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Evaluations Of Clinical Signs Currently And Not Currently Used In Syndromic Case Management (Scm) Of Reproductive Tract Infections (Rtis) Among Pregnant Women In Jamaica

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EVALUATIONS OF CLINICAL SIGNS CURRENTLY AND NOT CURRENTLY USED IN SYNDROMIC CASE MANAGEMENT (SCM) OF REPRODUCTIVE TRACT INFECTIONS (RTIS) AMONG PREGNANT WOMEN IN JAMAICA

by

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PUBLIC HEALTH

ABSTRACT

Reproductive tract infections include sexually transmitted infections, endogenous infections caused by overgrowth of organisms that can be present in the genital tract of a healthy woman, and iatrogenic infections.[3] In Jamaica, women in the reproductive age group of 15-44 years old accounts for 95% of all RTIs.[2] RTIs among Jamaican women of reproductive age can seriously impact the health of the women and their children.[10, 11, 12]

The advent of HIV/AIDS has had a significant impact on increasing awareness of the effect of STIs.[13,18,16] Health care organizations have reacted with great commitment to STI prevention and treatment as a significant factor in preventing the spread of HIV/AIDS.[3,5]

The traditional approach for diagnosing and managing infections in most developed countries is by identification of etiological agents by laboratory tests. The SCM approach has been recommended by the World Health Organization (WHO) as a cost-effective method of managing RTIs.[14,15] SCM uses groups of symptoms and easily recognized signs in the identification of well defined pathogens that cause RTIs.[5] This allows management of the patient's RTI in a single visit by providing treatment even where tests for etiological agents are unavailable.[5]

In 1997, the use of SCM among pregnant women was evaluated in Jamaica. The results of previous analyses show that SCM algorithm based solely on vaginal discharge has a marginal validity among pregnant women.[9] In this study an algorithm with two components was used: a risk assessment portion which contains behavioral risk factors predictive of RTI and a clinical portion which includes clinical assessment of vaginal discharge. During the implementation of this study, several other clinical signs such as cervical erosion, friable cervix, color of discharges were integrated in the algorithm. The validity of these added signs and the other clinical signs used in SCM have not been assessed.

The present study aims to evaluate the validity of the added clinical risk factors together with the current clinical signs used in SCM in diagnosing RTIs among pregnant women in Jamaica. From the results of these analyses, this study aims to develop modified algorithms/s that best suit this specific population.

Keywords: Reproductive tract infections (RTIs), syndromic case management, human immunodeficiency virus.

DEDICATION

This dissertation is proof that with hard work anything is possible, it may have taken me a long time to come to this point but it is all worth it. With my heartfelt affection, I dedicate all my work to my late mother, Lilia Receno del Rosario, who unfortunately did not see the end of my struggle, but her spirit serves as my guide in every word I wrote in this dissertation, to my father, Nazario del Rosario, for his strength and encouragement, to my brothers, sisters, nephews and nieces for their support and motivation, and to my friends, for believing in me. To all of you, I dedicate this paper.

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Above all, I thank God for my health, and strength in overcoming all the obstacles I encountered in reaching the "end of the tunnel." My goal is that through this work I would be able to make significant contributions in RTI control and prevention of the devastating effects of these dreaded infections and adverse pregnancy outcome. Through this, I'm hoping for healthy women and infants.

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LIST OF ABBREVIATIONS

AUC	area under the curve
BV	bacterial vaginosis
CA	candidiasis
CT	chlamydia
GC	gonorrhea
NPV	negative predictive value
PID	pelvic inflammatory disease
PPV	positive predictive value
ROC	receiver operating curve
RTI	reproductive tract infection
SCM	syndromic case management
STD	sexually transmitted disease
STI	sexually transmitted infection
TV	trichomoniasis
WHO	World Health Organization

INTRODUCTION

Although there is a considerable decline in the total cases of syphilis, the total cases of other reproductive tract infections (RTIs) have remained high in Jamaica.[1] In 2000, the report of the National AIDS Committee in Jamaica showed a considerable increase in the total cases of vaginal discharge syndrome (i.e., bacterial vaginosis , trichomoniasis and candidiasis) as compared to the total cases in 1999.[1] Similarly, an increase in the total cases of genital discharge syndrome which includes gonorrhea and chlamydia was also reported. Although both men and women are vulnerable to the impact of these infections, women and their infants bear the burden of sexually transmitted infections (STIs) disproportionately.[2] A number of conditions such as ophthalmia neonatorum (ON), pre-term deliveries, low birth weight and pre-maturity have been reported to have strong associations with RTIs.[2, 3] It has also been reported that RTIs, mostly STIs, facilitate HIV transmission.[3]

The traditional method of diagnosing RTIs in most developed countries is the use of laboratory tests. However, in most developing countries this approach is not currently feasible due to lack of infrastructure, resources and trained personnel. The World Health Organization (WHO) advocates the use of syndromic case management (SCM) as a cost-effective method of diagnosing RTIs, and as a means of preventing transmission through early detection and treatment.[4] SCM is a method wherein physicians base their diagnosis and treatment not on laboratory testing but rather on recognition of a clinical syndrome. The clinical syndrome includes a group of easily recognizable symptoms and signs associated with infection by a number of well-known etiological agents.[5,6] This approach relies on the use of a flow chart (algorithm), which is a step by step diagnostic guide in medical

decision making. Upon identification of a syndrome, treatment is provided that will deal with the most probable causative organisms responsible for the particular syndrome.

The use of SCM among women attending STI and family planning clinics in Jamaica has been evaluated.[7, 8] The results of these studies showed that SCM is feasible among women presenting in sexually transmitted disease (STD) clinics, but the utility of this method is uncertain among family planning clinic attenders due to its low sensitivity and specificity. In a 1997 study, evaluation of SCM among pregnant women in Jamaica showed marginal validity.[9] However, when the investigators of the 1997 study included clinical signs not in the current SCM algorithm, they failed to evaluate the performance of these added clinical signs.

From the data obtained among pregnant women in Jamaica (1997), this study will evaluate the performance of these added clinical signs together with the clinical signs currently used in SCM. These clinical factors will be compared with the results of the laboratory tests (gold standard). This will enable us to determine the validity of these clinical signs in diagnosing RTIs among pregnant women. The information from these analyses will be used in the development of algorithm/s that will be suited to this group who experience mostly asymptomatic infection. The results of this study can lead to the implementation of a cost-effective tool for management of RTIs in pregnant women, to enable early detection, prevent adverse pregnancy outcomes and reduce STI/HIV transmission. Precise etiological diagnosis for RTI in a resource-poor setting like Jamaica is difficult; SCM may be the most feasible approach for screening pregnant women for RTIs.

GOALS, AIMS AND HYPOTHESES

Goals

The goal of this study is to develop a modified algorithm with the highest efficacy that will serve as better diagnostic tool for RTIs. In this study, we will evaluate the clinical signs used in SCM in Jamaica for use among pregnant women. The clinical signs will be compared with laboratory tests in order to assess their validity (sensitivity and specificity) in diagnosing RTIs among pregnant women in Jamaica. The long-term goal of this study is to provide a screening method for RTIs that will allow early detection and treatment of RTIs of pregnant women. Early intervention in this group of women may lead to prevention of adverse pregnancy outcomes associated with RTIs.

Specific Aims

Aim 1.

1.a. To compare the RTI diagnosis based on clinical signs (e.g. runny/malodorous discharges, mucopus cervix) currently used in SCM algorithm in Jamaica with laboratory test results ("gold" standard).

Ho 1.a. The proportion of women with positive diagnosis for RTIs based on the clinical signs (e.g. runny/malodorous, mucopus cervix) currently used in SCM algorithm in Jamaica is the same as the proportion of women with positive diagnosis using laboratory tests.

Ha 1.a. The proportion of women with positive diagnosis for RTIs based on the clinical signs (e.g. runny/malodorous discharges, mucopus cervix) currently used in SCM algorithm in Jamaica is higher than the proportion of women with positive diagnosis using laboratory tests.

1.b. To compare the RTI diagnosis between the combination of clinical signs not currently (e.g. friable cervix, cervical erosion, yellow vaginal discharge) and currently (runny/malodorous, mucopus cervix) used in SCM algorithm in Jamaica with laboratory test results ("gold" standard).

Ho 1.b. The proportion of women with positive diagnosis for RTI based on the combination of clinical signs not currently (e.g. cervical erosion, friable cervix, yellow vaginal discharge) and currently (e.g. runny/malodorous, mucopus cervix) used in SCM algorithm in Jamaica is the same as the proportion of women with positive diagnosis using laboratory tests.

Ha 1.b. The proportion of women with positive diagnosis for RTI based on the combination of clinical signs not currently (e.g. cervical erosion, friable cervix, yellow vaginal discharge) and currently (runny/malodorous, mucopus cervix) used in SCM algorithm in Jamaica is higher than the proportion of women with positive diagnosis using laboratory tests.

Aim 2.

2.a. To develop algorithms modified by the addition of simple laboratory tests (e.g. vaginal pH, wet mount, whiff test) and added clinical signs with higher sensitivity for diagnosing RTIs among pregnant women.

Ho 2.a. The sensitivity of the current algorithm will be the same as those of the modified algorithms (e.g. combination of simple laboratory test such as vaginal pH, wet mount, whiff test and clinical signs).

Ha 2.1a. The modified algorithms (e.g. combination of simple laboratory test such as vaginal pH, wet mount, whiff test and clinical signs) will show a 50% increase in sensitivity when compared to current algorithm.

Ha 2.1b. The modified higher sensitivity algorithms (e.g. combination of simple laboratory test such as vaginal pH, wet mount, whiff test and clinical signs) will show a 30% decrease in specificity when compared to the current algorithm.

Aim 3.

3.a. To determine a modified algorithm with the highest efficiency by considering the greater importance of detecting true positives for each RTI as compared to excluding false positives.

Ho 3.a. The efficiency of the modified algorithm (e.g. combination of simple laboratory test such as vaginal pH, wet mount, whiff test and clinical signs) as defined by the receiver operating characteristic (ROC) curve will be the same as the current algorithm.

Ha 3.b. The efficiency of the modified algorithm (e.g. combination of simple laboratory test such as vaginal pH, wet mount, whiff test and clinical signs) as defined by the ROC curve will be the higher than the current algorithm.

LITERATURE REVIEW

Extent of the Problem on RTIs

Throughout the 20th century, the number of pathogens recognized as causing RTIs (STIs and vaginitis) and the morbidity associated with them has increased.[6] In 2000, the WHO reported a global prevalence of 340 million cases of curable STIs among adults. The annual estimated number of STI cases noted worldwide were as follows: 12 million cases of syphilis infection affecting adults between the ages of 15-49, 62 million cases of gonorrhea (GC), 89 million cases of chlamydia (CT), and 170 million cases of trichomoniasis (TV).[16] RTIs also rank as one of the top five conditions for which adults seek health care services.[5]

Although STIs have devastating effects on both men and women, the bulk of the complications and sequelae of these diseases are borne by women and children. Women are much more vulnerable for RTIs since transmission of infectious discharges (GC, CT, TV) appear to be more efficient from male to female. Women are also more likely to be asymptomatic and therefore, more difficult to be diagnosed early with an infection.[3, 44] WHO estimates that the morbidity and mortality due to STIs are 4-5 times greater among women as compared to men. Some of the detrimental complications associated with RTIs include pelvic inflammatory disease (PID), infertility, ectopic pregnancy, preterm delivery, and ophthalmia neonatorum.[17] Table 1 summarizes the proportion of women with

RTIs who experienced adverse pregnancy outcomes compared to pregnant women without RTIs.

Table 1 Proportion of Pregnant Women Experiencing Adverse Outcomes Associated with RTIs Compared to Pregnant Women without RTIs

Maternal Diagnosis	Fetal Wastage (%)	Low birth weight (LBW) or prematurity (%)	Congenital or perinatal infection(%)
Chlamydia	?rare	10-30	40-70
Gonorrhea	?rare	11-25	30-68
Early syphilis	20-25	15-50	40-70
Genital herpes			
Primary	7-54	30-35	30-50
Recurrent	?rare	?rare	0.4-8
Bacterial vaginosis	?rare	10-25	?rare
Trichomoniasis	?rare	11-15	?rare
No RTI	4-10	2-12	NA

Note: From Gernain, Piot et al.

In 1995, the Annual Report on Communicable Diseases in Jamaica reported that the incidence of gonorrhea and chlamydia had reached 10,620/100,000, and 12,219/100,000 respectively.[10] This represented a tremendous increase over the rates in 1987 wherein the incidence of gonorrhea was 8,482/100,000 and that of chlamydia was 6,532/100,000.[10] The incidence of vaginal discharge syndrome was reported to be 18,319/100,000 in 1995. Not only was there an increase in the number of RTIs among women, but, there was also a rise in the number of congenital syphilis and ophthalmia neonatorum. In 1995 alone, the incidence of congenital syphilis was recorded to be 46/100,000 where as, in 1986 the incidence was 15/100,000. In addition, the incidence of opthalmia neonatorum, which is considered to be the major STI affecting newborns, also grew from 13/100,000 in 1986 to 414/100,000 in 1995.[10] RTIs in Jamaica warrant even

greater concern because the numbers reported do not include cases seen in the private health sector that are underreported in the public sector.

In 2000, the National AIDS Committee in Jamaica reported the total number of STIs obtained from all the major STI clinics in the island.[1] The number of total cases of vaginal discharge syndrome was 20,229 from January-December of 2000. This showed an increase from 1999 when 15,978 total cases were reported. Similarly, an increase in the total number of genital discharge syndrome was also observed, 28,712 total cases was reported in 2000 as compared to 22,970 total cases reported in 1999.[1] Based on the studies performed in 1993 in Jamaica, 16% of genital discharge syndrome was due to gonorrhea and 25% was due to chlamydia. However, the committee also reported a decline in the total number of syphilis cases in Jamaica: from 702 total cases in 1999 to 586 total cases in 2000.[1] A decrease in total cases of opthalmia neonatorum was also observed; in 1999, 141 total cases of opthalmia neonatorum was reported compared with 67 cases in 2000. The observed decline in syphilis and ophthalmia neonatorum is credited to better screening methods and timely treatment for both syphilis and opthalmia neonatorum. These data shown that availability of reliable screening methods have a significant impact in reducing STIs. However, the observed increase in vaginal and genital discharge are attributed to improved STI surveillance in Jamaica.

In a study conducted among 752 women attending STI clinics in Jamaica, Behets et al.[7] reported the prevalence of cervical infections (gonorrhea and/or chlamydia) to be 34%. The prevalence of trichomoniasis in this population was documented to be 25%; and 54% of the women had at least one STI. RTIs, especially STIs, are also reported to be common among women attending family planning clinics in the island.

Behets et al.[8] observed that 26.9% of the 767 women who participated in a study on family planning clinic attenders had at least one STI. The prevalence of gonorrhea in this population was 2.7%, and of chlamydial infection was 12.2%. The prevalence of cervical infections was documented to be 14.1%, prevalence of trichomoniasis was 11.5% and syphilis seroreactivity was 5.9%.

Among 371 pregnant women in Jamaica, Kristensen et al.[18] (unpublished, 1997) reported that the prevalence of STIs in this population was 5.4% for gonorrhea, 17.8% for chlamydia, 3.6% for syphilis, and 1.3% for HIV (Appendix B). Similarly, Kamara et al.[19] reported that the prevalences of vaginal infections in this same study were 18% for trichomoniasis, 44.1% for bacterial vaginosis and 30.7% for candidiasis (Appendix B). These data show an overwhelming need for a sustainable and cost-effective screening tool for RTIs among pregnant women, in order to deliver prompt treatment and prevent transmission.

Syndromic Case Management

History and D*efinition*

Evidence on the role of RTIs, particularly STIs, in increasing vulnerability to HIV infection has been building since the 1980s.[20, 46] This association led to a mounting interest on RTI prevention and treatment by health care organizations. However, in most developing countries, testing citizens for RTIs by means of etiologic diagnosis can be problematic due to lack of funds, trained laboratory personnel and laboratory facilities.[20, 45] Variations in sensitivity and specificity of available laboratory tests for RTIs, mostly STIs are also observed.[5] Practitioners in resource poor settings, therefore, rely on their

expertise and experience in diagnosing patients infected with RTIs by means of patient history and clinical examination. This approach of clinical diagnosis, though inexpensive, has been reported to be of limited value in diagnosing RTIs due to non-standardization and highly variable skill levels.[4, 46]

As a response to the increasing number of undiagnosed STI cases worldwide, the WHO endorsed the use of syndromic case management (SCM) in 1988. This approach uses clinical algorithms (flow charts) based on STD syndrome and array of symptoms and clinical signs easily recognizable for a particular pathogen.[20, 47] These flow charts map out the steps needed for diagnosing and treating RTIs. SCM offers immediate diagnosis and treatment without the necessity of laboratory tests and advanced medical expertise. In addition, these algorithms may be displayed as posters in examination rooms, or can also be in the form of small pamphlets that can be easily referenced by health care providers. This approach towards diagnosing RTIs has been evaluated in the field and found to be feasible but in need of some improvement.[4] In 1993, a group of experts from the WHO developed a tool known as "risk assessment" designed to improve the validity and effectiveness of the algorithm-based RTI screening. Risk assessment is a short checklist of questions that include evaluation of an individual's behavior and social circumstances that have been identified as potential risk factors for RTI.[5] Some of the factors examined in risk assessment are the number of sexual partners of an individual, age, whether or not the individual had a new partner in the recent month, previous STI infections, presence of vaginal discharge, abdominal pain and urethral discharge of the client's partner. Each answer has a weighted score and a certain total score or higher indicate treatment for gonorrhea and chlamydia. For example, the vaginal discharge algorithm is used

as follows (Appendix A): History and risk score assessment are obtained from a woman with a complaint of vaginal discharge. If the observed nature of the vaginal discharge is runny/malodorous, the woman will be treated for trichomoniasis/bacterial vaginosis, if the discharge is white/curd-like, the woman will be treated for candidiasis. Inspection of the cervix will then be performed and if mucopus is observed, treatment for cervicitis (GC/CT) will be given. However, if there is an absence of mucopus but the risk score is $\geq$ 2, treatment for cervicitis will still be given. A risk score of < 2 and absence of mucopus indicates no treatment. Patients identified with gonorrheal infection will be treated with ciprofloxacin or cefixime. Doxycycline or tetracycline will be given as treatment for chlamydial infections. Nystatin or miconazole are given to patients with candidiasis.[21] Similarly, individuals diagnosed with trichomonas/bacterial vaginosis are treated with metronidazole.[21] Table 2 summarizes the WHO treatment recommendation for syndromic case management of RTIs.

Table 2 Summary of WHO Treatment Recommendations for RTIs

RTI	Treatment	Contraindications
Trichomonas/Bacterial vaginosis	*Metronidazole 2g orally in a single dose or Metronidazole 400-500 mg orally twice daily for 7 days	
Candidiasis	Nystatin 100,000 units intravaginally daily or Miconazole or clotrimazole 200 mg intravaginally daily for 3 days or *Clotrimazole 500 mg intravaginally as a single dose	
Gonorrhea	Ciprofloxacin 500 mg tablet as a single oral dose or Ceftriaxone 250 mg intramuscular (IM), as a single dose or *Cefixime 400 mg tablet as a single oral dose or Spectinomycin 2 g intramuscular as a single dose	Ciprofloxacin is contra-indicated during pregnancy
Chlamydia	Doxycycline 100 mg tablet, orally , twice daily or Tetracycline 500 mg tablet, orally, four times daily for 7 days	Doxycycline and tetracycline are contra-indicated during pregnancy
Syphilis	*Benzathine penicillin G MU IM in a single session or Aqueous procaine penicillin G 1.2 MU IM daily for 10 consecutive days	

* Antimicrobial drugs used as treatment for RTIs in Jamaica.

Studies have shown that among women with vaginal discharges, the sensitivity of detection of gonorrhea and or chlamydia significantly improved when risk assessment based on local factors such as demographic and behavioral characteristics were added in the algorithm. A study conducted in an antenatal clinic in Haiti showed that a syndromic case approach with risk assessment (risk-inclusive algorithm) correctly identified approx-

imately 9 out of 10 women infected with STIs.[22] An increase in sensitivity and specificity in the clinical diagnosis of symptomatic infected women was also observed in this study. Similarly, Mayaud et al.[23] reported that among 964 pregnant women in rural Tanzania, the use of a risk assessment inclusive algorithm in SCM improved the performance of correctly diagnosing gonorrhea and chlamydia as compared to an algorithm based solely on clinical examinations.

Advantages

One of the advantages of SCM is that physicians at primary health care sites can use this method. SCM lessens dependency on laboratory tests. In most resource poor settings, laboratory tests may be costly or non-existent, and often, it may take a few weeks to months to obtain the results.[5] Through using SCM, health care providers are able to allocate funds and time for other necessities such as treatment. SCM also allows health care providers to expedite care and decrease referrals to sometimes less accessible STD services. Studies have shown that providing patients with treatment at their first visits decreases loss of patients due to the need for follow-up to receive therapy. This greater coverage reduces further transmission and complications due to untreated infections.[5]

In places where the ratio between doctors and patients is large, non-physician health workers trained in SCM can provide additional help and expand the range of facilities that can diagnose and treat RTIs.[4] If effective and used efficiently, this would enable establishment of a well-organized surveillance system and improved management of STIs that would decrease the prevalence of RTIs and the adverse pregnancy outcomes related to such infections.[5]

Limitations in the Use of SCM

One of the disadvantages of using SCM is that this approach has no immediate impact on asymptomatic STD cases that are prevalent in most developing countries.[24,25] It has been estimated that 30% of women infected with *N. gonorrhoeae* are asymptomatic whereas up to 70% of women with *C. trachomatis* are asymptomatic.[26] These women tend to be misdiagnosed or not treated for infection. Asymptomatic individuals are not helped by SCM since this approach was developed as a tool to improve clinical care of patients coming spontaneously to health facilities with symptoms and signs. It is therefore critical that ways to increase the efficacy of the syndromic approach among asymptomatic women be given careful consideration in the development of enhanced algorithms that use simple laboratory screening tests along with SCM.

Another disadvantage of the SCM approach is the issue of over-treatment. The use of an algorithm in SCM allows health care professionals to treat for all possible STI causes of certain symptoms, therefore, patients may receive antibiotics and other drugs that they do not need.[20] The negative effects of over-treatment including adverse side effects and cost of the drugs may be substantial on the part of the patients. In addition, the SCM approach was also reported to misidentify uninfected individuals. A method that wrongly identifies a person as infected is often not acceptable in communities as a screening method for early detection of disease.

Evaluation of Syndromic Case Management

One of the parameters to be considered in the evaluation of SCM is its validity. In this case, the components of validity, sensitivity and specificity, are assessed by comparing the diagnosis made with the SCM algorithm with a gold standard (laboratory tests

results).[21] Sensitivity of a flow diagram is the proportion of infections correctly detected by the algorithm. Specificity is defined as the proportion of patients who are uninfected and are correctly diagnosed as such by the algorithm. The Positive Predictive Value (PPV) of the algorithm is the proportion of diagnoses confirmed by the gold standard. In contrast, the Negative Predictive Value (NPV) signifies the proportion of negative results confirmed by gold standard.[21] Several studies in different settings have evaluated the validity of SCM in assessing RTIs among women.

Use of SCM among women

The use of syndromic management among asymptomatic women is complicated, but, among symptomatic women, it is considered as the most cost-effective tool in diagnosing RTIs. Several studies reported that the use of SCM has a significant impact in the provision of prompt treatment for STIs. A study conducted in Mwanza, Tanzania [27] concluded that the use of SCM achieved an STI cure rate of 96-98%. In Zambia and Cote d'Ivoire, the SCM approach led to a cure rate of 87%-97% for vaginal discharge, 82%-100% for female genito-urinary disease.[28] The favorable outcome was attributed to improved management of STIs, regular supervision and availability of drugs to individuals diagnosed with STI through case management.

The WHO has recommended that SCM should be adapted to the setting where it is to be used, since no single algorithm works in all settings. For example, health care providers and decision makers should consider factors such as clinical setting and disease prevalence in the development of an algorithm. These factors can influence the optimum balance between sensitivity and specificity. Costello et al.[17] (1998) concluded in a study done in Malawi, that adding complaints of lower abdominal pain without physical signs

of upper tract disease, and external and bimanual examinations, improved the diagnostic performance of the flow chart used in SCM. This study was conducted among 550 Malawian women with non-ulcerative genitourinary complaints. The prevalences of RTI in this population were 19.5% for cervical infections, 33.8% for trichomoniasis, 22.6% for Bacterial vaginosis, 27.8% for candidiasis, 17.9% for syphilis and 82.8% for HIV. Among the Malawian women who participated in their study, the authors found that when compared to gold standards, the algorithm used has a sensitivity and specificity of 61% and 68% respectively. In addition, PPV of the approach was 31%.

Among 395 Tanzanian women attending a STI clinic in Tanzania, Mayaud et al.[29] showed that the use of WHO algorithm with risk assessment had a sensitivity of 62% and specificity of 64%. The PPV of the syndromic approach in this population was 18%. The mean age of the women in this study was 21-30 years. The prevalences of STI in this population of women were 11.4% for gonorrhea/chlamydia, 38% for candidiasis and 25% for trichomonas. In this study, the authors reported that the addition of risk assessment in the SCM algorithm in diagnosing women with vaginal discharges reduced over- treatment of gonorrhea/chlamydia. However, this risk assessment inclusive algorithm failed to identify 38% of the women with cervical infection. Therefore, the factors or elements of the risk assessment may require some adjustment in different settings. The investigators concluded that the use of a risk assessment tool in addition to the clinical algorithm was feasible regarding the time for administration, and acceptable to most of the health care providers in this particular setting. Sanchez et al.[30] evaluated the use of a WHO modified risk assessment algorithm among 324 Peruvian women complaining of a yellow vaginal discharge and/or lower abdominal pain. The performance of the modified algorithm

showed a sensitivity, specificity and PPV of 98%, 13% and 16% respectively in detecting RTI. Among those women who received a score of ≥ 2 in the risk assessment, clinical assessment was performed. The sensitivity, specificity and PPV of this tool were 46%, 90% and 36% respectively. Etiological diagnosis for cervical infection showed a prevalence of 14.8%, and that of BV or TV was 48%. The authors suggested that in a setting wherein resources are limited, a chief complaint of yellow discharge was predictive of vaginal and cervical infections. In this particular study, the mean age of the participants was 24.7 years. The prevalence rates of RTIs were 12.2% for gonorrhea/chlamydia, 7.3% for trichomonas, and 30% for bacterial vaginosis. In Morocco, Ryan et al.[31] detected an 8.4% prevalence of cervical infections among 656 women with vaginal discharge complaints. The prevalence of trichomonas/Bacterial vaginosis was 29.4%. The mean age of the women in this study was 30 years. Upon application of the WHO algorithm that included use of speculum and bimanual examination, the sensitivity, specificity and PPV of the approach were 61%, 43% and 10% respectively, among women whose risk assessment score were less than 2 (risk assessment negative).

In Benin, Alary et al.[32] validated the use of SCM among 192 symptomatic women. In this study, the prevalence of cervical infection was 7.8%. Upon application of the SCM, the sensitivity of the risk-inclusive algorithm was reported to be 86.7%, the specificity was 41.8%, and PPV was 11.2%. The application of the algorithm that includes speculum examination had a sensitivity of 93.3%, specificity of 34.5% and PPV of 10.8%. Moherdaui et al.[33] in a study done among 334 Brazilian women reported prevalence of cervical infections to be 17%. The prevalence of vaginal infection was 74%. In this study, the performance of clinical etiological diagnosis was compared with SCM and

the use of Brazilian flow chart in the diagnosis of RTIs. Results of this study showed that the sensitivity, specificity and PPV of clinical etiological diagnosis was 16%, 97.9% and 57.1% respectively in detecting cervical infections. However, validation of SCM showed sensitivity to be 54%, specificity was 79.6% and PPV was 31.8%. The national flow chart had a sensitivity of 68%, specificity of 48.6% and PPV of 31.8% for diagnosing cervical infections. Table 3 summarizes the variations in sensitivity, specificity, PPV and NPV reported in the evaluation of SCM among symptomatic individuals in different settings.

Table 3 Summary of Evaluation of SCM among Symptomatic Women

Authors, year	Study population	Method	Prevalence of STIs	Results of validation of SCM
Daly-Costello C et al, 1998	550 consecutive Malawian women with non-ulcerative genitourinary complains	Cross-sectional study design	Cervical infection-19.5% (17.1%GC, 3.7% CT) Dual infection with GC and CT-1.3% TV-33.8% BV- 22.6% CA- 27.8% Syphilis-17.9% HIV-82.8%	Sensitivity of WHO risk assessment was 43%, specificity was 73% and PPV was 28%. Addition of speculum showed sensitivity to be 62%, specificity was 61% and PPV was 27% Modified Malawi risk assessment showed sensitivity to be 61%, specificity was 68% and PPV was 31% Used of bimanual examination shows sensitivity to be 72%, specificity was 56% and PPV was 29%.
Mayaud et al, 1998	395 consecutive female patients with complaint of genital discharge and attending STD clinic and 628 consecutive pregnant women reporting at antenatal clinic (ANC) in rural Tanzania	Cross-sectional study	STD clinic attenders: GC/CT-11.4% CA-38% TV-25% ANC clinic attenders: GC/CT-8% CA-38% TV-34%	Sensitivity of WHO algorithm at STD clinic was 62%, and specificity was 64%, the PPV was 18% Sensitivity of algorithm at ANC was 46%, specificity was 84% and PPV was 18%
Sanchez et al, 1998	630 consecutive female with chief or elicited complain of yellow vaginal discharge in Lima, Peru	Cross-sectional study	CT-10.9% GC-1.6% GC/CT-12.2% TV-7.3% BV-30% TV/BV-33.2%	Modified WHO risk assessment algorithm had a sensitivity of 98%, specificity of 13% and PPV of 16% Sensitivity of algorithm that includes assessment of cervical infection was 46%, specificity 90% and PPV 36%
Ryan et al, 1998		Cross–sectional study with a duration of 8 months	Among women with complaint of vaginal discharge: GC/CT-8.4% TV/BV- 29.4%	Application of WHO algorithm which include speculum and bimanual examination has a sensitivity of 61%, specificity of 43% and PPV of 10% Results of second algorithm with risk assessment based on local data has a sensitivity of 24%, specificity of 93% and PPV of 27%
Alary et al, 1998	192 symptomatic women in Benin	Cross-sectional study	GC/CT-7.8%	Results of an algorithm with risk assessment and clinical signs showed a sensitivity of 86.7%, specificity was 41.8%, PPV was11.2% and NPV was 97.4%. Algorithm that include speculum examination has a sensitivity of 93.3%, specificity of 34.5%, PPV of 10.8% and NPV of 98.4%

Authors, year	Study population	Method	Prevalence of STIs	Results of validation of SCM
Moher-daui et al, 1998	334 symptomatic Brazilian women	Cross-sectional study Comparison of 1)clinical etiological diagnosis only of GC, CT, TV and BV , 2) clinical etiological diagnosis SCM and 3) Brazilian national flow chart	Cervical infection-17% Vaginal infection-74% Mixed infection-9%	Sensitivity for cervical infection was 16% by clinical etiological diagnosis, clinical plus SCM was 54% and the national flow chart was 68%. Addition of laboratory test for diagnosis of vaginal infection decreased sensitivity of vaginal infection from 94% to 45% With a corresponding increase in specificity, form 18% to 100%

SCM among Asymptomatic Individuals (Antenatal and Family Planning Clinic Attenders)

The consequences of RTIs have more serious impact among pregnant women because of the possible adverse effects on the unborn child. Several studies have shown RTIs to have significant association with infertility, spontaneous abortion, miscarriage, ectopic pregnancy, premature delivery, and low birth weight.[34,35,36,37] In most developing countries, RTIs have been implicated in increased maternal and perinatal mortality. Therefore, a simple, cost effective method like syndromic management is needed for diagnosing STD infection among pregnant women. However, most studies conducted with pregnant women have suggested that improvement should be made in the application of SCM in this group, since in most instances pregnant women do not recognize nor report symptoms of RTIs.

In 2000, Fonk et al.[38] reported that among 334 Kenyan pregnant women, the sensitivity of the current Kenyan SCM algorithm was 36%. The specificity was reported to

be 69% and PPV was 15%. When compared to five algorithms generated by the investigators, the observed sensitivity ranged from 45% to 70%. Specificities ranged from 63% to 46%. The prevalence of RTIs in this population were 3% for gonorrhea, 11% for chlamydia, 55% for candidiasis, 26% for trichomonas and 8% for Bacterial vaginosis. Hamzaoui et al.[39] reported that among 409 pregnant women in Tunisia, the sensitivity of WHO algorithm in diagnosing cervicitis was 50%. The specificity of the algorithm was 53.7% and NPV was 1.9%. In addition, the investigators also reported that the sensitivity of the algorithm for diagnosing vaginitis was 31.2%. Specificity and PPV of the algorithm were 97.4% and 73.9% respectively. The prevalence of trichomoniasis in this population was 5.6% and that of chlamydia was 1.7%.

A study conducted among pregnant women in Mwanza,Tanzania,[29] applied the syndromic approach using vaginal discharge and/or genital itching as risk factor/s for cervical infection. The result showed that the syndromic approach in this group of pregnant women had a sensitivity of 46%. The low sensitivity led to the conclusion that supplementary diagnostic techniques such as simple laboratory tests are necessary for managing and identifying asymptomatic women who are infected with RTI pathogens. Mayaud et al.[40] evaluated the validity of SCM in a sample of 660 pregnant women in Tanzania. When the WHO algorithm was compared to gold standard, only 49 (7%) pregnant women were correctly identified by the algorithm as positive for *N. gonorrhoeae* and/or *C. trachomatis*. The sensitivity of the approach was 10.2%. The specificity and PPV of the algorithm were 92% and 9.8% respectively, in this population of women, where the prevalence of any vaginal or cervical infection was 68%. Though the use of syndromic approach in this population of women is feasible and acceptable, the investi-

gators concluded that its low sensitivity indicates that there is a need for improvement in the application of SCM among pregnant women.

In Gabon, Bourgeois et al.[41] observed more encouraging results in the application of SCM among pregnant women. The prevalence of cervical infection by etiological diagnosis among pregnant women seeking antenatal care was 11.3%. Two groups of health providers participated in the study, midwives and physicians. The result of their study showed that the sensitivity and specificity of the algorithm as recorded by the midwives were 73.3% and 54.8% respectively. On the other hand, the sensitivity and specificity of the syndromic approach as recorded by the physicians were 76.7% and 50.6% respectively. This study concluded that the use of SCM in this population is feasible and well accepted by the health care providers and the recipients. However, the current flow chart in use for SCM needs to be improved prior to its routine use among pregnant women.

The validity of SCM has also been evaluated amid 908 family planning clinic attenders in urban Tanzania who presented as asymptomatic. Kapiga et al.,[42] applied the syndromic approach and evaluated its validity in this population. It was shown that the use of risk-inclusive algorithm has a sensitivity of 37.8%, and specificity of 87.5%. The PPV of the approach was 21.4%. Although the sensitivity of SCM as a screening tool was low, the investigators concluded that this method may be the only feasible way to identify women with STD infection in Tanzania. The prevalence of HIV in this population was 16.9%, and of trichomoniasis and/or candidiasis was 27.2%. Cervical infections were present among 8.2% of the study population. Table 4 summarizes the evaluation of SCM among antenatal and family planning clinic attenders.

Table 4 Summary of Evaluation of SCM among Family Planning and Antenatal Clinic Attenders (Asymptomatic Women)

Authors, year	Study population	Methods	Prevalence of RTIs	Results of evaluation of SCM
Fonk et al, 2000	621 women from Nairobi, Kenya with complaint of vaginal discharge-334 pregnant women and 287 non-pregnant women	Cross-section study Evaluation of Kenyan algorithms and generated algorithm Comparison of performance of algorithm between pregnant and non-pregnant women	Non-pregnant women: GC-12% CT-8% GC/CT-19% CA-46% TV-21% BV-10% Pregnant women: GC-3% CT-11% GC/CT-13% CA-55% TV-26% BV-8%	The current Kenyan algorithm has a sensitivity of 47%, specificity of 57% and PPV of 20% when used among non-pregnant women. The sensitivity of the generated algorithms ranged anywhere from 53% to 85%. The specificity ranged anywhere from 52% to 38%. When used among pregnant women, the sensitivity of the Kenyan algorithm was 36%, specificity was 69% and PPV was 15%. The generated algorithms had a sensitivity that ranged from 45% to 70%. The specificity ranged form 63% to 46%.
Aissa-Hamzaoui 1999	409 pregnant Tunisian women	Cross-sectional study	TV- 5.6% CT- 1.7%	Sensitivity of the WHO algorithm in diagnosing cervicitis was 50%, specificity was 53.7% and PPV was 1.9% Sensitivity of the algorithm in diagnosing vaginitis was 31.2%, specificity was 97.4% and PPV was 73.9%
Bourgeois et al, 1998	646 antenatal clinic attenders in Gabon	Cross-sectional study	Cervical infection-11.3%	Used of a flow chart based on age and marital status and simple clinical signs has a sensitivity of 73%, specificity of 55% and PPV of 17%
Kapiga et al, 1998	908 women attending family planning clinic in urban Tanzania	Cross-sectional	Cervical infection-8.2% TV/CA-27.2%	Risk assessment inclusive algorithm has a sensitivity of 38%, specificity of 88% and PPV of 21% in detecting cervical infection

SCM in Jamaica

Like many other developing countries, the STI infection among women of reproductive age in Jamaica is of great concern. Public health professionals together with policy makers have shown an increased commitment in improving the reproductive health of

women. The use of laboratory tests to identify individuals infected with RTI pathogen is problematic in a setting like Jamaica where resources are scarce. Behets et al.[8] reported that *N. gonorrhoeae* can only be cultured at two of the 13 public STI clinics in Jamaica, and that etiological diagnosis for chlamydia was non-existent prior to their study. Although the lack of laboratory testing may be an obstacle in diagnosing asymptomatic women, individuals with symptoms suggestive of RTI infection can be treated syndromically.[7] In compliance with the WHO recommendation, the use of a syndromic approach as a diagnostic tool for RTI was adapted in Jamaica in 1995.

The use of algorithms to treat vaginal discharge has been evaluated in STI clinic attenders in the island. Behets et al.[8] conducted a study among 752 women who attended an STI clinic and used different flow charts to diagnose STI infection. Upon comparison with the gold standard, the algorithm solely based on clinical symptoms (i.e., algorithm without risk assessment) had a sensitivity of 73% and specificity of 55%. In contrast, the risk assessment inclusive algorithm was 84% sensitive and 40% specific. The calculated PPV of the different algorithms used ranged from 42 to 43%. The prevalence of cervical infections in this population was 34%, trichomonas was documented for 25% and at least 54% of the women had at least one STI. The investigators concluded that the use of risk-inclusive algorithm, though not 100% specific, is one of the most feasible methods of identifying women with STI. This approach, coupled with education and condom promotion, could eventually lead to STI and HIV/AIDS prevention.

In a similar study, Behets et al.[8] also evaluated the use of the WHO algorithms among women attending Jamaican family planning clinics. The result of this investigation showed that the sensitivity of the clinical algorithm in detecting cervical infection,

and or trichomoniasis, was 63.5% and the specificity was 96.7%. However, the risk assessment inclusive algorithm had a sensitivity of 57.7% and specificity of 46.2% when applied to the same population. The study also reported that the prevalence of cervical infection was 14.1%, and of trichomoniasis was 11.5%. This is considered high in this group of mostly asymptomatic women. The authors suggested that based on the performances of the flow charts tested, appropriate detection tool is still needed in order to identify asymptomatic women infected with RTIs. Risk inclusive algorithm though believed to improve the accuracy of SCM, has to be modified to individual countries and regions within that country. The low sensitivity and specificity of the risk inclusive algorithm observed in this study shows that the list of factors included in the risk assessment is not definitive, but, rather needs to be adapted to a particular condition.

Hylton-Kong et al.[9] observed a marginal validity of SCM among 269 pregnant women. The sensitivity of the approach was 11.1% for BV, 35.4% for trichomonas, 66.7% for cervicitis, and 24% for candidiasis. The specificity was 88.8% for BV, 81.1% for candidiasis, 62.8% for cervicitis and 68.5% for trichomonas. In this study, the prevalences of STIs are as follows: 44.1% for BV, 18% for Trichomonas, 30.7% for candidiasis, 5.4% for gonorrhea and 17.8% for chlamydia. Table 5 summarizes the results of evaluation of SCM in Jamaica.

Table 5 Results of Evaluation of SCM in Jamaica

Authors, year	Study population	Method	Prevalence of STIs	Results of validation of SCM
Behets et al, 1995	752 Jamaican women attending STI clinic	Cross-sectional study	Cervical infection-34% TV-25% At least one STI-54%	Clinical algorithm for cervical infection has a sensitivity of 73% specificity of 55%. Risk assessment-inclusive flowchart has a sensitivity of 84%, specificity 0f 40% for cervical infection. PPV of the algorithms used range from 42% to 43%, NPV range from 78% to 81%
Behets et al, 1995	Family planning clinic attenders in Jamaica	Cross-sectional study	Cervical infections-14.1% Trichomoniasis-11.5%	Sensitivity of clinical algorithm was 63.5%, specificity was 96.7%. Sensitivity of risk-inclusive algorithm was 57.7% and specificity was 46.2%.
Hylton-Kong et al, unpublished	269 pregnant women from Jamaica	Cross – sectional study	BV-44.1% TV-18% CA-30.7% GC-5.4% CT-17.8%	Sensitivity, specificity of WHO algorithm for vaginal discharge were: *Se for BV-11.1%* Spe for BV-88.8% Se for TV-66.7% Spe for TV-68.5% Se for cervicitis –66.7% Spe foe cervicitis-62.8% Se for candidiasis-24% Spe for candidiasis-81.1%

STUDY RATIONALE

One of the advantages of RTI control is effective management through prevention of sequelae resulting from complications associated with untreated infections. The Mwanza study also indicated the reduction of HIV transmission that can result from effective SCM.[41] Treatment of RTIs at a patient's first encounter with a health care provider is one of the most important public health measures in preventing disease morbidity.[5]

In Jamaica, the use of the WHO algorithm has been evaluated among women attending STD and family planning clinics. These studies demonstrated that syndromic management is feasible among STD clinic attenders but were of less validity among women in family planning clinics. In 1997, 269 pregnant Jamaican women were recruited to determine the prevalence and risk factors associated with vaginitis (Kamara et al, 1999) and STDs (unpublished). The use of SCM in this population was also assessed and the results showed a marginal validity of the approach in the detection of RTIs. In this study, women presenting with complaints of vaginal discharge were treated for vaginitis according to WHO algorithm. In addition, the women were assessed for cervicitis as part of the study. Clinical signs such as friable cervix and cervical erosion were added as part of the clinical assessment for cervicitis, and color of discharge (yellow,/yellow green) for trichomonas were also included. These factors are not part of the current algorithm used in Jamaica, and the validity of these clinical signs has not been assessed among pregnant

women. In this proposal, we will first determine the sensitivity, specificity and PPV of the clinical signs (runny/profuse discharge, malodorous discharge, mucopus cervix) currently used in SCM among pregnant women in Jamaica and compare the performance of SCM with laboratory tests for each RTI. Secondly, the combination of clinical signs currently and not currently used (friable cervix, cervical erosion, yellow/yellow green discharge) in SCM will be compared with laboratory tests for each RTI. The sensitivity, specificity, PPV and NPV of the combination of clinical signs will be calculated.

Majority of women with RTIs are usually asymptomatic. Therefore, the impact of SCM is minimal in this group. Among pregnant women, the use of SCM is more problematic, since pregnancy usually presents with signs and symptoms such as vaginal discharge and abdominal pain which can be erroneously identified for RTI.[38] As previously stated, the SCM algorithm currently used among pregnant women in Jamaica needs some improvement due to its marginal validity. Therefore, from the results of the analyses on sensitivity and specificity of the clinical signs used in SCM, we will develop modified algorithm/s for diagnosing RTIs. Clinical signs with the highest sensitivity in diagnosing an RTI will be combined with simple laboratory test to develop modified algorithm/s. Simple laboratory tests such as vaginal pH and whiff tests for BV and wet mount for TV will be added to improve the assessment for vaginitis. These simple tests are cheap and feasible in Jamaica, and can be an added way for differentiating the pathogens for vaginitis. In addition, clinical signs such as friable cervix, and cervical erosion will be applied to improve the assessment for cervicitis. These clinical observations are consistently associated with cervicitis.[10] Therefore, our modified algorithms will be a combination of simple laboratory test and significant clinical signs specific for each RTI. The sensitivity,

specificity, PPV of these modified algorithm/s will be compared to the current SCM algorithm used among pregnant women in Jamaica. Laboratory test results will be used as the "gold" standard in these analyses. The results of this study will provide information that will guide health policy makers in decision-making paramount to prevention of sequelae associated with RTIs among pregnant women, adverse pregnancy outcome and HIV transmission.

DESCRIPTION OF STUDY ON SCM CONDUCTED AMONG PREGNANT WOMEN IN JAMAICA (JUNE-SEPTEMBER 1997)

Study Site

The island of Jamaica is divided into 14 administrative units known as parishes. Two of the parishes, Kingston and St. Andrew, operate as a single unit for most of the administrative activities and are often referred to as Kingston/St. Andrew or KSA. A bulk of the Jamaican population (50%) lives in urban areas (KSA, Spanish Town in the parish of St. Catherine, and Montego Bay in the parish of St. James). The other 10 parishes are rural. The health care infrastructure of Jamaica is quite well developed and widely distributed throughout the 14 parishes. A total of 364 primary health centers provide health services such as basic antenatal, postnatal and child health care to the population. In addition, 62 health districts provide curative and domiciliary midwifery services. Almost 90% of the population lives within 10 miles of a health center.

For logistical reasons and accessibility, the study on SCM for RTIs in pregnant women was conducted in four of the major prenatal care facilities in KSA: Duhaney Park Health Center, Olympic Gardens Health Center, Glen Vincent Health Center, and the Comprehensive Health Center (CHC). CHC is the most well equipped facility on the island for etiological diagnosis of RTIs. A large percentage of pregnant women seek prenatal care in KSA, therefore, recruitment of the optimal number of participants needed for this study was maximized in these health centers.

Target Population

The inclusion criteria required that the women attend any of the four chosen antenatal clinics for the first time during their current pregnancy. In addition, these women had to be past their second trimester. All willing and eligible pregnant women were included in the study. A signed informed consent form was obtained from each woman.

Study Design

This was a cross-sectional study designed to evaluate the clinical factors used in SCM against laboratory test results and to determine the clinical risk factors associated with RTIs. RTIs included bacterial vaginosis (BV), trichomoniasis (TV), candidiasis (CA), and gonorrhea (GC)/chlamydia (CT). The study was conducted among pregnant women in Kingston, Jamaica from June 1997 to September 1997. Three groups of health providers participated in the diagnosis of RTIs using SCM: public health nurses, midwives and physicians. A pelvic exam was performed and laboratory specimens were collected from all participating women. The WHO algorithm modified for STD clinic attenders in Jamaica was used in diagnosing RTI among study participants. Women suspected of having gonococcal infections based on syndromic management were treated with oral dose (400 mg) of cefixime, and chlamydial infections were treated with erythromycin 500 mg qid x 7d. Metronidazole was given to women who are suspected of having trichomoniasis based on SCM. The Jamaican Ministry of Health provided all the needed antimicrobials such as cefixime, erythromycin and metronidazole. Women who tested positive on laboratory tests, but not treated under the syndromic approach, also received antibiotic therapy. A counseling session was provided to each participating individual, discussing laboratory results and ways of preventing RTI and its transmission.

All partners of infected women were invited to STD clinics for assessment and treatment needed. Condom use was promoted among women and their partners.

Preliminary Activities

Training in using SCM for Diagnosing RTIs (WHO Algorithm)

Four nurses and four midwives participated in this study. These eight health professionals were trained within a three-day period to use the risk-inclusive syndromic management algorithm (Appendix A) to diagnose RTIs. The training included information on female RTI, practical training on pelvic examination, history taking, specimen collection and use of SCM algorithm. A standard teaching video from University of Washington training center that covered the techniques was shown to the trainees. In addition, slides of the different types of genital discharges in women were also shown. The different algorithms in use in the field were discussed and presented, and a thorough emphasis given to the vaginal discharge algorithm for the management of vaginitis and cervicitis. The trainers explained appropriate counseling messages, such as compliance, condom use and partner notification. During this period, a structured questionnaire was also developed. It was used in obtaining information such as marital, educational, history of RTIs and other socio-demographic factors from the women. Prior to recruiting participants, knowledge on SCM was assessed among the trainees through pre and post training questionnaires. Two physicians with prior experience in the use of risk-inclusive algorithm performed pelvic and bimanual examination and collected laboratory specimens.

Data Collection Materials and Methods

Questionnaires

Several components were included in the structured questionnaire. The first part of the questionnaire asked for information on demographics, obstetrical history, antenatal care, STIs and other medical history. Risk assessment questions which include information on partner's urethral discharge, age <21, having new partner in past 3 months, >1 partner in past 3 months and not living with steady partner were also included in this portion. Weighted scores were given to each item and the total score was recorded. This portion was administered by registered nurses and midwives who received training in the use of SCM.

After the interview, the clinical portion of the questionnaire was completed by the trained clinicians. This segment included information on vaginal and cervical discharges, and cervical observation. Blinded from the result of the risk-assessment obtained from the interview section, the clinicians observed the nature of any vaginal discharges that the women may have had. The vaginal discharge algorithm (Appendix A) was then applied: women with runny/malodorous discharge were treated for trichomoniasis/ bacterial vaginosis, women with white curd like discharge were given treatment for candidiasis. The clinicians also performed speculum examination. This begun with the careful observation of the external genitalia, the cervix was then exposed by insertion of the unlubricated speculum into the vagina. The physical characteristics of the cervix and vagina were noted. The results of the risk assessment was applied to interpret the results of cervical inspection: women with no mucopus cervix but obtained a total risk assessment score of ≥ 2 were treated for gonorrhea and/or chlamydia; those with mucopus cervix, regardless

of risk scores were treated for gonorrhea/chlamydia; women with no mucopus and a risk score of <2, were not given treatment. All treatments for a specific RTI were given on the day of diagnosis.

Laboratory tests

During the speculum examination performed by the trained clinicians, swab specimens were obtained both from the vagina and cervix from all participating women. The collected specimens were used for etiological diagnosis for RTI and serve as the gold standard for the study. The laboratory personnel were blinded to the results of the assessment made by the clinicians syndromically. Serum samples were also collected and tested for syphilis and HIV infections.

Bacterial vaginosis (BV). A swab of specimen obtained from the vagina was used to perform test for BV. The swab was gently rolled on a clean slide, heat fixed and gram stained by using safranin as counter stain (Nugent et al, 1991). Each gram stain was evaluated under oil immersion for *Lactobacillus*, *G. vaginalis*, *Bacteroides spp.* and *Mobiluncus spp.* morphotypes. Each morphotype was quantified based on presence or absence. The Nugent Score [43] for detecting the number of morphotypes in the smear was the gold standard used in diagnosing BV. A positive diagnosis for BV was based on a total score of 7, or more and a score of less than 7 was considered as within normal limits. The pH of the vaginal fluid was determined by applying pH paper (Boehinger Mannheim, Indianapolis, IN) to the wall of the vagina for a few seconds. A "whiff" test was performed by dipping a sterile cotton swab (applied to the vaginal wall) in 1ml of potassium hydroxide (10% KOH) to detect fishy odor.

Trichomoniasis. A swab of specimen obtained from the vagina was placed on a saline solution to perform direct microscopy (wet mount) for the presence of motile trichomonas. As a confirmatory test, sterile cotton swabs were used to collect specimens from the posterior fornix and cultured for five days into an "InPouch TV test kit" (Biomed Diagnostics, San Jose, CA). Women with a positive culture were identified as having trichomoniasis.

Candidiasis. A swab of specimen from the vagina was placed on a saline solution for direct microscopy for the presence and absence of pseudohypae (yeast). A gram stain was performed to diagnose yeast infection.

Gonorrhea. Endo-cervical swab specimens were obtained for direct plating of Thayer-Martin agar for the culture of *N. gonorrhoeae.* The culture was incubated for 72 hours and tested each day with oxidase for the presence of *N. gonorrhoeae*. In the event that colonies of *N. gonorrhoeae* were identified on the agar culture plate, they were collected with a sterile cotton swab and smeared on a clean glass slide. Gram stain procedure was performed by using safranin as counter stain and the slide was evaluated under oil immersion for gram-negative cocci (*N. gonorrhoeae).*

Chlamydia. A second set of endo-cervical swab specimen was collected to test for *C. trachomatis* using an on-site enzyme immunoassay (EIA, Clearview/Biostar). Ligase Chain reaction (LCR) was performed on a subset of specimens for quality control.

Syphilis/HIV. A blood sample was obtained from each woman to test for syphilis and HIV. These samples were used to perform serologic test for syphilis using the Toludine Red Unheated Serum Test (TRUST, New Horizon Diagnostics Corporation, MD). Reactive sera were diluted to determine endpoint reactivity and were confirmed by FTA-

Abs. Frozen sera were sent to University of Alabama in Birmingham for HIV antibody testing using ELISA and Western blot for confirmation of positive samples.

METHODS

Sample Size

In order to justify that the data collected from the 1997 study (269 pregnant women) are sufficient to carry out the sample size requirement of the proposed study, the null hypothesis that the sensitivity and specificity of the current SCM algorithm are equal to a specified value will be tested.

There are no data available to estimate the sensitivity and specificity of the clinical signs used in SCM algorithm among pregnant women in Jamaica. Therefore, the statistical assumptions will be based on the result of a study that evaluated the use of syndromic algorithm in diagnosing trichomoniasis compared to laboratory test (wet mount results) among non-pregnant women presenting in STD clinics in Jamaica (Behets et al., 1995). This study indicates that the sensitivity of the different algorithms tested can be anywhere from 84%-87% and the prevalence of trichomoniasis is 25%. The specificity of the different algorithms can be anywhere from 25%-37%. Table 6 lists the sample size requirement for varying estimates of sensitivity and specificity under the null and alternative hypotheses. For example, assuming that the sensitivity of an algorithm for diagnosing trichomoniasis is equal to 0.85, a sample of 250 pregnant women will detect a 10% absolute difference in sensitivity estimates (i.e. 0.75 vs. 0.85), with 97% power and 5% significance level based on a two-sided test for single proportion. Due to participant availability, logistic factors and time constraint, approximately 269 pregnant women were enrolled in this study.

Table 6 Sample Size Requirement Based on Comparison of Ho and Ha Sensitivity using Exact Test for Simple Proportion*

Ho (Sensitivity)	Ha (Sensitivity)	N (sample size)	% Power
.40	.30	250	90
.60	.50	250	88
.85	.75	250	97

*Based on 5% alpha and two-sided test

Table 7 Sample Size Requirement Based on Comparison of Ho and Ha Specificity using Exact Test for Simple Proportion*

Ho (Specificity)	Ha (Specificity)	N (sample size)	% Power
.25	.35	250	92
.35	.45	250	89
.40	.50	250	88
*Based on 5% alpha and two-sided test			

The proportion of women with suspected RTI based on clinical signs will be compared with the proportion of women with positive laboratory tests. Assuming that the proportion of positive diagnosis based on laboratory test for trichomoniasis is 0.25 (Behets et al., 1995), and the proportion of discordants based on SCM algorithm is anywhere between 0.50-0.60 (Behets et al., 1995), the available data from the 1997 study of 269 pregnant women will be able to detect at least a 15% absolute difference in proportion of RTIs with 94% power, 5% alpha based on a two-sided McNemar's test. A previous study on women attending an STD clinic showed a 40% difference in positive diagnosis (Behets, 1995) between clinical and laboratory tests for trichomoniasis. Thus, the assumed difference in the proportion of positive diagnosis appears to be reasonable. Table 8 sum-

marizes the sample size calculations based on difference in proportions of positive diagnosis using McNemar's test.

Table 8 Sample Size Calculations using McNemar's Test of Equality of Paired Proportions*

Difference in proportion	Proportion of discordant pairs	N (sample size)	% Power
.15	.50	269	94
.15	.60	269	89
.10	.60	269	56

*Based on 5% alpha and two-sided test

Data Analysis

Data management

All items on the questionnaire were pre-coded and entered in a database using EpiInfo 6.0 (CDC, Atlanta, GA), and imported into SAS 7.0 (SAS Institutute, Cary, NC) for statistical analysis.

Primary Analyses

Aim 1. 1.A. To compare the proportion of diagnosis for RTI between clinical signs (e.g. runny/malodorous discharges, mucopus cervix) currently used in SCM algorithm in Jamaica laboratory tests (gold standard).

The sensitivity and specificity of the each clinical sign for an RTI will be calculated. Table 9 shows a cross-tabulation of diagnosis for RTI based on clinical sign versus laboratory test results (gold standard).

Table 9 Comparison Between Laboratory Results and Clinical Risk Factors for an RTI

	Laboratory test results for a RTI		
Clinical Risk factor	Positive	Negative	Total
Positive	a (TP)	b (FP)	p_1 (TP+FP)
Negative	c (FN)	d (TN)	q_1 (FN+TN)
Total	p_2 (TP+FN)	q_2 (FP+TN)	1

TP= true positive *TN= true negative*
FP= false positive *FN= false negative*

Sensitivity will be determined as the number of pregnant women positive for a clinical sign for an RTI per syndromic case diagnosis that have positive laboratory results (true positive) divided by the total number of pregnant women who actually have the disease by etiological diagnosis (true positives plus false negatives). The specificity of the algorithm will be calculated as the number of pregnant women negative for a clinical sign for an RTI per syndromic case diagnosis that have negative test results (true negatives) divided by the total number of pregnant women who tested negative on laboratory tests (true negatives plus false negatives). The associated 95% confidence interval will also be calculated for sensitivity and specificity. Sensitivity and specificity will be calculated as follows:

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{PPV} = \frac{TP}{TP + FP}$$

$$\text{Specificity} = \frac{TN}{TN + FP} \qquad \text{NPV} = \frac{TN}{TN + FN}$$

McNemar's test of paired proportions. The difference in the proportion of women with positive diagnosis based on clinical sign used in SCM of an RTI as compared to laboratory tests will be evaluated using the McNemar's test (Q_M) for agreement between two proportions. The following formula will be used for calculations (Stokes et al., 1995):

$$Q_M = \frac{(b-c)^2}{(b+c)}$$

Kappa statistics to measure agreement. The Kappa statistics will be calculated in order to evaluate the degree of agreement between clinical signs currently used in SCM for diagnosis of an RTI and results of laboratory tests. The clinical portion of the questionnaire used in SCM includes a coded list of positive versus negative diagnosis for a clinical sign. Positive indicates presence of a sign for an RTI, negative indicates absence of a clinical sign. For example, a woman with a malodorous discharge will receive a positive diagnosis for this clinical sign, and a woman without a malodorous discharge will receive a negative diagnosis. Similarly, the results of the laboratory tests performed on each woman will also be coded as positive or negative. The positive and negative diagnosis for clinical risk factor will be cross-tabulated with the positive and negative laboratory test results (gold standard) in a 2 X 2 table (table 9). In order to correct the probability that the agreement did not occur by chance, the Kappa statistics will be calculated (Landis and Koch, 1977) based on the following formula:

$$\kappa = \frac{2(ad-bc)}{p_1 q_2 + p_2 q_1}$$

A kappa that is equal to 1 signifies complete agreement. For most purposes a value of $\kappa > .75$ represents excellent agreement, a value of $\kappa = 0.40\text{-}0.75$ represents fair to good agreement, and a $\kappa < .40$ represents poor agreement (Landis and Koch,1977). In order to test that the underlying value of kappa is significantly different from a hypothesized value, the standard error of estimate of the Kappa will be calculated and tested for significance using the z-test as described by Fleiss et al. (1969). Table 10-13 summarizes the results of the above mentioned analyses.

Table 10. Sensitivity, Specificity, PPV and NPV of Clinical Signs used in SCM for Diagnosing Bacterial Vaginosis among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (Nugent Score)			Sen.	Spec.	PPV	NPV	McNemar test	$\kappa \pm$ SE
Runny/profuse discharge	Pos.	Neg.	Total						
Pos.									
Neg.									
Total									
Malodorous	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Runny/profuse or malodorous	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Runny/profuse or malodorous									
Pos	Pos	Neg	Total						
Neg									
Total									

Table 11 Sensitivity, Specificity, PPV and NPV of Clinical Signs used in SCM for Diagnosing Trichomoniasis among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (In Pouch TV test)			Sen.	Spec	PPV	NPV	McNemar test	$\kappa \pm$ SE
Runny/profuse discharge	Pos.	Neg.	Total						
Pos.									
Neg.									
Total									
Malodorous	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Runny/ malodorous	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Runny/profuse and malodorous	Pos	Neg	Total						
Pos.									
Neg.									
Total									

Table 12 Sensitivity, Specificity, PPV and NPV of Clinical Signs used in SCM for Diagnosing Candidiasis among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (Gram stain for yeast)			Sen.	Spec.	PPV	NPV	McNemar test	$\kappa \pm$ SE
Thick-curd like discharge	Pos.	Neg.	Total						
Pos.									
Neg.									
Total									
White discharge	Pos	Neg.	Total						
Pos.									
Neg.									
Total									
Thick-curd like or white discharge	Pos	Neg.	Total						
Pos.									
Neg.									
Total									
Thick-curd like and white discharge	Pos	Neg	Total						
Pos.									
Neg.									
Total									

Table 13. Sensitivity, Specificity, PPV and NPV of Clinical Signs used in SCM for Diagnosing Cervicitis (Gonorrhea/Chlamydia) among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (Culture for GC and EIA for CT)			Sen.	Spec.	PPV	NPV	McNemar test	$\kappa \pm$ SE
Mucopus cervix	Pos.	Neg.	Total						
Pos.									
Neg.									
Total									
Risk score ≥ 2	Pos	Neg.	Total						
Pos.									
Neg.									
Total									
Mucopus or Risk score ≥ 2	Pos	Neg.	Total						
Pos.									
Neg.									
Total									
Mucopus and Risk score ≥2	Pos	Neg	Total						
Pos.									
Neg.									
Total									

1.B To compare the RTI diagnosis using the combination of clinical signs not currently (e.g. friable cervix, cervical erosion, yellow vaginal discharge) and currently (runny/malodorous, mucopus cervix) used in SCM algorithm in Jamaica and laboratory test results (“gold” standard).

The sensitivity, specificity, PPV and NPV of the combination of clinical signs currently and not currently used in SCM algorithm among pregnant women in Jamaica will be calculated as described in aim 1a. Similarly, the McNemar's test will be employed to assess the difference in proportion of women with positive diagnosis based on the combination of clinical signs currently and not currently used in SCM algorithm as compared to laboratory test. The method of analysis is described in aim1a. In order to determine the degree of agreement between the combination of clinical signs currently and not currently used in SCM and laboratory test results ("gold" standard), the kappa statistics will be employed as described in aim 1a. Results of the analyses in aims 1a and 1b will compared to determine if the addition of clinical signs not currently used in SCM algorithm for pregnant women in Jamaica has improved the sensitivity, specificity, and agreement between clinical signs and laboratory test results. Table 14-16 outlined the results for aim 1b.

Table 14. Sensitivity, Specificity, PPV and NPV of the Combination of Clinical Signs Currently and Not Currently used in SCM for Diagnosing Bacterial Vaginosis among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (Nugent Score for BV)			Sen.	Spec.	PPV	NPV	McNemar test	$\kappa \pm$ SE
Runny/Profuse plus creamy/ homogenous	Pos.	Neg.	Total						
Pos.									
Neg.									
Total									
Malodorous plus creamy homogenous	Pos	Neg.	Total						
Pos.									
Neg.									
Total									
Run-ny/malodorous plus creamy homogenous	Pos	Neg.	Total						
Pos									
Neg.									
Total									
Run-ny/malodorous and creamy homogenous	Pos	Neg	Total						
Pos.									
Neg.									
Total									

Table 15. Sensitivity, Specificity, PPV and NPV of the Combination of Clinical Signs Currently and Not Currently used in SCM for Diagnosing Trichomoniasis among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (In Pouch TV test)			Sen.	Spec.	PPV	NPV	McNmar test	$\kappa \pm$ SE
Runny/ Profuse plus frothy discharge	Pos.	Neg	Total						
Pos.									
Neg.									
Total									
Runny/profuse plus yellow/yellow green discharge	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Runny/profuse plus white discharge	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Malodorous plus frothy	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Malodorous yellow/yellow-green	Pos	Neg	Total						
Pos.									
Neg.									

Table16 Sensitivity, Specificity, PPV, NPV of the Combination of Clinical Signs Currently and Not Currently used in SCM for Diagnosing Cervicitis among Pregnant Women in Jamaica

Clinical Sign	Gold Std. (Culture for GCand EIA for CT)			Sen.	Spec.	PPV	NPV	McNemar test	$\kappa \pm$ SE
Mucopus plus friable cervix	Pos.	Neg	Total						
Pos.									
Neg.									
Total									
Mucopus plus cervical erosion	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Mucopus plus rusty/bloody dis.	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Risk score $\geq$2 plus friable cervix	Pos	Neg	Total						
Pos.									
Neg.									
Total									
Risk score $\geq$2 plus cervical erosion	Pos	Neg	Total						

Aim 2. 2.a To develop modified algorithm/s (e.g. addition of simple laboratory tests such as vaginal pH, wet mount, whiff test) with higher sensitivity and lower specificity for diagnosing RTIs among pregnant women.

Development of modified algorithms. From the results of the analyses of the sensitivity and specificity of the clinical signs currently and not currently used in SCM algorithm among pregnant women, clinical sign/s with the highest sensitivity for each RTI will be included in the development of modified algorithm. Similarly, results of previous studies in different settings identifying clinical signs predictive of an RTI will also be used in constructing modified algorithm. Significant clinical signs obtained from the analyses and previous studies will be combined with simple laboratory tests. A logistic regression analysis will be employed to determine the best model in the development of modified algorithm/s.

Sensitivity, specificity, percent increase and decrease of modified algorithms. The sensitivity and specificity of the modified algorithm/s will be calculated and compared with the current algorithm. Sensitivity will be determined as the number of pregnant women positive for an RTI per syndromic case diagnosis that have positive laboratory results (true positive) divided by the total number of pregnant women who actually have the disease by etiological diagnosis (true positives plus false negatives). The specificity of the algorithm will be calculated as the number of pregnant women negative for an RTI per syndromic management assessment and have negative test results (true negatives) divided by the total number of pregnant women who tested negative on laboratory tests (true negatives plus false negatives). The associated 95% confidence interval will also be calculated for sensitivity and specificity, and comparison will be made between modified

and current algorithms. In 1997, Fonk et al al.[38] compared the validity of the current algorithm used among pregnant women in Nairobi, Kenya to five modified algorithms. The study showed that the increase in sensitivity between current and modified algorithm is anywhere between 25%-90%. Based on the results of this study, our proposed study hypothesis that there will be a 50% increase in sensitivity between our modified algorithm and the current algorithm in used for pregnant women in Jamaica seems reasonable. The percent increase in sensitivity of the modified algorithm/s from the current algorithm will be calculated as follows:

$$\frac{\text{Sensitivity of Modified algorithm} - \text{Sensitivity of Current algorithm}}{\text{Sensitivity of Current Algorithm}}$$

Similarly, Fonk et al.[38] showed that the percent decrease in specificity of the modified algorithms as compared to the current algorithm in used among pregnant women in Nairobi, Kenya, is anywhere between 8%-33%. In our proposed study, we hypothesizes that there will be a 30% decrease in specificity in our modified algorithm/s. The percent decrease in specificity of the modified algorithm/s from the current algorithm will be calculated as follows:

$$\frac{\text{Specificity of Modified algorithm} - \text{Specificity of Current algorithm}}{\text{Specificity of Current algorithm}}$$

Table 17 shows a comparison of sensitivity, specificity, PPV, NPV of the current algorithm for BV and TV and modified algorithm/s to be evaluated.

Table 17 Comparison of Sensitivity, Specificity, PPV the Current Algorithm and Modified Algorithms for RTIs among Pregnant Women in Jamaica (N=269)

RTI	Algorithm	Factors	Sen (95%CI)	Spec. (95%CI)	PPV (%)	% Inc. in Sens.	% Dec. in Spec.
BV	Current SCM	Runny/malodorous dis.					
	Modified Algorithm A	Runny/malodorous dis. plus pH ≥ 4.5					
	Modified Algorithm B	Malodorous Discharge plus whiff pos.					
TRIC	Current SCM	Runny/malodorous dis.					
	Modified Algorithm A	Runny/ profuse dis. plus Wet mount					
	Modified Algorithm B	Yellow/yellow green dis. plus Wet mount					
CERVICITIS (GC/CT)	Current SCM	Cervix: mucopus Risk Score: ≥ 2					
	Modified Algorithm A	Friable cervix plus cervical erosion					
	Modified Algorithm B	Friable cervix plus white gray dis.					

Aim 3. To determine the modified algorithm with the highest efficacy and compare to the current algorithm.

In order to compare the modified algorithm/s with the current algorithm in used among pregnant women in Jamaica, the efficacy of the algorithms will be determined. Efficiency is the extent in which a diagnostic test has delivered its maximum benefit. In this proposed study, we hypothesize, that there will be a variation in the sensitivity and specificity of the modified algorithms. Efficacy will be evaluated based on the area under

the curve (AUC) of the ROC and based on the average of sensitivity and specificity. In general, an increase in sensitivity corresponds to a decrease in specificity.

Efficiency based on AUC of the ROC. To determine a modified algorithm with the maximum efficacy, the receiver operating curves (ROC) will be employed (SAS version 8). ROC entails the construction of a graph with sensitivity (true pos. rate) on the vertical axis, and 1-specificity (false pos. rate) on the horizontal curve. Figure 1 shows an example of an ROC curve used in comparing modified algorithms and current algorithm.

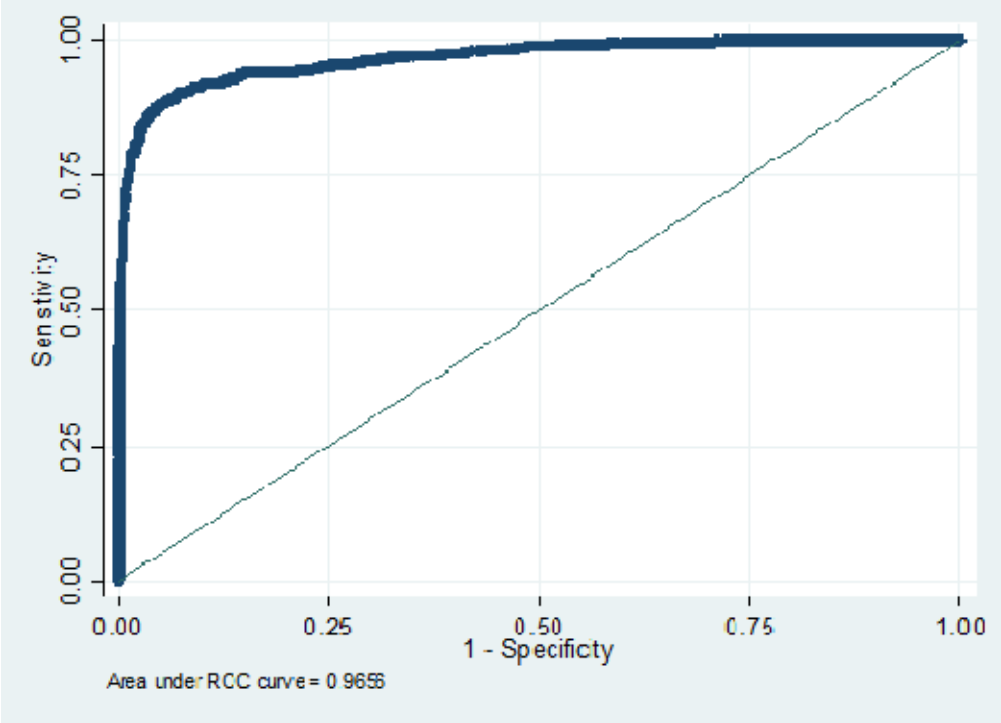

Figure 1: The area under the curve depicts the overall performance of the algorithms, that is, the greater the area, the better the performance of an algorithm. The maximum value for the area under the ROC curve is 1, an indication of a perfect algorithm. However, the area under the dashed diagonal line, which corresponds to an algorithm which does not distinguish between a woman with and without an RTI is 0.5. Therefore, the closer the area to 1 than to 0.5 the better the performance of the algorithm.

Efficacy based on the average of sensitivity and specificity. To compare and contrast the efficacy of the modified algorithm and current algorithm, we will make an assumption that sensitivity and specificity are of equal significance. The performance of the modified and current algorithm will be compared according to the formula:

$$\text{Efficiency} = \frac{\text{Sensitivity} + \text{Specificity}}{2}$$

Table 18 outlines the efficacy of the modified and current algorithm.

Table 18 Comparison of the Efficacy of the Current Algorithm and Modified Algorithms for RTIs among Pregnant Women in Jamaica (N=269)

RTI	Algorithm	Factors	Sen (95%CI)	Spec. (95% CI)	Efficacy
BV	Current SCM	Runny/malodorous dis.			
	Modified Algorithm A	Runny/malodorous dis. plus pH ≥ 4.5			
	Modified Algorithm B	Malodorous dis. plus whiff pos.			
TRIC	Current SCM	Runny/malodorous dis.			
	Modified Algorithm A	Runny/ profuse dis. plus wet mount			
	Modified Algorithm B	Yellow/yellow green dis. plus wet mount			
CERVICITIS (GC/CT)	Current SCM	Cervix: mucopus Risk Score: ≥ 2			
	Modified Algorithm A	Friable cervix plus cervical erosion			
	Modified Algorithm B	Friable cervix plus white gray dis.			

EVALUATION OF CLINICAL SIGNS CURRENTLY AND NOT CURRENTLY USED IN SYNDROMIC CASE MANAGEMENT OF RTIS AMONG PREGNANT WOMEN IN JAMAICA

by

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ABSTRACT

Introduction: The World Health Organization (WHO) advocates the use of syndromic case management (SCM) as a cost effective method to diagnose and treat reproductive tract infections (RTIs) in developing countries that cannot sustain laboratory confirmations at present.

Methods: A cross-sectional study was conducted in pregnant women in Jamaica to compare the effectiveness of the clinical characteristics currently versus not currently used in syndromic case management using laboratory test results as the "gold standard" for RTI diagnosis. The sensitivity and specificity of each clinical sign for bacterial vaginosis (BV), trichomoniasis (TV), gonorrhea/chlamydia (GC/CT), and candidiasis (CA) were calculated for 269 pregnant women who responded to a questionnaire on demographic, sexual, and medical information, underwent a pelvic examination from a trained clinician, and provided swab specimens for laboratory diagnoses.

Results: For BV, runny/profuse or malodorous discharge has the highest sensitivity (27%), and malodorous discharge only has the highest specificity (95%). Adding creamy homogenous discharge, (not in SCM) to runny/profuse or malodorous discharge improved sensitivity to 41% but decreased specificity to 67%. For TV, runny/profuse or malodorous discharge (23%), have the highest sensitivity and malodorous discharge only has the highest specificity (91%). Adding white discharge (not in SCM) improved the sensitivity to 77%, but decreased specificity to 13%. For CA, white discharge alone and the combination of white discharge or thick curd-like discharge have the highest sensitiv-

ity (68%), and thick curd-like discharge alone has the highest specificity (74%). For cervicitis (GC/CT), mucopurulent cervicitis or risk score ≥2 have the highest sensitivity (61%) and mucopurulent cervicitis alone has the highest specificity (78%). Adding friable cervix (not currently in SCM) increased the sensitivity to 72% and decreased specificity to 45%.

Conclusion: Addition of clinical signs not currently used in the modified WHO algorithm has the potential to improve the sensitivity for diagnosing RTIs in pregnant women though specificity would decline. Modified algorithms for diagnosing RTIs in lower risk pregnant women may be indicated.

INTRODUCTION

In 2001, the WHO reported the global prevalence of curable sexually transmitted infections (STIs) among adults as 340 million cases worldwide.[1] Although STIs have devastating effects on both men and women, the bulk of the complications and sequelae of these diseases are borne by women and children. Women are more vulnerable to reproductive tract infections (RTIs) since transmission of infectious agents such as *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (CT), and *Trichomonas vaginalis* (TV) appear to be more efficient from male to female.[2] Women are more likely to be asymptomatic for RTIs and, therefore, less likely to be diagnosed early.[2] The World Health Organization (WHO) estimates that the morbidity and mortality due to STIs are 4-5 times greater among women compared to men.[3] Some of the detrimental complications associated with RTIs include pelvic inflammatory diseases (PID), infertility, ectopic pregnancy, preterm delivery, and opthalmia neonatorum.[3]

With the exception of syphilis, the reported cases of RTIs are high in Jamaica.[4] In 2000, data reported by the National HIV/STI Control Programme in Jamaica suggested a substantial increase in the total number of cases of vaginal discharge syndrome (Bacterial vaginosis [BV], TV, Candidiasis [CA]) as compared to 1999.[4] An increase in the total number of cases of genital discharge syndrome (including GC/CT) was also reported, thought to be a genuine rise not due merely to improved surveillance.

The standard method of diagnosing RTIs in most industrialized countries is with the aid of laboratory tests. In most developing countries, laboratory-based diagnosis is not

currently feasible due to the limited of infrastructure, financial resources or trained personnel. The WHO advocates the use of syndromic case management (SCM) as a cost-effective method of diagnosing RTIs, and as a means of preventing transmission through early detection and treatment.[5] The use of SCM among women attending STI and family planning clinics in Jamaica has been evaluated.[6,7] The results of these studies showed that SCM is feasible among women presenting in STD clinics, but the efficiencies of this method is low among family planning clinic attenders due to both low sensitivity and specificity. We evaluated SCM among pregnant women in Jamaica and showed relatively poor efficiency.[8] Since we included clinical signs that are not currently included in the SCM algorithm, but maybe predictive of RTIs, the present study evaluated the performance of SCM after adding these clinical signs to the current algorithm, compared to "gold standard" laboratory tests.

METHODS

Clinical

A cross-sectional study was designed to evaluate the clinical factors used in SCM against laboratory test results and to determine the clinical predictors associated with RTIs (BV, TV, CA, and GC/CT). Two hundred and sixty-nine pregnant women who attended any of four selected prenatal care facilities for their initial visit in the second or third trimesters of their current pregnancy were recruited for this study in Kingston, Jamaica from June to September 1997. Signed informed consent was obtained from each woman. Prior to study onset, a 3-day training session was conducted for the nurse and other health workers from the four participating clinics. Training included information on female RTI, practical training for pelvic examination, reproductive history taking, specimen collection, and the use of SCM algorithm.

The pre-tested questionnaire administered by a trained nurse, contained information on demographics and sexual/medical histories of the participant. After the interview, each participating women received a pelvic examination by one of the trained supervised clinicians and specimens were collected (see below). The WHO algorithm modified for STI clinic attenders in Jamaica [6] was used in diagnosing RTIs. Women suspected of having GC/CT infections based on syndromic management were treated with one oral dose (400mg) of cefixime; and oral erythromycin 500 mg qid x 7days. Oral metronidazole was given to women who were suspected of having TV based on SCM.

Laboratory Procedures

Swab specimens were obtained from the vagina and cervix from all participating women. The collected specimens were used for etiological diagnosis for RTI and serving as the gold standard for diagnosis. Serum samples were collected and tested for syphilis (RPR and TPHA) and HIV (ELISA and Western blot) infections, results reported elsewhere [8]. A specimen collected from the vagina by swabbing was examined on saline wet prep for TV and clue cells for BV. Yeast buds and pseudohyphae by direct microscopy on KOH were identified. The specimens were then cultured for 5 days for T. vaginalis using an "InPouch TV test kit" (Biomed Diagnostics, San Jose, CA). A "whiff" test was performed by dipping a sterile cotton swab (applied to the vaginal wall) in 1 ml potassium hydroxide (10% KOH) and assessing for a fishy odor. The pH of the vaginal fluid was determined by applying pH paper (Boehinger Mannheim, Indianapolis) to the wall of the vagina for a few seconds. A gram stain of the vaginal discharge was also prepared, and evaluated under oil immersion for *Lactobacilli spp., Gardenella vaginalis*, *Bacteroides spp*., and *Mobiluncus spp*. morphotypes. The Nugent score [9] was used in detecting the number of morphotypes in the smear and served as the gold standard in diagnosing BV. BV was defined as a total score of 7 or more morphotypes, and a score of less than 7 was considered as within normal limits.[9]

Endocervical swab specimens were obtained for direct plating of Thayer-Martin agar for the culture of *N. gonorrhoeae*. The culture was incubated for 72 hours and tested each day with oxidase. In the event that colonies of *N. gonorrhoeae* were identified on

the agar culture plate, they were collected with a sterile cotton swab and smeared on a clean glass slide. Gram-stain procedure was performed by using safranin as counter stain and the slide was evaluated under oil immersion for intracellular gram-negative diplococci. A second set of endocervical swab specimen was collected to test for *C. trachomatis* using an on-site enzyme immunoassay (EIA, Clearview/Biostar). Ligase chain reaction (LCR) for CT was performed on a 10% subset of specimens for quality control.

The laboratory personnel were blinded to the results of the syndromic assessment of the clinicians. The laboratory test results were given to the women on their next visit and treatment was provided to all infected women not previously treated under SCM assessment. All partners of infected women were invited to STD clinics for assessment and treatment if needed. Condom use was promoted among women and their partners.

Statistical Analysis

All items on the questionnaire were pre-coded and entered in a data base using EpiInfo 6.0 (CDC, Atlanta, GA), and imported into SAS 9.0 (SAS Institute, Cary, NC) for statistical analysis. The sensitivity and specificity and associated 95% confidence interval of each clinical sign or combination of clinical signs for an RTI compared to the gold standard was calculated. Positive predictive value (PPV) and negative predictive value (NPV) are presented as well.

The efficiencies of different combinations of clinical signs were calculated in two ways. One method was based on the average of sensitivity and specificity. The other method utilized a weighted score. In public health and medical settings, more weight may be

given to sensitivity rather than to specificity of a screening tool since the benefits of treating more STDs may outweigh the risks of over-treatment of false positive SCM-based diagnoses. We gave 80% weight for sensitivity and 20% weight for specificity, in our calculation of weighted efficiencies.

RESULTS

Demographic and RTI prevalence

The ages of the 269 pregnant women ranged from 14-40 years with a mean of 23 years. Forty-three percent of the women had received some secondary education and 51% were employed. About half (51%) were either married or in a steady monogamous relationship. For 33% of the women, this was their first pregnancy.

Culture positive *T. vaginalis* was detected in 18% of the women and 44% had BV based Nugent criteria. Thirty-one percent had CA by microscopy and 21% had cervicitis (GC/CT) based on gonorrhea cultures and chlamydia EIA.

Bacterial Vaginosis (BV)

Two clinical signs that are currently used in the syndromic diagnoses of BV (runny/profuse, or malodorous discharge) were evaluated. When used singly, these signs had poor sensitivity but high specificity (Table 1). When combined, these signs had a higher sensitivity (27%), but, slightly lower specificity (85%). When "creamy homogenous discharge" (not currently used in SCM but deemed predictive of BV) was examined in combination with either or both of the currently used clinical signs, the sensitivity was increased to 41%, but at the expense of a decrease in specificity (Table 1).

Table 1 Comparison of clinical signs with laboratory tests (Nugent Score) for BV

	Current Clinical Signs	Combination of Clinical Signs
	Runny/ profuse discharge (95% CI[1])	Runny/profuse or creamy homogenous discharge (95% CI)
Sensitivity (%)	20 (13-28)	38 (30-48)
Specificity (%)	88 (81-92)	68 (60-75)
PPV (%)	55	48
NPV (%)	59	60
Average Efficiency[2]	54	53
Weighted Efficiency[3]	33	44
	Malodorous discharge (95% CI)	Malodorous or creamy homogenous discharge (95% CI)
Sensitivity (%)	15 (9-23)	29 (21-38)
Specificity (%)	95 (90-98)	77 (69-83)
PPV (%)	70	48
NPV (%)	60	59
Average Efficiency	54	53
Weighted Efficiency	30	39
	Runny/profuse or malodorous discharge (95 % CI)	Runny/profuse or malodorous or creamy homogenous discharge (95 % CI)
Sensitivity (%)	27 (20-36)	41 (32-51)
Specificity (%)	85 (78-90)	67 (59-74)
PPV (%)	58	48
NPV (%)	61	60
Average Efficiency	56	54
Weighted Efficiency	39	46

[1]CI = Confidence interval

[2]Average Efficiency = Sensitivity + Specificity/2

[3]Weighted Efficiency= 80% Sensitivity + 20% Specificity/10

Efficiency of the Clinical Signs

The weighted efficiencies of any of the combinations of those clinical signs that are currently and not currently used for diagnosing BV were higher than the weighted efficiencies of only using the clinical signs currently in the SCM for diagnosing BV. However, when the efficiencies were calculated on a simple average of sensitivity and specificity, no additional benefit was noted when those clinical signs not currently in the SCM were added.

Trichomoniasis (TV)

Two clinical signs (runny/profuse or malodorous discharge) are currently used in diagnosing TV. These signs were evaluated singly or in combination with other clinical signs not currently used in SCM and believed to be predictive of TV (frothy, yellow/yellow-green, white discharge). Runny/ profuse or malodorous discharge has a sensitivity of 23%, and specificity of 81%. The addition of the clinical sign "white discharge" to either or both of the clinical signs (runny/profuse and malodorous discharge) currently used in SCM resulted in statistically significant increases in sensitivity but substantial decreases in specificity (Table 2).

Table 2 Comparison of clinical signs with laboratory test (Culture) for TV

	Current Clinical Signs	Combination of Clinical Signs		
	Runny/profuse discharge (95% CI[1])	Runny/profuse or frothy discharge (95% CI)	Runny/profuse or yellow/yellow green discharge (95% CI)	Runny/profuse or white discharge (95% CI)
Sensitivity (%)	20 (11-34)	30 (18-44)	30 (19-45)	77 (62-87)
Specificity (%)	86 (80-90)	83 (77-87)	76 (70-82)	16 (11-21)
PPV (%)	24	27	21	16
NPV (%)	83	84	84	76
Average Efficiency[2]	53	56	53	46
Weighted Efficiency[3]	34	40	39	64
	Malodorous discharge (95 % CI)	Malodorous or frothy discharge (95 % CI)	Malodorous or yellow/yellow green discharge (95 % CI)	Malodorous or white discharge (95 %CI)
Sensitivity (%)	11 (5-24)	20 (11-34)	28 (17-43)	70 (55-81)
Specificity (%)	91 (87-95)	90 (85-93)	79 (73-84)	19 (14-25)
PPV (%)	23	30	22	16
NPV (%)	83	84	84	75
Average Efficiency	51	55	54	45
Weighted Efficiency	27	34	38	60
	Runny/profuse or malodorous Discharge (95 % CI)	Runny/profuse or malodorous or frothy discharge (95 % CI)	Runny/profuse or malodorous or yellow/yellow green discharge (95 % CI)	Runny/profuse or malodorous or white discharge (95 % CI)
Sensitivity %)	23 (13-37)	32 (20-47)	33 (20-47)	77 (62-87)
Specificity (%)	81 (75-86)	79 (73-84)	72 (66-78)	13 (9-19)
PPV (%)	20	25	20	16
NPV (%)	83	84	83	73
Average Efficiency	52	55	52	45
Weighted Efficiency	34	41	40	64

[1]CI=Confidence interval

[2]Average Efficiency = Sensitivity + Specificity/2,

[3]Weighted Efficiency= 80%Sensitivity+ 20% Specificity/10

Efficiency of the Clinical Signs

The weighted efficiencies of any of the combinations of the clinical signs currently and not currently used in SCM was higher compared to the weighted efficiency of only using the clinical signs currently in the SCM for TV. No improvement in efficiency was observed based on the average of sensitivity and specificity (Table 2).

Candidiasis (CA)

"Thick curd-like discharge", used in diagnosing CA has low sensitivity (28%), and moderately high specificity (74%). White discharge had a statistically significantly higher sensitivity (68%) but the poorest specificity (26%) compared to thick curd-like discharge (Table 3). We did not evaluate any added clinical signs for the diagnoses of CA beyond what is used in the current SCM, i.e., thick, curd-like or white discharge.

Table 3 Comparison of clinical signs with laboratory test (KOH prep) for Candidiasis

	Current Clinical Signs		
	Thick-curd like discharge (95 % CI[1])	White discharge (95 % CI)	Thick-curd like or white discharge (95 % CI)
Sensitivity (%)	28 (19-40)	68 (57-78)	68 (57-78)
Specificity (%)	74 (67-80)	26 (20-32)	26 (20-32)
PPV (%)	32	28	28
NPV (%)	71	66	66
Average Efficiency[2]	51	47	47
Weighted Efficiency[3]	38	60	60

[1]CI=Confidence interval

[2]Average Efficiency =Sensitivity + Specificity/2

[3]Weighted Efficiency= 80%Sensitivity + 20% Specificity/10

Efficiency of the Clinical Signs

The weighted efficiencies of white discharge alone and combinations of white and thick curd-like discharge for CA were higher than the weighted efficiency of thick curd-like discharge alone.

Gonorrhea/Chlamydia (Cervicitis)

Mucopurulent cervix or risk score ≥ 2 are the clinical and epidemiological features currently used in the SCM of GC/CT. The sensitivity of the combination of mucopus cervix or score ≥ 2 was 61% and the specificity of 57%. The addition of individual clinical signs not currently used in SCM (friable cervix, cervical erosion or rusty/bloody discharge), to mucopurulent cervix and risk score ≥ 2 increased sensitivity, but decreased specificity, these differences were not statistically significant (Table 4). The addition of friable cervix (not currently used in SCM) increased the sensitivity to 72% and decreased specificity to 45%.

Table 4 Comparison of clinical signs with laboratory tests (Culture/EIA) for Gonorrhea/Chlamydia

	Current Clinical Signs	Combination of Clinical Signs		
	Mucopus cervix (95 % CI*)	Mucopus or friable cervix (95 % CI)	Mucopus or cervical erosion (95 % CI)	Mucopus cervix or rusty/bloody discharge (95 % CI)
Sensitivity (%)	35 (24-49)	54 (41-66)	43 (41-66)	39 (41-66)
Specificity (%)	78 (72-83)	63 (57-70)	70 (57-70)	76 (57-70)
PPV (%)	28	27	27	29
NPV (%)	83	84	83	83
Average Efficiency**	57	59	57	57
Weighted Efficiency+	44	56	48	47
	Risk score ≥2 (95 % CI)	Risk score ≥2 or friable cervix (95 % CI)	Risk score ≥2 or cervical erosion (95 % CI)	Risk score ≥2 or rusty/bloody discharge (95 % CI)
Sensitivity	35 (24-49)	61 (48-73)	54 (41-66)	42 (29-56)
Specificity (%)	73 (67-78)	57 (50-64)	65 (59-71)	70 (64-76)
PPV (%)	25	27	28	26
NPV (%)	82	85	85	83
Average Efficiency	54	59	60	56
Weighted Efficiency	42	60	56	48
	Mucopus or risk score ≥2 (95 % CI)	Mucopus or risk score ≥2 or friable cervix (95 % CI)	Mucopus or risk score ≥2 or cervical erosion (95 % CI)	Mucopus or risk score ≥2 or rusty/ bloody discharge (95 % CI)
Sensitivity (%)	61 (48-73)	72 (59-82)	67 (53-78)	65 (52-77)
Specificity (%)	57 (50-63)	45 (39-52)	51 (44-58)	54 (47-61)
PPV (%)	26	25	26	27
NPV (%)	85	86	86	86
Average Efficiency	59	59	59	60
Weighted Efficiency	60	67	64	63

*CI=Confidence interval

**Average Eff. =Sensitivity + Specificity/2

+Weighted Efficiency= 80%Sensitivity + 20% Specificity/10

Efficiency of the Clinical Signs

The weighted efficiencies of any of the combinations of those clinical signs that are currently and not currently used for diagnosing GC/CT were higher than the weighted efficiencies of only using the clinical signs. However, when the efficiencies were calculated on a simple average of sensitivity and specificity, no additional benefit was noted when those clinical signs not currently in the SCM were added (Table 4).

DISCUSSION

Syndromic case management among pregnant women or among family planning attendees in Jamaica has shown only a marginal validity for SCM.[7,8] This result is alarming since the prevalence of RTIs is still relatively high in these so-called "lower risk groups".[10,11]

We have found that among the clinical signs currently used in SCM for the diagnoses of BV, the combination of runny/profuse or malodorous discharge provided the highest sensitivity and acceptable specificity for pregnant women whereas, when used independently, these signs were far less predictive. Previous studies suggest that malodorous discharge is strongly associated with BV, whereas, profuse/runny discharge is not.[10,11] This study has shown that the addition of clinical sign "creamy homogenous discharge," which is not currently used in SCM, to runny/profuse or malodorous discharge showed substantial increases its sensitivity but with a corresponding decrease in specificity. The enhanced algorithm is more efficient when one uses a weighted average that considers sensitivity to be more important than specificity.

Using the current WHO algorithm for TV, the combination of runny/profuse or malodorous discharge has the highest sensitivity and acceptable specificity for diagnosing trichomoniasis. However, the sensitivity and specificity of this combination was not much different from the sensitivity and specificity obtained when runny/profuse discharge was used solely in the diagnosis of TV. This implies that it is reasonable to use runny/profuse discharge alone as a clinical sign in the syndromic management of TV.

The addition of white discharge (not currently used in SCM) to profuse/runny or malodorous discharge significantly increased the sensitivity of the algorithm for TV but lowered its specificity; weighting of the average did not alter these conclusions.

The clinical sign "white discharge" currently used in the diagnoses of candidiasis has the highest sensitivity, but lowest specificity. Therefore, if the purpose of the screening is to capture women with CA, the clinical sign "white discharge" is a reasonable way to assess this population syndromically.

The addition of clinical signs such as friable cervix, cervical erosion, which are not currently used in SCM, increased the sensitivity of the algorithm for GC/CT. Results of studies in different settings showed that the current WHO risk score needs to be adjusted for the community where it will be applied and should be more population specific.[11,12] The results of this study revealed the difficulty in the diagnoses of GC/CT syndromically owing to its asymptomatic nature. In a study done in Malawi, investigators reported that among women with vaginal discharge, only 29% of women with cervical infection had mucopus cervix.[3] Addition of simple laboratory tests to the current algorithm for GC/CT will facilitate better diagnoses of these RTIs more than addition of more clinical signs.

A larger sample size would have improved the statistical power of our study. In addition, the clinicians involved in our study were relatively new to the SCM approach such that our findings may differ in a context of more experienced practitioners. However, we did offer a three-day SCM training course prior to initiating the study.

Inclusion of additional clinical signs to the current SCM algorithm and weighing of sensitivity more than specificity may provide a better tool in the assessment of RTIs

among pregnant women syndromically particularly for BV and to a lesser extent for GC/CT. In areas wherein the prevalence of RTIs is high, emphasis on improving the sensitivity of the algorithm should be a priority. The high prevalence rates of RTIs among pregnant women in Jamaica warrant special attention; improving laboratory capacities for RTI diagnosis should be a part of this effort.

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IMPROVING SYNDROMIC CASE MANAGEMENT FOR CERVICITIS, BACTERIAL VAGINOSIS, AND TRICHOMONIASIS WITH BASIC LABORATORY TESTS OR CLINICAL SIGNS

by

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ABSTRACT

Introduction: Laboratory tests for the diagnosis of reproductive tract infections (RTIs) are not feasible in most developing countries. Syndromic case management is proposed as a cost-effective alternative. The present study seeks to develop algorithms that will better identify RTI-infected pregnant women.

Study Design: A cross-sectional study was conducted to assess the World Health Organization algorithm for antenatal attendees and to explore additional clinical signs for diagnosing RTI among pregnant women in Jamaica. Two-hundred sixty-nine women participated in this study from June to September 1997. A questionnaire that collected information on demographic factors, sexual behaviors, and medical histories was completed by each participant. A pelvic examination was performed by a trained clinician. Specimens were collected for laboratory diagnoses. Clinical signs, including those currently used in the WHO algorithm and additional clinical signs were considered to craft a more predictive model to predict RTIs, including clinical data, simple laboratory tests (e.g., wet mount, whiff test, and oxidase test). The area under the curve (AUC) of the receiver operating characteristic curve was employed to determine the best algorithm to predict each RTI in this population.

Results: The current algorithm (runny/profuse or malodorous discharge) for diagnoses of bacterial vaginosis has an AUC of 0.56. The addition of laboratory tests whiff test to the combination of clinical sign runny/profuse discharge or malodorous discharge has an

AUC of 0.61. For trichomoniasis, the current algorithm (runny/profuse or malodorous discharge) has an AUC of 0.52. The addition of wet mount to the current algorithm has an AUC of at least 0.65). For gonorrhea/chlamydia, the current algorithm (mucopurulent cervix or risk score ≥2) has an AUC of 0.60. The addition of an oxidase test to the current algorithm has an AUC of 0.69.

Discussion: Whiff test for bacterial vaginosis, wet mount for trichomoniasis, and oxidase test for gonorrhea/chlamydia improved the diagnostic performance of syndromic case management among pregnant women. Middle income countries like Jamaica may improve the value of syndromic case management with clinical and simple laboratory test modifications of the screening algorithms for RTIs.

INTRODUCTION

The term reproductive tract infections (RTIs) include three types of infections: sexually transmitted infections (STIs) (i.e. chlamydia, gonorrhea, trichomoniasis, syphilis, chancroid, genital herpes, and HIV), endogenous infections caused by overgrowth of organisms that can be present in the genital tract of a healthy woman (Bacterial vaginosis, candidiasis), and iatrogenic infections, e.g., those associated with surgery.[1] RTIs are a leading cause of morbidity among women of reproductive age and with HIV, a major global public health priority. Women and their infants bear the burden of RTIs disproportionately.[2] Ophthalmia neonatorum (ON), pre-term deliveries, low birth weight and prematurity are associated strongly with RTIs. RTIs facilitate HIV transmission making their control even more compelling.[1,3,4,5]

The traditional method of diagnosing RTIs in most developed countries is clinical suspicion followed by examination and the use of laboratory tests. However, in most developing countries, this approach is not currently feasible due to lack of infrastructure, resources and trained personnel. The World Health Organization (WHO) advocates the use of syndromic case management (SCM) as a cost-effective method of diagnosing RTIs, and as a means of interrupting transmission through early detection and treatment.[6] SCM is a method wherein physicians base their diagnosis and treatment not on laboratory testing, but rather on recognition of a clinical syndrome. The clinical syndrome includes a group of easily recognizable symptoms and signs associated with infection by common etiological agents. [7,8] A flow chart (algorithm), is the step by step diagnostic guide for

medical decision making. Upon identification of a syndrome, treatment is provided that will deal with the most probable responsible organisms. Sensitivity and specificity of SCM vary in different settings; there is still a need for field appropriate, inexpensive tools for the detection of STDs among women.[9]

In Jamaica SCM was feasible among women presenting to STD clinics, but, SCM performed less well in family planning clinics.[10,11] In 1997, we conducted the validity of SCM among pregnant women in Jamaica.[12] SCM proved to be unreliable predictor of infections, an unfortunate finding since the prevalence of RTIs among pregnant women was high.[12,13] We subsequently identified additional clinical signs that proved helpful in SCM-based diagnosis for pregnant women in Jamaica.[15] In the current study, we evaluated modified algorithms to assess whether they are more suitable for diagnosing different RTIs among pregnant women in Jamaica compared with the current WHO algorithms.

METHODS

Clinical

A cross-sectional study designed to evaluate the clinical factors used in SCM against laboratory test results and to determine the clinical risk factors associated with RTIs (Bacterial vaginosis [BV], Trichomoniasis [TV], Candidiasis [CA], and Gonorrhea [GC]/ Chlamydia [CT]) was conducted among pregnant women in Kingston, Jamaica from June 1997 to September 1997. A total of 269 pregnant women who presented in the second trimester for their first prenatal visit were recruited for the study. Each woman was asked to complete a questionnaire that collected information on demographics, sexual behaviors, and medical histories of the participant. After the interview, each woman was examined by a trained clinician who conducted a pelvic examination and specimens were collected for laboratory diagnoses. The WHO algorithm currently used for STD clinic attenders in Jamaica was used to diagnose RTIs. Women suspected of having gonococcal infections and chlamydial infections, based on syndromic management were treated with an oral one time dose of cefixime (400mg), and with an oral erythromycin, 500 mg qid x 7days. Metronidazole was given to women who were suspected of having trichomoniasis based on SCM. Prevalences of RTIs, performance of the WHO algorithm, and clinical signs in the subjects have been reported previously.[12,15,16]

Laboratory Procedures

All specimens collected from the vagina by swabbing were examined on saline wet prep for TV, clue cells for BV, and yeast (for buds and pseudohyphae) by direct mi

croscopy. The specimens were then cultured for 5 days for Trichomonas vaginalis using an "InPouch TV test kit" (Biomed Diagnostics, San Jose, CA). A "whiff" test was performed by dipping a sterile cotton swab (applied to the vaginal wall) in 1 ml potassium hydroxide (10% KOH) and assessing for a fishy odor. The pH of the vaginal fluid was determined by applying pH paper (Boehinger Mannheim, Indianapolis, In) to the wall of the vagina for a few seconds. A gram stain of the vaginal discharge was also prepared, and evaluated under oil immersion for *Lactobacilli spp*, *Gardenella vaginalis*, *Bacteroides spp*. and *Mobiluncus spp*. morphotypes. The Nugent score [17] was used in detecting the number of morphotypes in the smear and served as the gold standard in diagnosing BV. Endo-cervical swab specimens were obtained for direct plating of Thayer-Martin agar for the culture of *N. gonorrhoeae*. A second set of endocervical swab specimen was collected to test for *C. trachomatis* using an on-site enzyme immunoassay for Chlamydia (EIA,Clearview/Biostar). Ligase chain reaction (LCR) for Chlamydia was performed on a subset of specimens (10%) for quality control. The laboratory test results were given to the women on their next visit and treatment was provided to all infected women not previously treated under SCM assessment. All partners of infected women were invited to STD clinics for assessment and treatment if needed. Condom use was also promoted among women and their partners.

Statistical Analysis

Using the results of our evaluation of the clinical signs currently and not currently used in the SCM [15], we used the combinations of clinical signs that had the highest sensitivities, and specificities in the development of new algorithms for GC/CT, TV, and BV. Simple laboratory tests (whiff test, wet mount, and oxidase test) were added to these clin-

ical signs in modification of the current algorithm for BV and TV. Different combinations of clinical signs and laboratory tests for each RTI were developed and evaluated. Specifically, the highest sensitivities observed for BV is in the combination of creamy homogenous discharge with runny/profuse and malodorous discharge.[15] We then added the whiff test to these clinical signs to arrive at four modified algorithms based on combinations of these four variables. Under TV, the combination of white discharge with runny/profuse and malodorous discharge produced statistically significantly higher sensitivities[15] for culture proven TV. Wet mount was then added to these clinical signs to arrive at four modified algorithms based on combinations of these four variables. Finally, the addition of friable cervix, cervical erosion, and rusty/bloody discharge to mucopus cervix and risk score >=2 was selected based on improved sensitivities [15] for GC/CT. Oxidase test was added to these clinical signs to arrive at six modified algorithms resulting from combinations of five variables. The sensitivities and specificities of these modified algorithms along with SE and 95% CI were compared to the current algorithm for each RTI.

To determine a modified algorithm with the maximum efficacy, receiver operating characteristic (ROC) curve techniques were employed (SAS version 9). ROC is a graphical assessment of the predictive characteristic of an algorithm. The graph poses sensitivity (true positive rate) on the vertical axis and 1-specificity (false positive rate) on the horizontal axis. The area under the curve (AUC) is interpreted as the average value of sensitivity for all possible values of specificities [19] and can have any value between 0 and 1. In this study, the area under the curve of the ROC depicts the overall performance of the algorithms, that is, the greater the area, the better the efficiency of an algorithm. The

closer the value of the AUC to 0.5, the more likely that we are relying on pure chance to distinguish those women with RTI versus those without. The maximum value for the area under the ROC curve is 1, an indication of an algorithm that is a perfect screening tool versus the gold standard diagnosis.

A categorical ordinal variable representing levels of combinations of variables in each modified algorithm was created. For each modified algorithm within each RTI, a logistic regression model was fitted to model women with RTI versus those without using the categorized ordinal variable as independent variable in the model. ROC and AUC of the ROC were estimated from the model. Standard errors or the AUCs were estimated using the method described by Hanley et al.[18]

RESULTS

Demographic and RTI Prevalence

The ages of the 269 pregnant women ranged from 14-40 years with a mean of 23 years. Forty-three percent of the women had received some secondary education and 51% were employed. About half (51%) were either married or in a steady monogamous relationship. For 33% of the women, this was their first pregnancy.

Culture positive *T. vaginalis* was detected in 18% of the women in this study and 44% of the study participants had BV based on the gram stain scored according to the Nugent criteria. Thirty-one percent of the women were positive for Candidiasis by microscopy and 47% had cervicitis (GC/CT) based on gonorrhea cultures and chlamydia EIA.

Bacterial Vaginosis

Three modified algorithms had better diagnostic performance for BV compared to the current algorithm (Table 1). These modified algorithms are termed A (runny/profuse discharge or positive whiff test), B (runny/profuse or malodorous or creamy homogenous discharge or positive whiff test), C (runny/profuse or creamy homogenous discharge or positive whiff test). Algorithm D which used whiff test solely in the diagnosis of BV had a similar diagnostic performance to the current algorithm (AUC=0.59, and 0.56 respectively). Nonetheless modified algorithms A, B and C exhibited significant improvements in sensitivities (Table 1).

Table 1 Summary of the sensitivities, specificities, PPV, NPV and AUC of the current and improved algorithms for BV

RTI	Algorithm	Clinical signs/Laboratory Tests	Sensitivity (%) (95 % CI[2])	Specificity (%) (95 % CI)	PPV (%)	NPV (%)	AUC of ROC (95% CI)
BV[1]	Current	Runny/profuse or Malodorous discharge	27 (CI=21-33) SE[3]=.03	85 (CI=81-89) SE=.02	58	61	.56 (CI=.49-.63) SE=.03
	Modified A	Runny/profuse or Positive whiff test	40 (CI=34-46) SE=.03	64 (CI=58-70) SE =.03	61	64	.61 (CI=.51-.71) SE=.05
	Modified B	Runny/profuse or Malodorous or Creamy homogenous discharge or Positive whiff test	57 (CI=51-63) SE=.03	66 (CI=60-72) SE=.03	53	66	.61 (CI=.54-.68) SE=.03
	Modified C	Runny/profuse or Creamy homogenous discharge or Positive whiff test	55 (CI=49-61) SE=.03	63 (CI=57-69) SE=.03	53	65	.60 (CI=.54-.67) SE=.04
	Modified D	Positive whiff test	25 (CI=19-31) SE=.03	94 (CI=92-96) SE=.01	74	63	.59 (CI=.52-.66) SE=.03

[1]BV as confirmed by Nugent Score
[2]CI= 95 % Confidence Interval
[3]SE=Standard Error

Trichomoniasis (TV)

In comparison to the current algorithm (runny/profuse or malodorous discharge, AUC=.52), three modified algorithms (A,B and C) wherein wet mount (not used in SCM) was added to the combination of clinical signs currently and not currently used in SCM (runny/profuse, malodorous discharge, white discharge) performed better in the diagnosis of TV (Table 2). Algorithm D which used wet mount as the only screening tool for TV performed better (AUC=.67) than the current algorithm (AUC=.52). Although these improvements in performance are not statistically significant based on AUC of ROC, all four modified algorithms (A, B, C, D) have significant increases in sensitivities (Table 2).

Table 2 Summary of the sensitivities, specificities, PPV, NPV and AUC of the current and improved algorithms for TV

RTI	Algorithm	Clinical signs/Laboratory Tests	Sensitivity (%) (95 % CI[2])	Specificity (%) (95 % CI)	PPV (%)	NPV (%)	AUC of ROC (95% CI)
TV[1]	Current	Runny/profuse or Malodorous discharge	23 (CI=17-29) SE[3]=.03	81 (CI=77-85) SE=.02	20	83	.52 (CI=.42-.62) SE=.05
	Modified A	Runny/profuse or malodorous discharge or Wet mount positive	52 (CI=46-58) SE=.03	80 (CI=76-84) SE=.02	36	89	.68 (CI=.55-.75) SE=.05
	Modified B	Runny/profuse or Malodorous discharge white discharge or Wet mount positive	86 (CI=82-90) SE=.02	13 (CI=9-17) SE=.02	17	82	.65 (CI=.53-.73) SE=.05
	Modified C	Runny/profuse or white discharge or wet mount positive	86 (CI=82-90) SE=.02	15 (CI=11-19) SE=.02	18	83	.67 (CI=.57-.77) SE=.05
	Modified D	Wet mount positive	35 (CI=29-41) SE=.03	98 (CI=96-100) SE=.01	81	87	.67 (CI=.56-.76) SE=.05

[1]TV as confirmed by Culture
[2]CI= 95 % Confidence Interval
[3]SE=Standard Error

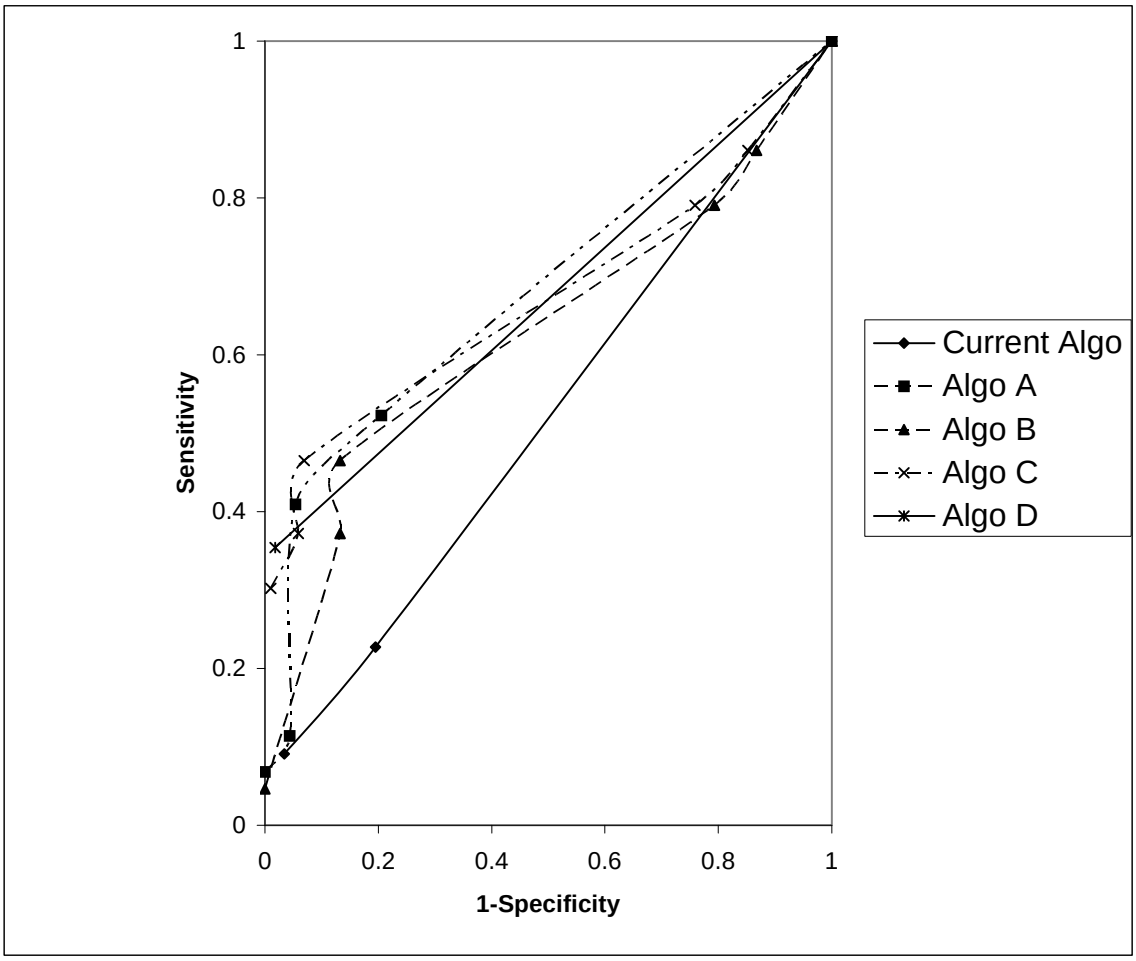

Figure 1. Receiver Operating Characteristic (ROC) for Trichomoniasis. Graphically represents the AUC of the ROC for the different algorithms for TV

Gonorrhea and/or Chlamydia

Mucopurulent cervicitis and risk score ≥ 2 (AUC=0.60), which are currently used in SCM when used in combination with clinical signs not currently used in SCM (friable cervix, cervical erosion, rusty/bloody discharge) had a fair performance in the syndromic diagnosis of GC/CT. Interestingly, even the addition of these clinical signs presumed to be predictive of cervicitis did not improve the performance of the modified algorithms

compared to the current algorithm (Table 3). However, the addition of laboratory test oxidase improved the performance of the algorithm (AUC=.69). Modified algorithms A, B, C, D exhibited a moderate increased in sensitivities but these are not statistically significant (Table 3).

Table 3 Summary of the sensitivities, specificities, PPV, NPV and AUC of the current and improved algorithms for GC/CT

RTI	Algorithm	Clinical signs/Laboratory Tests	Sensitivity (%) (95 % CI[2])	Specificity (%) (95 % CI)	PPV (%)	NPV (%)	AUC of ROC (95% CI)
GC/ CT[1]	Current	Mucopus cervix Risk score ≥2	61 (CI=55-67) SE=.03	57 (CI=51-63) SE=.03	26	85	.60 (CI=.52-.68) SE=.04
	Modified A	Mucopus cervix Risk score ≥2 Cervical erosion	67 (CI=61-73) SE=.03	51 (CI=45-57) SE=.03	26	86	.61 (CI=.40-.62) SE=.04
	Modified B	Mucopus cervix Risk score ≥2 Rusty/bloody discharge	65 (CI=59-71) SE=.03	54 (CI=48-60) SE=.03	27	86	.60 (CI=.52-.68) SE=.04
	Modified C	Mucopus cervix Risk score ≥2 Friable cervix	72 (CI=66-78) SE=.03	86 (CI=82-90) SE=.02	25	86	.63 (CI=.54-.72) SE=.04
	Modified D	Mucopus cervix Risk score Oxidase positive	72 (CI=66-78) SE=.03	57 (CI=51-63) SE=.03	30	89	.69 (CI=.61-.77) SE=.04

[1]GC/CT as confirmed by culture/EIA
[2]CI= 95 % Confidence Interval
[3]SE=Standard Error

The Improved Algorithm. Considering that sensitivity is more important than specificity to prevent adverse pregnancy outcome due to RTIs, our proposed improved algorithm is presented in Figure 2. Using modified algorithm B (addition of creamy homogenous discharge and whiff test) the sensitivity of diagnosing BV increased from 27% (current algorithm) to 57%. For TV, the sensitivity of the modified algorithm C (addition of white discharge and wet mount) increased from 23% to 86%. For cervicitis (GC/CT), modified algorithm C (addition of friable cervix) increased the sensitivity from 61% to 72%.

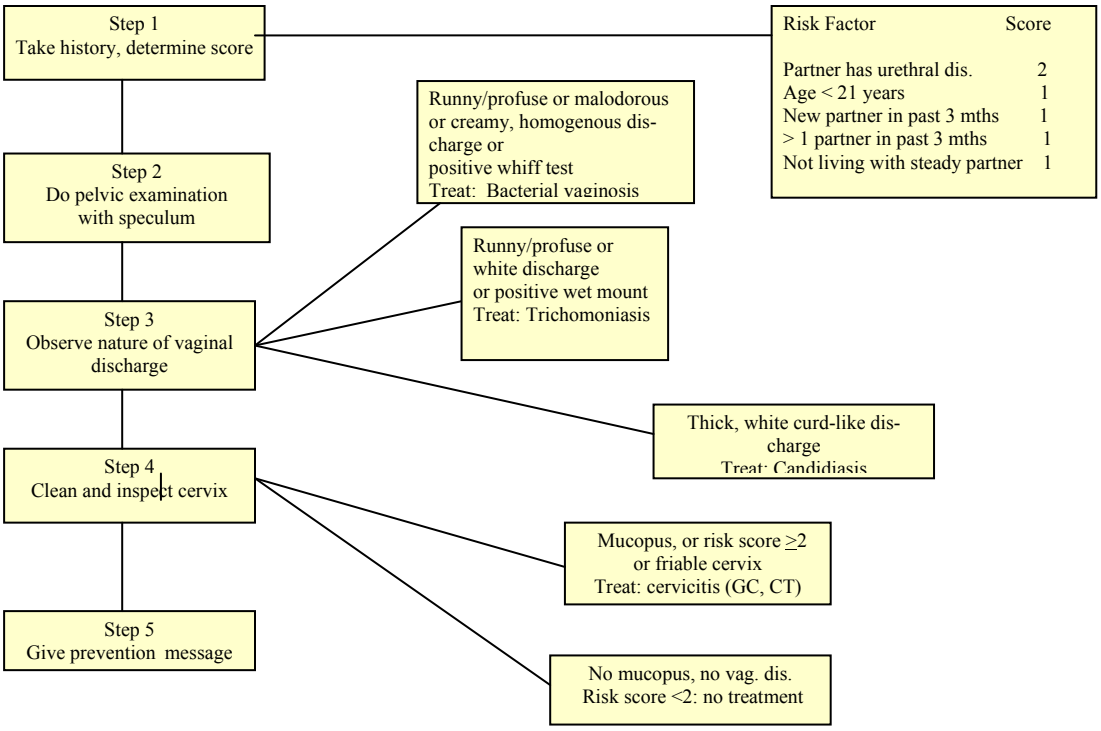

Figure 2. The Improved Algorithm.

DISCUSSION

In our previous studies, we showed the marginal validity of the use of syndromic case management for the diagnosis of RTIs among pregnant women in Jamaica.[12] Studies in different settings reported that SCM even with risk score assessment has a low sensitivity in the detection of RTIs among pregnant women [20, 21] and the pursuit for simple, cheap and reliable test for the diagnosis of BV, TV and GC/CT still remains to be a high priority.

This study developed modified algorithms that will accurately diagnose RTIs among pregnant women in Jamaica. The addition of simple laboratory test such as whiff test for BV, wet mount for TV, oxidase for cervicitis (GC/CT) increased the sensitivities of the current algorithms but the performance of these improved algorithms, although better than the current algorithm were not statistically significant. In theory, a good diagnostic tool is one that is 100% sensitive and specific [22] but in most cases an increase in sensitivity has a trade off of a decrease in specificity. When screening for a potentially serious disease like RTIs in pregnancy where the sequelae affect not only women but also their unborn children, an algorithm that provides higher sensitivity should be considered. BV has been implicated in the pathogenesis of pelvic inflammatory disease [23], and both BV and TV predispose to preterm delivery.[24, 25] Untreated RTIs also facilitates HIV transmission.[2,3,4,5] The increased sensitivity of our proposed modified algorithms would lead to fewer missed cases, fewer false positives by a syndromic approach and early de

tection and treatment of these dreaded infections. The trade-off is that some uninfected pregnant women would be treated unnecessarily.

Addition of other laboratory tests such as leukocyte esterase dipstick (LED) test may also improve the diagnostic performance of the algorithm for cervicitis (GC/CT) but this was not done in our study and considered as one of our study's limitations. A larger would have been helpful to measure the effectiveness of these improved algorithms.

One of the disadvantages of these improved algorithms is the cost of the added laboratory tests and the complexity of the assessment of RTIs by syndrome. In settings where gloves for speculum exams or slides for wet mount may not be available, the use-fulness of these improved algorithms maybe limited. However, middle income countries like Jamaica can improve SCM with the addition of these simple, affordable laboratory tests and clinical signs.

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ETHICAL CONSIDERATIONS

The participants were pregnant women past their second trimester. The questionnaires were administered by trained health professionals at the time of their first visit in the antenatal clinic. Therefore no financial burden was placed on the women, since they were not asked to return to the clinic in order to participate in the study. The speculum exam was performed by physicians, and the blood sample was taken under sterile condition from each woman. No risk of physical harm was associated with these gentle and professional examinations.

Informed consent was obtained from each woman after the study was explained by the health professionals. The women were informed that the information gathered would be treated confidentially and that their identity would not be revealed to anyone. The study protocol was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board and the Jamaican Ministry of Health.

The direct benefit of this study to the women was that individuals who tested positive for an RTI by either by the syndromic approach or laboratory diagnosis were given antibiotic therapy. The benefit of the study to the society is that the validity of the clinical risk factors used in SCM will be evaluated among pregnant women. In addition, the results of this study will be used in constructing a cost-effective modified algorithm that is acceptable and feasible among pregnant women. Development of a cheap diagnostic tool for RTI should allow early detection and treatment of infection in pregnant women that may eventually lead to prevention of adverse pregnancy outcome.

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APPENDIX A

SUMMARY OF STD PREVALENCE AMONG PREGNANT WOMEN IN JAMAICA (N=371)

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SUMMARY OF STD PREVALENCE AMONG PREGNANT WOMEN IN JAMAICA (N=371)

STD	PREVALENCE (%)
Syphilis	3.6
Gonorrhea	5.4
Chlamydia	17.8
HIV	1.3

APPENDIX B

SUMMARY OF VAGINITIS PREVALENCE AMONG PREGNANT WOMEN IN JAMAICA (N=269)

APPENDIX B

SUMMARY OF VAGINITIS PREVALENCE AMONG PREGNANT WOMEN IN JAMAICA (N=269)

VAGINITIS	PREVALENCE (%)
Bacterial vaginosis	44.1
Trichomoniasis	18.0
Candidiasis	30.7

APPENDIX C

SUMMARY OF PRELIMINARY ACTIVITIES AND DATA COLLECTION POINTS

APPENDIX C

SUMMARY OF PRELIMINARY ACTIVITIES AND DATA COLLECTION POINTS

Pre-Training	Month 1	Month 2	Month 3	Month 4	Month 5
Recruitment of nurses, midwives and doctors	Pre-testing for nurses and midwives				
Development of questionnaires	Introduction on RTIs to nurses and midwives Showing of video and slides of different RTIs, introduction on different vaginal discharge In-field training of the nurses and midwives Training in using speculum and obtaining specimen Administration of post-test questionnaire for nurses and midwives				
	Recruitment of participants and collection of samples Introduction on syndromic case management and use of algorithm	Recruitment of participants and collection of samples Syndromic case management and use of algorithm	Recruitment of participants and collection of samples Syndromic case management and use of algorithm		
	Laboratory testing for culture (on-site testing), preparation of frozen sera Monitoring and data management and analysis	Laboratory testing for culture (on-site testing), preparation of frozen sera Monitoring and data management and analysis	Laboratory testing for culture (on-site testing), preparation of frozen sera Monitoring and data management and analysis	Laboratory testing Data analysis	Data analysis

APPENDIX D

SUMMARY OF VARIABLES AND COLLECTION SOURCE

APPENDIX D

SUMMARY OF VARIABLES AND COLLECTION SOURCE

Source	Variables (examples)	Categorized level (examples)
Demographic data	Age	1= < 21; 2=≥ 21
	Schooling	1= no schooling; 2= with schooling
	Occupation	1=with occupation; 2= no occupation
	Marital Status	1=married; 2=not married
Obstetrical History	Past history of pregnancy	1=been pregnant before 2= first time pregnancy
	Number of children alive	1=1; 2=2; 3=3
	Outcome of previous pregnancy	1=live born; 2=stillbirth
	History of blood transfusion	1= yes; 2=no
Antenatal care	Use of contraceptives	1= yes; 2=no
	Type of contraceptives used	1=OCP; 2=Depo; 3=IUCD
RTI Medical Record	Previous treatment for RTI	1=yes; 2=no
	Sex with new partner	1=yes; 2=no
	Number of partners within 1 month	1=1; 2= >1; 3=0
	STD or VD complain	1=yes; 2=no
Clinical Exam	Observed vaginal discharge	1=yes; 2=no
	Malodorous vaginal discharge	1=yes; 2=no
Laboratory Tests	EIA	1=pos; 2=neg
	GC Culture	1=pos; 2=neg