the results of the simple laboratory tests from the local laboratories (figs 1-3). These results were compared with the same gold standard diagnosis in order to compare their validity with the validity of the clinical presumptive diagnosis.

Gold standard diagnoses of STDs were defined as follows: gonococcal infection by a positive culture of *N gonorrhoeae*; chlamydial infection by a positive antigen test; candidiasis by a confirmed positive Gram stain for *C albicans*; trichomoniasis by the visualisation of mobile trichomonads on wet mount or a confirmed positive Gram stain. Diagnosis of bacterial vaginosis was made in the presence of three or four of the following signs: (1) abnormal vaginal discharge; (2) vaginal fluid

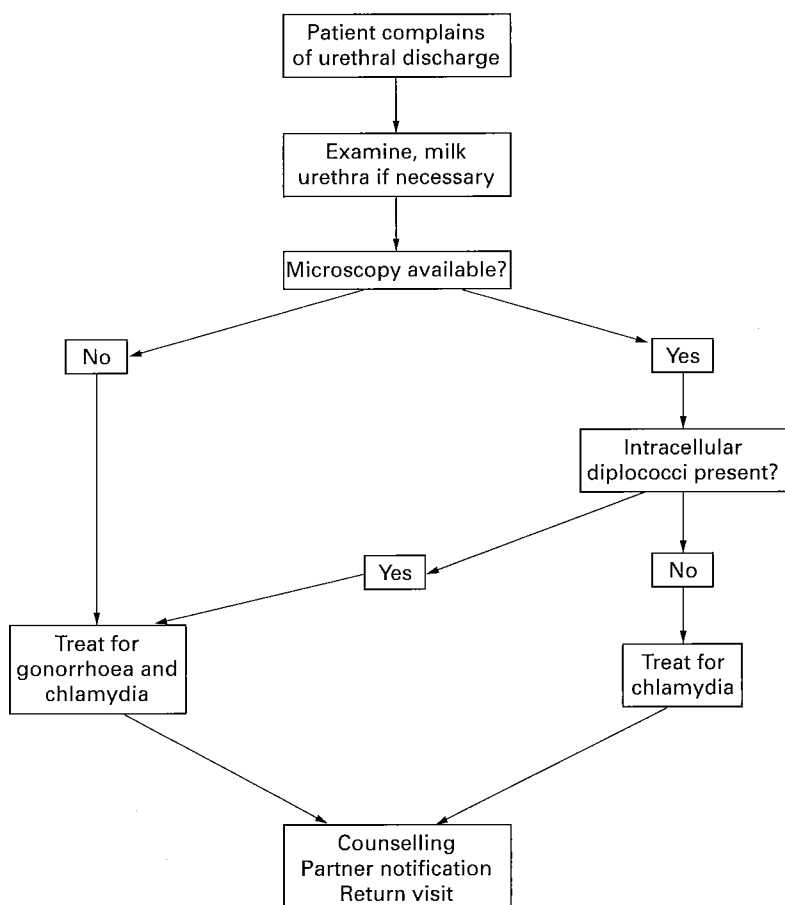


Figure 1 National flow chart for the management of urethral discharge in Brazil.

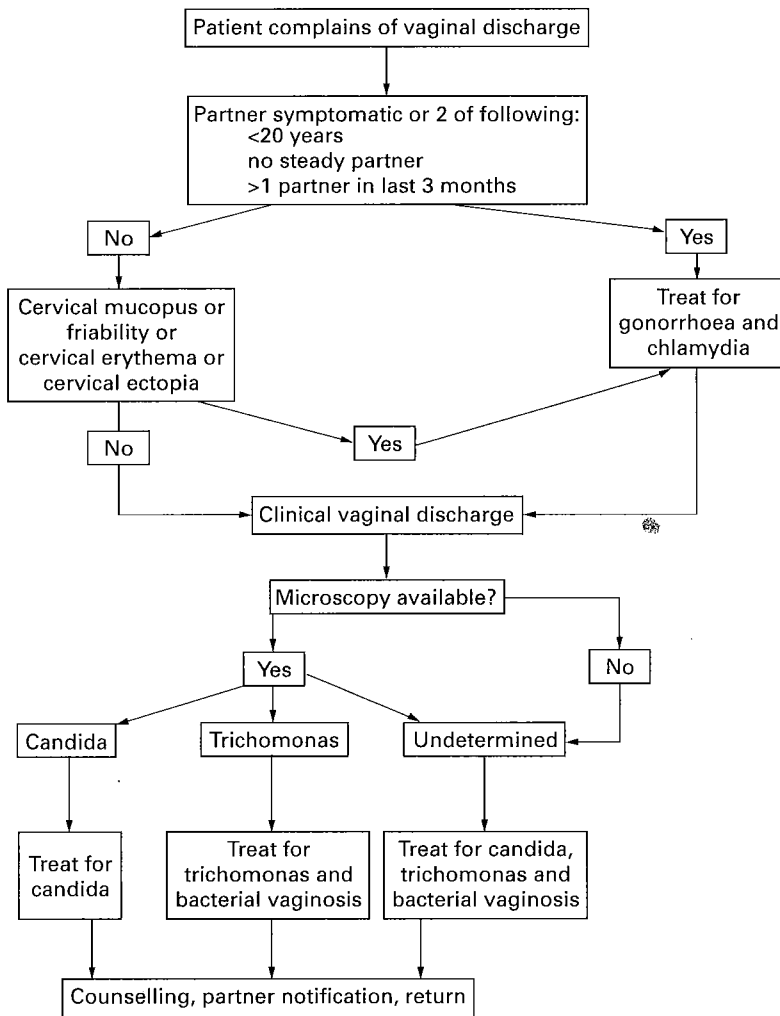


Figure 2 National flow chart for the management of vaginal discharge in Brazil.

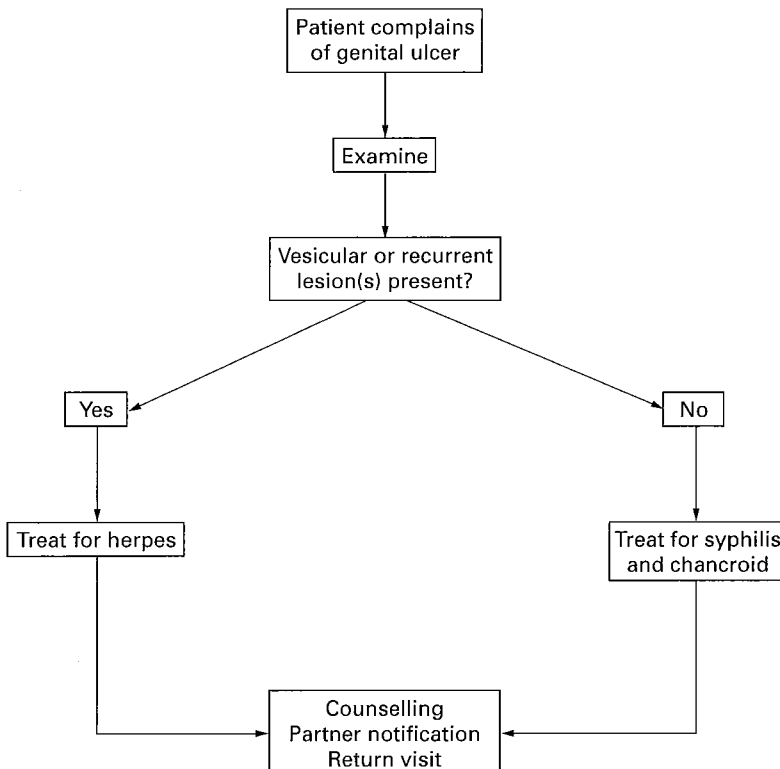


Figure 3 National flow chart for the management of genital ulcer in Brazil.

pH >4.5; (3) positive KOH test; and/or (4) presence of clue cells.

#### STATISTICAL ANALYSIS

Statistical analysis was performed using EPI-INFO 6.3 (Centres for Disease Control and Prevention, Atlanta and World Health Organisation, Geneva). Univariate analysis was performed using Yates's corrected  $\chi^2$  or Fisher's exact test for comparing proportions and Student's *t* test or Kruskal-Wallis test for comparing means and medians.

The study protocol was reviewed by one national and one international independent scientific board.

#### Results

##### CHARACTERISTICS OF THE STUDY POPULATION

A total of 955 patients, 607 men and 348 women, participated in the study. The relative contribution of the centres ranged from 3% to 42%, owing to differences in patient attendance. The mean age was 26.4 years for both men and women, but 16% of the men and 23% of the women were younger than 20 years. A higher proportion of men were single, compared with women, 70% *v* 43% ( $p < 0.001$ ). Men had started their sexual activities at a median age of 15, women at 16 years. Men also reported new or multiple sex partners more frequently than women (80% of the men and 33% of the women had a new sexual partner in the last 3 months). Eleven per cent of the men and 8% of the women reported consistent condom use. For patients without a regular partner, these proportions were 16% for men and 23% for women.

The median duration of symptoms before attending the health centre was 7 days for men and 35 days for women ( $p < 0.001$ ). Self medication or obtaining medication through some other route than a clinic or physician, before consultation, was frequent in both men (28%) and women (14%).

##### URETHRAL DISCHARGE SYNDROME

A total of 472 men presented with complaints of urethral discharge. The laboratory results were distributed as follows: *N gonorrhoeae* in 210 (44%);  $\geq$  five leucocytes, but no pathogens identified in 126 (27%); no leucocytes or pathogens in 53 (11%); *N gonorrhoeae* and *C trachomatis* in 39 (8%); *C trachomatis* alone in 35 (7%); and *T vaginalis* alone in nine (2%) of the men.

In table 1, a comparison was made between the laboratory diagnosis and the clinical presumptive diagnosis. A correct clinical presumptive diagnosis of gonorrhoea was made in 185 out of 210 cases of laboratory confirmed gonorrhoea (88%), a diagnosis of "chlamydia" or "non-gonococcal urethritis" was made in 77% of the confirmed cases of chlamydia, but no correct diagnosis of multiple infection was made.

The sensitivity, specificity, and positive predictive value of the clinical diagnosis for

Table 1 Comparison between a laboratory diagnosis and a clinical presumptive diagnosis in the urethral syndrome in men

Clinical diagnosis	Laboratory diagnosis						Total (n = 473)
	<i>N gonorrhoeae</i> (Ng) (n = 210)	<i>C trachomatis</i> (Ct) (n = 35)	Ng + Ct (n = 39)	<i>T vaginalis</i> without Ng or Ct (n = 9)	≥ 5 leucocytes, no germs identified (n = 126)	No leucocytes, no germs (n = 53)	
Gonorrhoea	185	6	30	1	26	9	257
Chlamydial infection	0	1	0	0	3	3	7
Non-gonococcal urethritis (NGU)	25	26	9	7	95	35	197
Gonorrhoea + NGU	0	0	0	0	0	2	2
Urethritis	0	2	0	1	2	4	9

Table 2 Validation of three different approaches for the diagnosis of gonococcal and/or chlamydial urethritis in men

Approaches	Gonococcal urethritis (n = 249)			Chlamydial urethritis (n = 74)		
	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
Clinical presumptive diagnosis*	86.3%	80.3%	83.0%	48.6%	57.3%	17.5%
National flow chart without laboratory†	98.8%	15.4%	57.5%	91.4%	7.4%	15.5%
National flow chart with Gram stain†	96.7%	99.1%	99.1%	91.4%	7.4%	15.5%

\*Gonorrhoea for gonococcal urethritis; Chlamydia or NGU for chlamydial urethritis.

†See figure 1.

gonococcal and/or chlamydial urethritis was calculated in table 2. The outcome of the national flow charts was simulated and the results of this validation were also added to table 2. The sensitivity of the national flow chart without laboratory tests was higher than that of the clinical presumptive diagnosis for both gono-

coccal and chlamydial urethritis (98.8% v 86.3% and 91.4% v 48.6%, for gonococcal and chlamydial urethritis respectively). Adding laboratory tests did not improve the validity of the flow chart for chlamydial urethritis, but the specificity and the positive predictive value for gonorrhoea increased significantly (specificity 99.1% v 15.4%; positive predictive value 99% v 57%,  $p < 0.001$ ).

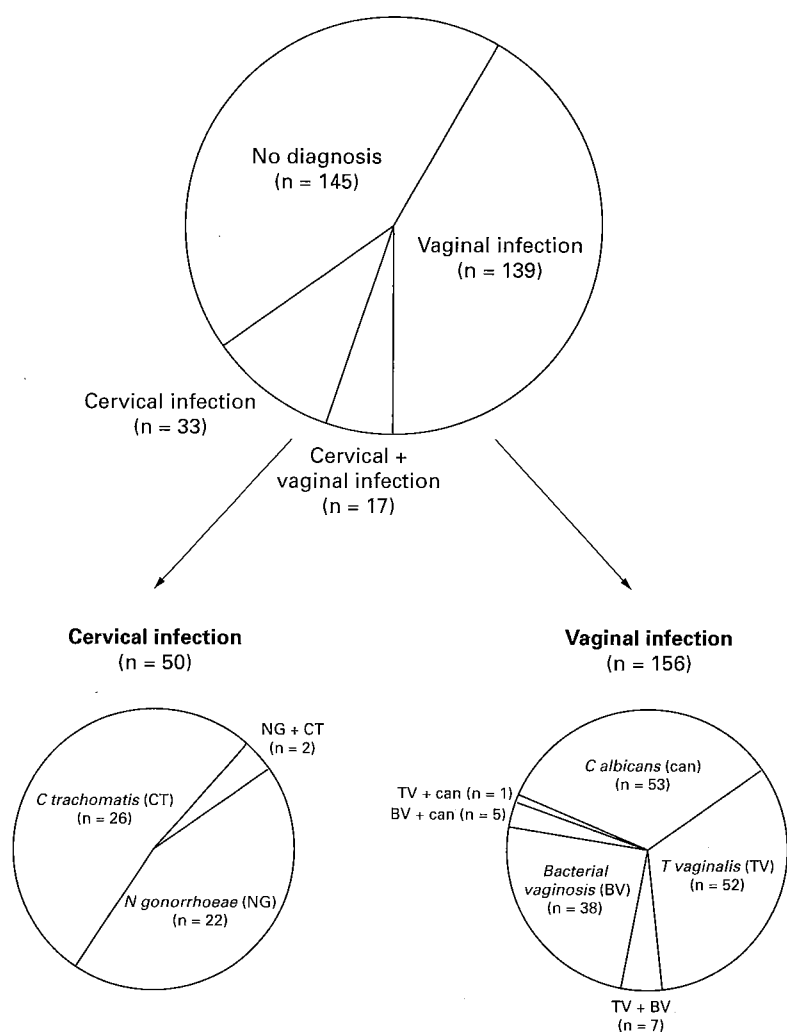


Figure 4 Aetiology of vaginal discharge complaints in women attending STD clinics in Brazil.

#### VAGINAL DISCHARGE SYNDROME

For a total of 334 women with complete laboratory results, no aetiological agents were detected in 145 (43%), vaginal agents were detected in 139 (42%), cervical agents in 33 (10%), and both vaginal and cervical agents in 17 (5%). A detailed description of the aetiologies of the different syndromes is presented in figure 4.

Two different clinical approaches were validated: one approach based on a clinical aetiological diagnosis only ("gonorrhoea", "chlamydia", "trichomoniasis", "bacterial vaginosis", or "candidiasis") and the other based on a clinical aetiological or syndromic diagnosis made by the clinician (presumptive aetiological diagnoses and "cervicitis" and "vaginosis"). The results of these validations, and of the validations of the national flow chart, are presented in table 3. The national flow chart includes, besides a syndromic approach, a risk assessment, which is positive when the women has a symptomatic partner, or when at least two of the following conditions are met: younger than 20 years, no steady partner, or more than one partner in the past 3 months (see fig 2). The sensitivity of the approach for cervical infection increased from 16% (clinical aetiological approach) to 54% (clinical + syndromic approach) and to 68%, when applying the national flow chart. Adding a laboratory examination for the diagnosis of vaginal infection decreased the sensitivity (from 94% to 45% and from 90% to 66%, for trichomoniasis/bacterial vaginosis and candidiasis respectively) but increased the specificity (from 18% to

Table 3 Validation of four different approaches for the diagnosis of vaginal discharge

Diagnostic approaches	Gold standard diagnoses		
	Gonococcal and/or chlamydial cervicitis (n = 50)	Trichomoniasis and/or bacterial vaginosis (n = 103)	Candidiasis (n = 59)
Clinical aetiological approach			
Sensitivity	16.0%	43.7%	50.8%
Specificity	97.9%	87.4%	84.2%
PPV*	57.1%	60.8%	41.1%
Clinical approach including syndromic diagnosis†			
Sensitivity	54.0%	54.5%	61.0%
Specificity	79.6%	72.3%	70.0%
PPV*	31.8%	46.7%	30.5%
National flow chart without laboratory tests‡			
Sensitivity	68%	94.2%	89.8%
Specificity	48.6%	18.5%	15.5%
PPV*	18.9%	34.9%	19.1%
National flow chart with laboratory tests‡			
Sensitivity	—	44.7%	66.1%
Specificity	—	100%	90.4%
PPV*	—	100%	60.0%

\* PPV = positive predictive value.

† Allowing for the presumptive diagnosis "cervicitis" and "vaginosis".

‡ See figure 2.

100% and from 15% to 90%, for trichomoniasis/bacterial vaginosis and candidiasis respectively).

#### GENITAL ULCER SYNDROME

A total of 156 patients with genital ulcer participated in the study. A positive syphilis serology, which indicates past or recent syphilis, was obtained in 31% of them. Nine of the patients presented with vesicular lesions or a history of vesicular lesions. The remaining 147 patients received a combined treatment for syphilis and for chancroid, according to the national flow chart (fig 3). Fifty nine patients returned for at least one follow up visit (38%). After 1 week the cure or improved rate for patients who received a syndromic treatment was 96.3% (52/54).

#### Discussion

This study allowed us to describe the aetiologies of common STD syndromes in Brazil as well as to compare the validity of different diagnostic approaches. The results underline the poor predictive value of a clinical aetiological diagnosis for genital discharge syndrome. A syndromic approach will result in the highest cure rate, as the sensitivity of this method of diagnosis is much higher than the clinical approach.

The validity of flow charts is probably dependent on the clinical setting, patient population characteristics, and clinicians' skills. The STD clinics in which the study was conducted were all easily accessible for patients with STDs. In these clinics, physicians were taking care of the patients, as is the case in most primary healthcare centres in Brazil. It is possible, however, that physicians in the study centres were more experienced in STD diagnosis than physicians in primary healthcare centres. If this is the case, the validity of the clinical approach when applied in a primary healthcare setting could be even lower than the validity found in this study.

The validity of different approaches was assessed by comparing the outcome of the approach with the results of reference laboratory tests, which were considered "gold standard". However, the reference laboratory tests used in this study are not 100% sensitive themselves. Immunofluorescence, for instance, might be only 70% sensitive for detecting chlamydia antigen.<sup>3</sup> It is thus likely that a proportion of cases that we labelled as false positives were in fact true infections. It is also possible that the proportion of the laboratory negative syndromes (11% of the urethral discharge and 43% of the vaginal discharge) could be reduced by using more sensitive tests, such as PCR for chlamydia.<sup>3</sup> However, the sensitivity, or the proportion of infections detected by the different approaches, is not likely to be influenced by the sensitivity of the gold standard method used.

The very low sensitivity of clinical aetiological diagnosis for urethral discharge syndrome found in this study was not unexpected. Indeed, many other studies have shown that typical clinical presentations of gonorrhoea or chlamydial infection have a low diagnostic accuracy and that an aetiological "guess" is highly unreliable.<sup>4</sup> Moreover, it is impossible to identify clinically dual or multiple infections, which are very common. A low sensitivity results in a lot of untreated infections, which places the infected person at continued risk of more serious complications and results in further disease dissemination. The national flow charts for the management of urethral discharge yielded the highest sensitivity compared with the other approaches. The flow charts using a syndromic approach, as promoted by the National AIDS Control Programme in Brazil, are the best way to obtain prompt and effective treatment of STDs in settings where laboratory facilities are lacking. Including simple laboratory tests in the flow charts will result in a higher specificity and positive predictive value. Using a Gram stain for the diagnosis of gonococcal urethritis, for instance, increased the positive predictive value from 57% to 99%. The higher positive predictive value means less overtreatment, which in turn reduces unnecessary drug costs, partner notification, and psychological problems caused by inappropriate labelling. However, the validity of a Gram stain, and hence the validity of a diagnostic flow chart including Gram stain, varies substantially with the experience of the laboratory technician and field conditions.<sup>5</sup> Moreover, a diagnostic flow chart including Gram stain should only be advised when results can be given within reasonable time delays—that is, no return visit is necessary for treatment.

Vaginal infection was the most common cause of vaginal discharge. The sensitivity of the laboratory diagnosis for vaginal infections was very high, but this is not surprising, as laboratory tests used in the flow chart, such as wet mount and Gram stain, were included in the gold standard diagnosis for trichomoniasis and candidiasis. More sensitive tests should be used for evaluating the simple diagnostic tests

for vaginal infections, such as culture for the detection of *T vaginalis*.<sup>6</sup> While vaginal discharge is most often caused by vaginal infections, cervical infection is more important with respect to potential sequelae and public health.<sup>7</sup> Moreover, the low sensitivity of symptoms and clinical signs for cervical infections hinders a syndromic approach. Several studies have demonstrated that risk markers, rather than signs and symptoms, are predictive for gonococcal and/or chlamydial infection.<sup>8,9</sup> In our study, the addition of a risk assessment increased the sensitivity of the diagnosis from 16% (clinical aetiological approach) and 54% (clinical syndromic approach), to 68% (syndromic approach including risk assessment). Although this approach is not ideal in women with vaginal discharge, because of the low specificity and positive predictive value, it is a clear improvement to the current practices in Brazil.

The validity of different approaches for the diagnosis of genital ulcers could not be assessed in this study, as gold standard laboratory tests were not available. However, the high cure rate of genital ulcers with a syndromic treatment for syphilis and chancroid suggests that syphilis and chancroid may be the most common causes of genital ulcers in Brazil. Other aetiologies may play a role in some regions, such as donovanosis in the Amazon region.<sup>10</sup> Further research should be done in Brazil to assess the aetiology of genital ulcers in the different regions, and to adapt the syndromic approach to genital ulcers, if necessary.

In conclusion, the syndromic approach should be further promoted as an essential part of STD control activities in Brazil. The results of the current study will help to convince policy

makers and those involved in the training of healthcare workers of the public health advantages of the syndromic approach in STD management.

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