

When is Syndromic Management of
Sexually Transmitted Diseases Useful?
An Analysis of the Literature

Catherine Gergen
Victoria Wilkins
Pratyma Rangunathan, Ph.D.
Julia Walsh, M.D.

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TABLE OF CONTENTS

| | |
|--|------------------|
| I. INTRODUCTION..... | 4 |
| II. MATERIALS AND MEASURES OF EVALUATION..... | 6 |
| III. RESULTS..... | 7 |
| A. Urethral Discharge (UD) | 7 |
| 1. <i>The WHO Algorithm for UD in the Absence of Laboratory Support.....</i> | <i>7</i> |
| 2. <i>The WHO Algorithm for UD with Laboratory Support Available.....</i> | <i>8</i> |
| 3. <i>Conclusions about the WHO Algorithms for UD</i> | <i>9</i> |
| B. Genital Ulcer Disease (GUD)..... | 9 |
| 1. <i>The WHO Algorithm for GUD without Laboratory Support</i> | <i>9</i> |
| 2. <i>The WHO Algorithm for GUD with Laboratory Support</i> | <i>10</i> |
| 3. <i>The Use of More than One GUD Model: The Case of Kigali, Rwanda</i> | <i>11</i> |
| 4. <i>Conclusions about the WHO Algorithms for GUD</i> | <i>12</i> |
| C. Vaginal Discharge | 12 |
| 1. <i>The WHO Algorithms for Vaginal Discharge</i> | <i>12</i> |
| <u>a. <i>Women Seeking Care Because of Symptoms.....</i></u> | <u><i>12</i></u> |
| 1) <i>The WHO Algorithm for Vaginal Discharge with No Speculum or Laboratory Support Possible</i> | <i>12</i> |
| 2) <i>The WHO algorithm for Vaginal Discharge with Speculum Examination</i> | <i>13</i> |
| 3) <i>Conclusions about the WHO Algorithm when Women Seek Treatment for Vaginal Discharge</i> | <i>13</i> |
| <u>b. <i>Women Seeking Care for Reasons other than Vaginal Discharge or STD Treatment</i></u> | <u><i>13</i></u> |
| 1) <i>The WHO Algorithm for Vaginal Discharge with No Speculum or Laboratory Support</i> | <i>13</i> |
| 2) <i>The WHO Algorithm for Vaginal Discharge with Lower Abdominal Pain (LAP).....</i> | <i>14</i> |
| 3) <i>Conclusions about the WHO Algorithms when Women Seek Care for Reasons other than Vaginal Discharge</i> | <i>15</i> |
| <u>c. <i>Low-Risk Versus High-Risk Populations: A Study of Kinshasa, Zaire</i></u> | <u><i>15</i></u> |
| 2. <i>Studies Done on Non-WHO Algorithms for Vaginal Discharge.....</i> | <i>16</i> |
| 3. <i>Meta Analysis of Vaginal Discharge Algorithms.....</i> | <i>16</i> |
| 4. <i>Risk Scores for Vaginal Discharge.....</i> | <i>16</i> |
| a. <i>Using Risk Scores Only</i> | <i>17</i> |
| b. <i>Using Risk Scores Plus Medical Exams</i> | <i>18</i> |
| c. <i>Other Uses of the Risk Score Chart</i> | <i>21</i> |
| d. <i>Conclusions about Risk Scores</i> | <i>21</i> |

| | |
|--|-----------|
| IV. PROBLEMS IN IMPLEMENTING STD TREATMENT | 22 |
| A. Supply of Drugs and Equipment in Syndromic Management | 22 |
| B. Incorrect Use of Syndromic Diagnosis and Treatment by Providers..... | 22 |
| C. Patients and Syndromic Management | 23 |
| D. Clinic Populations and Syndromic Management | 23 |
| V. CONCLUSIONS ABOUT IMPLEMENTING SYNDROMIC MANAGEMENT FOR STDs | 25 |
| VI. SUMMARY OF FINDINGS: | 27 |
| REFERENCES..... | 29 |

I. INTRODUCTION

Developing countries have been ravaged by sexually transmitted diseases (STDs). In 1996, the World Health Organization (WHO) estimated that, worldwide, there are 333 million new STD infections per year. The largest number of cases occur in South East Asia (an estimated 150 million new STD cases annually) and sub-Saharan Africa (65 million cases annually) (Adler, 1996). The serious consequences of STDs include infertility, ectopic pregnancy, low birth weight, stillbirth, chronic pain in women who have had pelvic inflammatory disease, late symptomatic syphilis, and mutilating lesions for individuals suffering genital ulcers (WHO, 1991). Further consequences include perinatal infections, ophthalmia neonatorum, spontaneous abortion, cervical cancer, and congenital infections (Costello, et al. 1994).

Perhaps the worst consequence, however, is the increased risk of the transmission of HIV with STDs. Improved management of STDs by primary health care workers in the Mwanza region of Tanzania reduced incident cases of HIV-1 infection by 42% in the treatment communities compared to controls. Ghys, *et al.* (1997) have shown that shedding of HIV in vaginal secretions is strongly correlated with gonococcal (odds ratio: 1.9, C.I. 1.2-3.0) and chlamydial infections (odds ratio: 2.5, C.I. 1.1-5.8) and with cervical or vaginal ulcers (odds ratio: 3.9, C.I. 2.1-7.4). Furthermore, treatment resulted in a decrease of the genital shedding of the HIV virus from 42% to 21% (Ghys, *et al.* 1997). Finally, Wasserheit (1997) reviewed a number of studies examining the risk of HIV seroconversion relative to different STDs. For genital ulcer disease in women, odds ratios ranged from 3.3 in Nairobi, Kenya, to 7.7 in Chang-Rai, Thailand. In the presence of chlamydia, odds ratios for women ranged from 2.7 in Nairobi to 4.9 in Chang-Rai, while for gonorrhea odds ratios for women ranged from 4.2 in Dar-es-Salam, Tanzania to 9.8 in Belle Gladde. Transmission in the presence of STDs is much more likely to occur from males to females.

Commonly, the prevalence and incidence of STD infection is greatest in areas that lack the trained personnel and advanced equipment for accurate diagnoses and treatment. In 1990, the World Health Organization (WHO) developed a set of eighteen binary algorithms to be used by health care providers in diagnosing the presence of STDs. This laid the groundwork for the syndromic management of STDs. **Syndromic management** is based upon the premise that there are strong correlations between syndromes (signs and symptoms) and the presence of a particular disease. Thus, the health care provider diagnoses and treats STDs based primarily on the history and physical diagnosis, rather than upon evidence obtained from laboratory tests or microscopy. The WHO algorithms, eight of which are used in the papers reviewed here, involve the diagnosis of urethral discharge, genital ulcer disease, vaginal discharge and lower abdominal pain.

In addition to syndromic management, a number of providers have developed systems of risk scores to identify individuals with STDs. These scoring systems are based on patient demographics, history, and symptoms. This report also examines those systems that are well-evaluated. Syndromic treatment ideally represents a simple, feasible treatment strategy for resource-poor settings. The immediate treatment also avoids further transmission and complications that can occur as a result of loss to follow-up. Additionally, it cuts the cost of laboratory testing and potentially avoids false negatives or positives that might come from poor laboratory methods. Theoretically, it also could include partner notification, health education and counseling. In reality, however, how well does syndromic treatment work? How accurate are the current treatment algorithms for specific organisms? How many asymptomatic infections (which for some STDs may account for nearly half of the cases) are missed? As reported symptoms are subjective, and atypical infections might not be detected, what is the risk of overtreatment (treating false positives) or under-treating, and possible development of antibiotic resistance? Do taboos about STDs, especially among women, make patients reluctant to identify signs and symptoms, therefore making syndromic treatment

problematic? Does the lack of appropriate training of health care providers undermine the optimal usage of syndromic treatment?

While syndromic management and risk scores for STDs represent important options for treatment, there is still much work that needs to be done in developing strategies for effective management of STDs in individuals and populations. The present paper is a review of published, as well as some unpublished studies on syndromic treatment around the world. We report the results of the various studies and discuss the advantages and shortcomings of the approaches as reported to date. After completing a review of these studies, we make recommendations for a more successful approach to treatment of STDs worldwide.

II. MATERIALS AND MEASURES OF EVALUATION

The following report was researched from the fall of 1997 to the spring of 1998. Reports of syndromic treatment were first located, and further studies were then found through a cross-reference of the initial articles. By searching the World Wide Web and Medline, references in the published articles were reviewed. Experts in the field were contacted to identify other published and unpublished reports. Organizations such as Family Health International and the Population Council were contacted to identify topical monographs. In addition, through various experts, we obtained abstracts of related recent international meetings.

The effectiveness of each algorithm and risk score system is assessed by its sensitivity, specificity, and positive predictive value (PPV). As defined by Last *et al.* (1995), **sensitivity** is “the true proportion of diseased persons in the screened population who are identified as diseased by the screening test. Sensitivity is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test. (Synonym: true positive rate)” (p. 154). Historically, the sensitivity levels for syndromic STD management algorithms have been deemed important markers for effectiveness. In light of recent studies, the growing rate of antibiotic resistance due to falsely identified STDs has made considerations of specificity increase in importance. In illustration, a study conducted in an urban STD clinic and 26 rural integrated clinics in Tanzania detected a significant drop (from 95% to 90%) in antibiotic efficacy when used repeatedly to treat gonorrhea (Mayaud *et al.* 1997).

As defined by Last *et al.* (1990), **specificity** is “the proportion of truly non-diseased persons who are so identified by the screening test. It is a measure of the probability of correctly identifying a non-diseased person with a screening test. (Synonym: true negative case)” (p. 154).

In the studies presented here, sensitivity and specificity are determined by the use of syndromic algorithm criteria as compared to laboratory diagnosis. However, several studies use other measures of efficacy, including “cure rates.” These differences, as well as variations in the type of laboratory back-up will be discussed as they arise.

III. RESULTS

The following report assesses eighteen published studies and thirteen unpublished studies. The studies are from around the world but have a clear emphasis on Africa. The three primary syndromes addressed are urethral discharge in men, genital ulcer disease in both men and women, and vaginal discharge in women. Each syndrome requires a different algorithm. Urethral Discharge Syndrome and Genital Ulcer Disease Syndrome have been evaluated using two different WHO algorithms each. For vaginal discharge, a total of four different algorithms were used, each slightly altered according to the health setting and the questions being asked. The evaluation of syndromic treatment algorithms has occurred in different health care settings: antenatal clinics, commercial sex worker (CSW) clinics, STD clinics, family planning clinics, a teaching hospital outpatient clinic, and primary health care clinics.

A. Urethral Discharge (UD)

The treatment of STDs (gonorrhea and chlamydia) using syndromic algorithms for urethral discharge in men has been largely successful. In general, the reported sensitivity levels have been high (91-99%) and the diagnosis straightforward. Two primary algorithms were used: the WHO algorithm for UD, modeled for areas without microscopy, and the WHO algorithm for UD that incorporates the use of microscopy. Two studies used cure of infection as an outcome measure, while three studies used sensitivity of diagnosis. When cure of symptoms or microbiological cure is used, the sensitivity measures accuracy of diagnosis plus efficacy of treatment. A treatment with low efficacy will result in low sensitivity. A treatment with a broad spectrum will cure not just the organism measured, but other less common causes. Urethral discharge is one of the most obviously identifiable syndromes; its presence usually indicates gonorrhea, an STD which can be effectively treated with a single dose of antibiotics, and less commonly indicates other organisms. In Cote d'Ivoire, prevalence of the STDs was not measured (La Ruche, *et al.* 1995). Culture was positive for gonorrhea in 70.4% of men in Lusaka, Zambia; the prevalence of chlamydia was not given for this population (Hanson, *et al.* 1996).

1. The WHO Algorithm for UD in the Absence of Laboratory Support

The WHO algorithm for UD with no microscopy available consistently had the highest sensitivity rate, from 91% to 99%. (See Table 3.) In this algorithm, the health worker confirms the presence of urethral discharge and treats for gonorrhea and chlamydial infection, gives health education and counseling, examines and treats the partners, and checks results in a follow-up appointment seven to fourteen days after treatment. If treatment adherence is good and discharge persists, the patient is referred. If treatment adherence is bad, the provider starts the protocol again.

Djajkusumah, *et al.* (1998) report that in a primary health clinic in Bandung, Indonesia, 119 out of 140 patients who complained of urethral discharge were treated according to the WHO algorithm; 107 patients completed follow-up; and 106 were cured. Treatment covered gonococcal and chlamydial infections (ciprofloxacin, 500 mg, single oral dose; and doxycycline, 100 mg, twice daily for seven days). Microbiologic assessment included culture for *N. gonorrhoea*, with confirmation by Gram stain, oxidase reaction, and carbohydrate degradation tests. Chlamydial infection was identified by EIA, and positive specimens were re-tested with a blocking assay. Of the 119 men treated, 9 were positive for chlamydia only;

50 were positive for gonorrhea only; and 30 were positive for both gonorrhea and chlamydia. The overall sensitivity rate of the algorithm was 99%. However, the specificity was only 40%, indicating that many individuals were falsely diagnosed and treated as positive (Djajkusumah, *et al.* 1998).

In ten peripheral health centers in Abidjan, Côte d'Ivoire, the use of the algorithm resulted in a 92% "therapeutic success" (La Ruche *et al.* 1995). The treatment regimen consisted of using a single 250 mg intramuscular injection of ceftriaxone or a single 500 mg oral dose of ciprofloxacin (targeting gonorrhea), combined with 200 mg of doxycycline once daily for seven days (targeting chlamydial infections). Less than 10% of the patients had to be referred to higher levels of health care.

In a study conducted in five urban public health STD assistance centers in Brazil, 472 men complaining of urethral discharge between January and June of 1995 were treated according to the first UD algorithm. Gonorrhea was defined by the use of a culture, and chlamydia was detected by antigen testing. Of the 472 men, 44% (210) were culture positive for gonorrhea; 7% (35) were positive for chlamydia; and 8% (39) were positive for both gonorrhea and chlamydia (Moherdaui *et al.* 1997). The flowchart for UD in the absence of laboratory support performed with 98.8% sensitivity, 15.4% specificity, and 57.5% PPV. Clinical diagnosis performed nearly as well, with a 86.3% sensitivity, 80.3% specificity, and 83% PPV (Moherdaui *et al.* 1998).

Alary *et al.* (1998) performed a study of the WHO algorithm for UD without microscopy in three primary health centers in Benin, West Africa. The 105 men in the study had a 39% prevalence of gonorrhea (41), 7.6% prevalence of chlamydia (8), and 2.9% prevalence of both gonorrhea and chlamydia. Gold standard diagnosis for gonorrhea included culture and PCR, while diagnosis of chlamydia included an EIA and PCR. Two methods of testing were used because of the difficulty in Benin of implementing these techniques, especially culture for gonorrhea. The WHO algorithm without microscopy performed with a sensitivity of 91%, a specificity of 60.3%, and a PPV of 65.2%. Adding microscopy to the algorithm lowered the sensitivity and increased the specificity only slightly, while increasing costs and complicating patient care. The former has therefore been applied to health care settings in Benin.

2. The WHO Algorithm for UD with Laboratory Support Available

In this algorithm, once urethral discharge is confirmed, a stained smear of urethral sample is examined for polymorphonuclear leukocytes (PMN) per oil-field immersion in the urethral specimen and intracellular diplococci (ICDC). If present, the patient is treated for gonorrhea and chlamydial infection. If the urethral specimen contains more than 5 PMN, but there are no ICDCs present, the patient is treated for chlamydial infection. Treatment includes health education, counseling, partner treatment, and a follow-up of seven to fourteen days after initial treatment. If discharge persists, the provider must assess the treatment compliance and either begin the protocol again or refer the patient to the next level of care.

In a study done in a teaching hospital outpatient clinic in Lusaka, Zambia, the use of the WHO algorithm for UD (with microscopy available) had a high sensitivity rate. Specificity rate was not recorded. Here the UD algorithm was coupled with a brief history of sexual activity taken by an experienced clinical officer, a physical examination, and laboratory investigation. Ninety men complaining of urethral discharge were positively identified as having either gonorrhea or chlamydia and given a 2 g dose of kanamycin IM. They were asked to return for a follow-up visit in seven days and to notify their partners. During the second examination, patients were asked about their compliance with medication and abstention from sexual activity. If discharge persisted, they were then given 500 mg of tetracycline to be

taken four times a day for seven days, with a follow-up appointment in seven days. Those with still persistent discharge were then referred. Of the 90 men following the UD protocol, 79 were cured after the first visit, and Seven were felt to be cured after the second visit. Only one patient was lost to follow-up, and one continued to have discharge—yielding an overall 98% “cure” rate (Hanson *et al.* 1996).

3. Conclusions about the WHO Algorithms for UD

With or without microscopy, the WHO algorithms for UD yield a sensitivity greater than 90%, indicating that a large number of those with urethral discharge, not related to gonorrhea or chlamydia, were effectively treated. Only one of the four reports discussed above gave data for specificity—40% in Bandung, Indonesia. This low specificity indicates that in this case, a large number of people who were not infected with gonorrhea and chlamydia were treated unnecessarily. High cure rates may be a result of individuals being infected with other organisms that cause urethral discharge other than GC or CT and treatment being effective against these other organisms.

B. Genital Ulcer Disease (GUD)

The algorithms used for genital ulcer disease try to identify the presence of herpes, syphilis, and/or chancroid. The studies included different health care settings: primary health care clinics in Kigali, Rwanda, and Abidjan, Côte d’Ivoire; a teaching hospital in Lusaka, Zambia; and an STD clinic in Brazil. Two different algorithms are evaluated: the WHO algorithm for GUD with clinical support, and that without clinical support.

1. The WHO Algorithm for GUD without Laboratory Support

In this algorithm, the provider checks for vesicular lesions and, if present, asks the patient whether the lesions are recurrent. If the patient responds affirmatively, the patient is treated for herpes. If not consistent with herpes, the provider treats for syphilis and chancroid. When this simple algorithm was used in Brazil (Moherdaui *et al.* 1997) and in Côte d’Ivoire (La Ruche *et al.* 1995), it yielded good results.

In a primary health care clinic in Abidjan, Côte d’Ivoire, the WHO algorithm yielded treatment success of 100% among 26 patients presenting genital ulcers (out of a total of 207 patients seen for possible STDs). Treatment success was defined as the marked improvement of genital ulcers. Treatment involved either a single intramuscular injection of 250 mg of ceftriaxone (to treat both chancroid and syphilis) or a single dose of ciprofloxacin (for chancroid), combined with a single intramuscular injection of 2.4 million units of benzathine benzyl-penicillin G (for syphilis). All patients received antibiotics for ulcers, as nearly all were considered to be chancroid. All patients returned for follow-up, and ulcers persisted for more than a week in 81% of cases, but all were subsequently cured (La Ruch, *et al.* 1995).

Among 960 men and women coming to an STD clinic in Brazil, 151 presented complaints of genital ulcers. Using the algorithm, 22% were diagnosed and treated for primary syphilis; 26.1% were diagnosed and treated for chancroid; and 15.5% were diagnosed and treated for genital herpes. (There was no antibiotic information given.) An unknown number of the 136 patients with genital ulcers returned for follow-up. In 90% of those who returned, the ulcers had either disappeared or were healing at the time of the follow-up visit (Moherdaui, *et al.* 1997).

Both Brazil and Côte d'Ivoire have cure rates of over 90%. These results indicate that when laboratory support is not available, the use of these algorithms in syndromic treatment is a very effective method of genital ulcer disease detection and treatment. Specificity levels were not, however, reported in either study.

2. The WHO Algorithm for GUD with Laboratory Support

Unlike the previous algorithm, this algorithm is hierarchical and intended for locations where a rapid plasma reagent (RPR) test, a treponema pallidum haemagglutination test (TPHA), or dark field microscopy can be performed. In a teaching hospital outpatient clinic in Lusaka, Zambia, 237 male and female patients presented complaints of ulcers (Hanson *et al.* 1996). As with the urethral discharged study in Lusaka, the GUD algorithm was accompanied by a physical examination, laboratory investigation, and a brief history of the patient's sexual activity, taken by a clinical officer who had more than ten years of clinical work on STDs. According to the laboratory findings, 28% of men and 43% of women had either a positive RPR confirmed by TPHA and/or findings of spirochetes by phase contrast microscopy. Culture for *H. dureyi* met with limited success and therefore is not reported in detail.

In the physical examination of these patients in Lusaka, careful attention was given to ulcers and lymph nodes, and the results were described in detail. This included the location of ulcers, their associated tenderness, their depth, and whether they were irregular, dirty, or clean. The lymph nodes were characterized by size, confluence, consistency, tenderness, and position, as well as presence of Groove's signs. It was hoped that these descriptions would assist clinical officers in the diagnosis of chancroid, primary and secondary syphilis, and herpes simplex. Diagnosis was further supported by laboratory diagnosis using the standards listed in the WHO algorithm: dark field microscopy and serological tests for syphilis: rapid plasma reagent (RPR), these tests were confirmed by treponema pallidum haemagglutination test (TPHA).

One hundred thirty-nine men and 98 women with ulcers were given benzathine penicillin 2.4 MU I.M. in addition to trimethoprim-sulpha (10 tablets daily for two days). They were asked to return for follow-up visit in seven days and were requested to notify their partners. Thirteen of the men and seven of the women were lost to follow-up before the first re-visit. During the second exam, patients were asked about their compliance with medication and abstention from sexual activity. If the ulcer was healing, they were observed by the physician and asked to return for another follow-up visit. Ten men and four women did not return for the second follow-up. If the ulcers were stable or worse, the patients were referred, as was the case with eight men and one woman.

The study discovered differences in reaction between males and females. Of the 91 females, 39 were cured in the first visit, 29 more were cured by the end of the second visit, and six were healing—yielding an overall 81.8% cure rate. Among the 126 men following the GUD algorithm, 24 were cured by the first visit, 41 were cured by the end of the second visit, and 20 were healing—yielding an overall cure rate of 67.4%. The report suggests that this difference probably reflects a higher prevalence of syphilis in women (treatment for which is relatively rapid and effective). One hundred percent (100%) (35/35) of RPR-positive females and 90% (27/30) of RPR-positive males were either cured or healing at the first follow-up, compared to 83.7% (45/54) of RPR-negative females and 87.5% (77/88) of RPR-negative males. Because a higher percentage of women were RPR-positive, relatively more were cured by the first visit, whereas more men were lost to follow-up (Hanson, *et al.* 1996).

3. The Use of More than One GUD Model: The Case of Kigali, Rwanda

At a primary health care clinic in Kigali, Rwanda, a cross-sectional study was conducted by Bogaerts *et al.* (1995) among 395 patients with genital ulcers. Three different approaches to curing the signs and symptoms of genital ulcer disease were employed and results compared.

The first method was the application of the WHO algorithm for GUD without laboratory support on 395 patients (both male and female) who presented with signs of symptoms of GUD (ulcers, vesicular lesions). Based on the use of this algorithm, 108 out of 110 known positive patients were correctly treated for syphilis; 115 out of 115 known positive patients were correctly identified and treated for chancroid; and 29 out of 29 patients were correctly identified and treated for syphilis and chancroid. However, only 4 out of 89 patients were correctly identified and treated for herpes. Overall, this algorithm yielded the following rates of sensitivity: 98.2% for syphilis, 100% for chancroid, 100% for syphilis and chancroid, and 4.5% for herpes. The average specificity rate, on the other hand, was a low 2.1%, indicating a very high rate of over-treatment.

The application of the WHO algorithm for GUD with lab support in the Kigali population was more successful in yielding both a high sensitivity and a high specificity rate. This algorithm correctly identified and treated 78 out of 81 patients for syphilis, 83 out of 86 for chancroid, 0 out of 29 for syphilis and chancroid, and 4 out of 90 for herpes. While these results have an overall lower rate of sensitivity (97.3% for syphilis, 72.2% for chancroid, 0% for syphilis and chancroid, and 4.5% for herpes), it increased the average specificity of diagnosis to 96.8%.

Finally, a third method—clinical diagnosis—was employed. In this approach, all undetermined ulcers were treated clinically as syphilis and chancroid, and all superficial ulcers (and not just vesicles) were treated as herpes. Clinical diagnosis alone correctly identified and treated 18 out of 81 patients for syphilis, 57 out of 86 for chancroid, 0 out of 29 for syphilis and chancroid, and 48.3% for herpes. Overall, this resulted in low sensitivities: 22.2% for syphilis, 66.3% for chancroid, 0% for syphilis and chancroid, and 48.3% for herpes. The specificity, on the other hand, was fairly high at 89.1% (Bogaerts, *et al.* 1995). In looking at the results of this final approach, it should be noted that in this study, clinical diagnosis was made by a qualified physician (the study's author), which is not always the case in other developing countries. There was no training in syndromic treatment, as the criteria were only applied retrospectively.

Results from Kigali, Rwanda indicate the following.

- a.) Syndromic treatment without lab facilities leads to substantial over-treatment but does not miss individuals infected with both chancroid and syphilis (high rates of sensitivity but low rates of specificity). According to the study, the use of this algorithm was most preferable from a public health perspective: "It resulted in the highest proportion of correctly treated chancroid and syphilis cases." (Bogaerts *et al.* 1995, p.766)
- b.) Syndromic treatment with laboratory tests (serological tests for syphilis, including the RPR and the TPHA and/or dark field microscopy) is less sensitive but more specific for syphilis and chancroid.
- c.) Methods one and two (the GUD algorithms) are preferable to method three (clinical diagnosis alone).

- d.) Clinical diagnosis was the only way that herpes was identified but overall has an extremely low rate of sensitivity.

4. Conclusions about the WHO Algorithms for GUD

The sensitivity levels of the WHO GUD algorithms with or without laboratory support are equivalent in most cases (Rwanda, Brazil, and Côte d'Ivoire). The specificity levels are much higher (96.8% in Kigali, Rwanda) for the GUD algorithm with laboratory support than the GUD algorithm without laboratory support (2.1% in Kigali). Female cure rates were higher than men's in the Lusaka, Zambia study, probably because of the higher syphilis rates in women.

C. Vaginal Discharge

Vaginal Discharge Syndrome is the most difficult syndrome to diagnose, as the presence of discharge may be subtle and many organisms can cause the same symptoms. It is not surprising, therefore, that the algorithms for vaginal discharge give the broadest range of results. The studies we examine span six different health care settings and fourteen combinations of algorithms, including clinical exams, risk factors, and socio-demographic scores. Because so many algorithm combinations have been tested, the results are disaggregated into specific components for analysis. First, we will analyze the use of algorithms for vaginal discharge as they are applied to women with and without symptoms. Secondly, we will examine the use of risk factors in various ways: a) risk factors alone; b) risk factors with medical exams; and c) the combination of risk factors, medical exams, and vaginal discharge algorithms.

1. The WHO Algorithms for Vaginal Discharge

In 1990, WHO developed three basic algorithms for vaginal discharge. (See Flow Charts 5, 6, and 7.) These have been tailored to suit the needs and resources of individual communities. The simplest algorithm uses neither speculum nor laboratory examination, whereas more clinically based algorithms are designed for communities that have more resources.

a. Women Seeking Care Because of Symptoms

1) The WHO Algorithm for Vaginal Discharge with No Speculum or Laboratory Support Possible

In Lusaka, Zambia, 96 women came into a teaching hospital clinic presenting with complaints of vaginal discharge (Hanson *et al.* 1996). The WHO algorithm for vaginal discharge with vaginal examination and lab tests not possible was then implemented, each patient receiving kanamycin 2g IM and metronidazole 2g IM for the treatment of gonorrhea infection and trichomoniasis/bacterial vaginosis. Health education and counseling were also given, and the patients were told to return in seven days. If in seven days discharge still persisted and the compliance was felt to be good, the provider then administered tetracycline 500 mg four times a day for seven days (for treatment of chlamydia) and nystatin vag. (for treatment of candidiasis). Patients were again told to follow-up in seven days. If at that point discharge still persisted, each patient was given a referral to a higher level of care. Of the 96 women in the study, 80 were "cured", and 16 had persistent discharge (five of these were non-compliers and excluded from further analysis). By the second visit, 8 more were cured, 2

had persistent discharge, and one was lost to follow-up. Overall, this gave a high “cure rate” of 96.4%, based on symptoms alone (Hanson, *et al.* 1996).

When the same WHO vaginal discharge algorithm (Flow Chart 5) was applied to 92 female patients presenting with genital discharge at a primary health care clinic in Abidjan, Côte d'Ivoire, “success” (as defined by disappearance of discharge) was again high (La Ruche *et al.* 1995). (See Attachment 9b). Each patient was given 250 mg IM or one 500 mg tablet of ceftriaxone, plus 200 mg of doxycycline (once daily for seven days). In addition, each patient was given 100,000 U nystatin intravaginally (14 days) and, if discharge was malodorous, 2 grams tinidazole orally (once). Finally, each patient was given education and counseling, and told to return in seven days’ time. There was also “management” of the women’s sexual partners. If in seven days time the discharge still persisted, the patient was referred to the next level of health care. Overall, this method yielded a cure rate of 87%, with all 92 women being seen in follow-up (La Ruche, *et al.* 1995).

These two reports suggest that when women actually came to the provider presenting with vaginal discharge, the simplest WHO algorithm (without speculum or lab support) had high cure rates of 87-96%.

2) The WHO algorithm for Vaginal Discharge with Speculum Examination

In an STD clinic in Kingston, Jamaica, women with any urogenital complaint were entered into the WHO algorithm for vaginal discharge with speculum and examination of discharge (Appendix 1 and Flow Chart 7). If the discharge was profuse, runny, or malodorous, the patient was treated for trichomoniasis and bacterial vaginosis; if the discharge was white and curd-like, the patient was treated for a yeast infection; if there was cervical mucopus, the patient was treated for gonorrhea and chlamydia; finally, if there was no discharge or mucopus, the patient was not treated (Behets *et al.* 1995). The study yielded a moderate sensitivity level of 72.8% and a specificity rate of 55.5%. Gold standard diagnosis included culture in Thayer-Martin medium for *N. gonorrhoea*; Bartels Chlamydia enzyme immunoassay for *C. trachomatis*; and serum screening with toluidine red unheated serum test (TRUST) and confirmation with microhemagglutination for *T. pallidum*.

3) Conclusions about the WHO Algorithm when Women Seek Treatment for Vaginal Discharge

Treating women presenting with vaginal discharge based on the WHO algorithms (with or without speculum and laboratory examination) leads to more than 70% resolution of symptoms within one to two weeks, when antibiotics that effectively treat most major causes of vaginal discharge are used. However, some of these symptoms may have spontaneously resolved without treatment, and cure rates may be lower if fewer less effective drugs are used.

b. Women Seeking Care for Reasons other than Vaginal Discharge or STD Treatment

The success of the WHO algorithms for vaginal discharge was significantly different when the algorithms were applied to women coming to clinics for reasons other than vaginal discharge or STD treatment.

1) The WHO Algorithm for Vaginal Discharge with No Speculum or Laboratory Support

In an antenatal clinic setting in Mwanza, Tanzania, the specificity and sensitivity results were lower than any of the results from the application of this algorithm to high-risk populations. In this study, 1,149 consecutive antenatal clinic attendees were enrolled over a two-week

period at twelve different health centers (Mayaud *et al.* 1995). Primigravida pregnancies accounted for 217 (25%) of the women seen, and of the remaining 924, a total of 342 (37%) had previously experienced either spontaneous abortion (25%) or stillbirth (16%). Symptoms relating to genital tract infection were reported by 752/1,141 (66%) of the women. (Eight women refused examination.) Upon examination, 422/1,141 (37%) had observable vaginal discharge, 305 of whom (72%) had reported a symptom relating to genital infection. Further analysis was restricted to the 964 women with laboratory results. Gold standard diagnosis was used to calculate sensitivities and specificities. The following laboratory tests were used: NG culture and Gram staining and Antigen detection enzyme immunoassay (IDEIA) were performed to diagnose chlamydia; RPR and hemagglutination tests were performed for diagnosis of syphilis.

Syndromic management included algorithms for vaginal discharge with genital itching—because women in the study population often used this term to describe vaginal discharge—and for lower abdominal pain with only external abdominal and genital examination possible. The first algorithm used (without examination or microscopy) yielded a sensitivity of 43%, specificity of 58% and PPV of 8.6%. The exact numbers of women treated by this algorithm were not given, nor was follow-up data provided.

2) *The WHO Algorithm for Vaginal Discharge with Lower Abdominal Pain (LAP)*

This same Mwanza antenatal clinic study also evaluated the algorithm for vaginal discharge with lower abdominal pain. This algorithm includes symptoms not usually thought of as indicative of STDs. For this algorithm, the sensitivity rose to 72% and specificity fell to 34% (Mayaud *et al.* 1995). Once again, the exact number of individuals treated, cured, and followed-up were not provided in the paper.

A combined algorithm was then also tested by Mayaud *et al.* (1995). In this algorithm, women who reported symptoms were not just treated but were first examined and then treated for abnormal vaginal discharge only if it were evident on exam. The number of women who were falsely diagnosed as positive (in comparison to the numbers using the WHO algorithm without clinical support available) fell, as did the number of people who were truly diagnosed as positive. The overall yield was 27% sensitivity and 82% specificity.

Similar results were found among a population of 645 pregnant women attending two different antenatal clinics in Ouagadougou and Bobo-Dioulasso, Burkina-Faso. There, vaginal discharge was linked to clinical screening and a leukocyte esterase test (LET). A nurse administered a questionnaire, and a physician followed-up with a general and gynecological examination, genital samples to confirm the presence of STD pathogens, and an LET (Meda *et al.* 1997). No further details were given regarding training of health care providers. Three hundred and seventy-nine women (59%) complained of vaginal discharge, vulvovaginal itching, lower abdominal pain, dysuria, genital ulcers, and/or genital warts. Upon clinical examination, signs were seen in 254 women (39.4%). Of the 645 women enrolled 32.4% had a laboratory-confirmed STD, including trichomoniasis, vaginosis, syphilis, chlamydia, genital warts, and gonococcal infection. Criteria for bacterial vaginosis were three of the following: vaginal fluid PH > 4.5; release of a fish amine odor from vaginal fluid mixed with 10% KOH; clue cells; and abundant Gram negative bacilli (for *G. vaginalis* and/or *Mobiluncus* spp.). Confirmation for *N. gonorrhoea* was done by culture and Gram stain. *C. trachomatis* was confirmed by EIA and blocking assay. Syphilis was detected by RPR and TPHA. The application of this algorithm with the clinical support yielded a sensitivity rate of 23.3% and a specificity rate of 89.9% for the treatment of vaginal candidiasis; a sensitivity rate of 77.2% and a specificity rate of 57.3% for the treatment of trichomoniasis and/or bacterial vaginosis; and a sensitivity rate of 80% and a specificity rate of 50.6% for the treatment of gonorrhoea and chlamydia (Meda *et al.* 1997).

3) Conclusions about the WHO Algorithms when Women Seek Care for Reasons other than Vaginal Discharge

Clearly, these outcomes show that the application of the WHO algorithm with laboratory support has varying degrees of success depending on the STD. However, both the Burkina Faso and the Tanzania studies indicate that when used in low-risk populations, algorithms for vaginal discharge with clinical support generally yielded a higher level of specificity than the WHO algorithm without clinical support.

c. Low-Risk Versus High-Risk Populations: A Study of Kinshasa, Zaire

The difference between using syndromic algorithms on low-risk populations versus high-risk populations was demonstrated in a study by Vulysteke *et al.* (1993). In this study, the WHO algorithms for vaginal discharge and LAP both an antenatal clinic and a women's health care clinic for commercial sex workers (CSWs).

The first combined algorithm was tailored for clinics where examinations were not possible. This algorithm treated for trichomoniasis and bacterial vaginosis if the patient had vaginal discharge; it treated for gonorrhea and chlamydial infection if the patient had either lower abdominal pain or vaginal discharge and was considered high-risk. The second algorithm, designed for areas where clinical examinations are possible, also followed the WHO model. There, patients who had vaginal discharge were given a speculum examination and, based on the results, were treated. If the speculum exam yielded a profuse, funny, or malodorous vaginal discharge, the woman was treated for trichomonas and bacterial vaginosis. If the results were a white, curd-like vaginal discharge, the woman was treated for candidiasis. If the results yielded a positive swab test, the woman was treated for gonorrhea and chlamydial infection. If, on the other hand, a woman had lower abdominal pain, the provider would perform both a speculum and a bimanual examination. The treatment of STDs according to the results of the speculum examination follows the same treatment as that for vaginal discharge. Additionally, if the patient had tenderness on cervical motion during the bimanual examination, she was treated for gonorrhea and chlamydial infection. (See Flow Chart 9.)

At the antenatal clinic, 1,160 pregnant women were enrolled at random into the two hierarchical algorithms. The following gold standard diagnosis techniques were used in the calculation of sensitivity and specificity: wet mount and LET for *T. vaginalis*; gram staining and culture for gonorrhea; EIA for chlamydia; and RPR/TPHA for syphilis. By laboratory diagnosis, 13 patients (1.1%) had positive syphilis serology; 19 (1.6%) had gonorrhea; 60 (5.2%) had chlamydia; and 75 (6.5%) were found to have gonorrhea and/or chlamydia. Thus, 75 pregnant women were infected, and 36 true positives were diagnosed—leading to a sensitivity of 48% and a specificity of 75.2% for the screening of gonococcal/chlamydial cervicitis. The addition of the speculum examination and a swab test greatly reduced the sensitivity of the diagnostic model to 29.3% but increased its specificity to 85.3%, as only 22 cases were detected.

At the CSW clinic, 1,222 patients were entered into the first algorithm. The WHO algorithm for LAP and vaginal discharge yielded a sensitivity of 54.9% and a specificity of 52.2%. According to laboratory diagnosis, 286 (23.4%) had gonorrhea; 159 (13%) had chlamydia; and 379 (31%) tested positive for gonorrhea and/or chlamydia. In other words, the same algorithm used for the low-risk population yielded a higher sensitivity but lower specificity when applied to a high-risk population. These results (both more true positives and false positives) are not surprising given that there were bound to be more cases of STDs among the high-risk population and that the providers had a higher expectation of positivity among the higher-risk population than the low-risk population.

Interestingly, the results from the Kinshasa study show that the hierarchical algorithms, whether applied to the low-risk or the high-risk populations, were not sensitive enough to diagnose *N. gonorrhoea* or *C. trachomatis*, the leading causes of cervicitis.

2. Studies Done on Non-WHO Algorithms for Vaginal Discharge

Studies testing algorithms outside of the WHO model are more rare but also show interesting results. In an antenatal clinic in Kakar, Senegal, a flow chart for the diagnosis of cervicitis was developed, yielding a sensitivity of 35.9% and a specificity of 70.9%(Seck *et al.* 1997). These fairly low numbers suggest that the flow-chart method was not useful in public health centers that serve low-risk women and the resource-poor . The flow chart for this study is unavailable, as the results are given in abstract form only.

In North Carolina, the CDC algorithm for vaginal discharge was applied to 4,925 women undergoing pelvic examinations at both family planning clinics and STD clinics. When used at the family planning clinic (low-risk population), the algorithm had a high sensitivity (84%) but a low specificity (39%)(Miller *et al.* 1997). Among the STD clinic population (high-risk), the CDC algorithm yielded a higher sensitivity of 90% (i.e. more true positives) but an even lower specificity of 27% (Miller *et al.* 1997). These results hearken back to the Kinshasa studies, where the high-risk population also had a higher sensitivity and lower specificity than the low-risk population.

3. Meta Analysis of Vaginal Discharge Algorithms

Meta analysis techniques were applied to identify whether factors of study design, location, and training of health care providers influenced the outcome measures of sensitivity, specificity, and PPV. Ten studies were scored based on the thoroughness of the study design. The resulting scores were then compared to study outcomes, including sensitivity, specificity, and PPV. Those with higher scores generally had higher positive predictive values in both STD and other clinics. This suggests that the most rigorously conducted studies had better outcomes. Still, the reality of implementation under non-trial conditions is likely to result in much lower sensitivities, specificities, and PPVs than these studies, casting doubt on the utility of vaginal discharge algorithms.

4. Risk Scores for Vaginal Discharge

As an alternative to algorithms, several recent studies have assessed the usefulness of risk scores for identifying women with genital infection. Risk scores use variables that are common risk predictors for STDs. Risk predictors include such variables as young age, multiple partners, and having a partner who is positive with an STD. Because determinants of risk vary based on factors such as population and geographic region, each study has also tailored specific risk indicators to the study area.

The variations in sensitivity and specificity are, in large part, predicted by the setting of the study, the populations screened, the number of women in the study, inclusion or exclusion of physical exams, and the specific questions that are asked of the women. We first discuss the use of risk scores alone, followed by risk scores plus medical exams, and finally risk scores plus the WHO algorithm for vaginal discharge.

a. Using Risk Scores Only

One of the first studies done in the examination of risk score charts was conducted by Mayaud *et al.* (1995) in twelve rural health centers in Mwanza, Tanzania. One hundred consecutive antenatal clinic attendees at each health center (1,200 women in total) were interviewed about age, marital status, number of previous pregnancies, timeframe of their last-born child, whether they had more than one sexual partner during the previous year, and whether they had any symptoms related to genital infection. Training was given to the staff of the participating health centers. From each center, two staff members participated in a three-week training course in Mwanza town. Participants were either medical assistants or rural medical aides. One week of classroom instruction was given, followed by two weeks of practical experience. Training manuals were provided in both English and KiSwahili. After training, supervisory visits were conducted and follow-up training was provided annually.

If a woman scored greater than or equal to three on this score chart, she was diagnosed as having *N. gonorrhoea* and *C. trachomatis* and treated accordingly. By using gold standard diagnosis (culture and Gram stain for gonorrhoea, EIA and blocking antibody assay for chlamydia), 20 out of 964 women (2.1%) were positive for gonorrhoea; 64 (6.6%) were positive for chlamydia; and 81 (8.4%) were positive for gonorrhoea and/or chlamydia. The risk score algorithm using socio-demographic information and symptoms found 48% of these women positive. Thus, the risk score chart yielded a 69% sensitivity, a 54% specificity, and a 12.1% PPV (Mayaud *et al.* 1995). Results for the antenatal setting in Mwanza, Tanzania indicate that using risk scores based on symptoms and socio-demographics are simple but miss many women and over-treat others.

A study conducted by Behets *et al.* (1995) in Cité Soleil, Haiti shantytowns among pregnant women visiting antenatal clinics shows similar results for the use of risk score charts alone in diagnosing cervical infections. Nurses trained in syndromic management, under direct supervision of the study clinicians, obtained history and demographic data, performed exams, and collected specimens for laboratory analysis. Laboratory diagnosis consisted of culture for *N. gonorrhoea* and EIA for *C. trachomatis*. The risk score chart here includes the number of sexual partners in the past six months, the age of "coital debut" of the patient, whether or not she is living with her sexual partner, and whether or not her partner has an STD. Using a risk score cut-off value of 4, sensitivity was 71% (59/83), specificity was 62% (345/561), and PPV was 22%.

In Libreville, Gabon, a study was conducted by Bourgeois *et al.* (1998) in which 646 pregnant women attending three different antenatal clinics were enrolled. The study's aim was to determine the efficacy of the risk score charts they had developed in accurately diagnosing cervicitis and vaginitis. The first step of the study was to interview all women and, based on their answers, classifying them as low-, middle-, or high-risk women. This step was based only on the risk assessment score, using very simple criteria. If the women were high-risk (having a score greater than 2), they were immediately treated for cervicitis (gonorrhoea and chlamydia), whereas women with low risk (score less than 2) were further investigated for vaginitis only (trichomonas and/or candida). Women with medium risk (risk score of 2) were taken through a series of clinical exams to distinguish between vaginitis and cervicitis (as discussed in the next section). By using gold standard diagnosis, 73 cases (11.3%) of cervical infections were detected. Twelve of the cases were gonorrhoea; 64 cases were chlamydia. Two-hundred and fifty-five cases of vaginal infection were diagnosed, 69 of which were trichomonas and 199 of which were *C. albicans*. In using the risk score flow chart (without medical exams), the diagnosis of cervicitis had a 74% sensitivity rate and 50% specificity rate for women at high-risk (Bourgeois *et al.* 1998). On the other hand, the

diagnosis of vaginitis among low-risk populations based on risk score alone had a much lower sensitivity rate (47.8%) and only a slightly higher specificity rate (65.2%)(Bourgeois *et al.* 1998). These results indicate that the higher the risk score, the more likely the diagnosis will be accurate in diagnosing the true positives but less likely to diagnose the true negatives.

In a family planning clinic in Dar-es-Salaam, Tanzania, a specific algorithm was used in which trained female interviewers asked 2,285 women patients questions regarding socio-demographic characteristics, types of contraceptive used, sexual history, and other potential risk factors for HIV (Gertig *et al.* 1997). These factors were then tested in the risk score algorithm for gonorrhea developed by Vuylsteke *et al.* (1993), discussed in the next section. However, rather than using a risk score cut off of 8 (as used among prostitutes by Vuylesteke *et al.*), this study used risk score totals of 8, 13, 20, and 28 to diagnose and treat for gonorrhea and then compared the differences. When a risk score total of 8 was used to treat gonorrhea, there was a 97% sensitivity but only a 17% specificity. On the other hand, when a risk score cut off of 13 was used, the sensitivity fell to 72%, while the specificity rose to 37%(Gertig *et al.* 1997). Again, we can see that the more “high-risk” the cohort of women, the lower the sensitivity but the greater the specificity of risk score application.

In Cobancesme, Turkey, the diagnostic validity of risk scores was assessed by Ronsmans *et al.* (1996) using a population of married women. Home visits were performed by two female interviewers who invited women to attend the maternal Child Health and Family Planning Centre (MCH/FP). Six hundred and ninety-six women were seen in the clinic, but one was excluded from analysis due to invalid cervical sample for chlamydia. Two physicians with extensive training and clinical experience conducted 43% of the examinations, while the rest were performed by one junior physician with one month of training in STD diagnosis techniques. Questionnaires, physical examinations, and laboratory testing were used to measure efficacy for chlamydia diagnosis. The gold standard for comparison was EIA followed by direct fluorescent assay (DFA). Risk assessment was considered positive if a woman’s partner was symptomatic or any of the two following: age less than 21 years, single, more than one partner, and/or new partner in the past three months. Sensitivity and specificity were determined based on a simulation of the model. In this case, the sensitivity was only 8.82%, but the specificity was 96.19%. PPV was 10.71%. 25 of the 28 women who tested positive by risk score did not test positive by EIA. A major drawback of this study is that it did not test for *N. gonorrhoea*, a major cause of cervicitis; the sensitivity therefore may be too low. However, serosurveys in this area indicate no or very low prevalences of gonococcal infection (Ronsmans *et al.* 1996).

In the above examples, we can see that the studies done in Mwanza, Cité Soleil, Libreville, Gabon, and Dar-es-Salaam all yielded high sensitivities (69%, 71%, 75%, and 97% respectively). However, as the sensitivities rise, the specificity generally declines (54%, 62%, 50%, and 17% respectively). From the results of the Cobencesme, Turkey study, we can also see that, unfortunately, among asymptomatic patients (low-risk), risk scores have a very low ability to identify infected women.

b. Using Risk Scores Plus Medical Exams

The studies that couple women’s risk scores with a medical exam comprise the majority of the work done in this field. The 1990 study by Vuylesteke *et al.* (1983) was one of the first to implement risk scores in treating STDs. The report on the efficacy of risk scores was done as a part of a larger study, the other portions of which have already been discussed. The risk score charts were modeled after the original WHO suggestions and applied to Zairian women at both high risk and low risk. One thousand One hundred sixty pregnant women attending antenatal clinics and 1,222 commercial sex workers (CSWs) attending STD clinics

were randomly enrolled and asked by a trained nurse about their sexual and medical histories, their demographic data, and information on their current urogenital symptoms (Vuylesteke, 1993). Gynecological examinations were then conducted by a physician. For CSWs, the examination included a cervical swab. The pregnant women, on the other hand, only had a leukocyte esterase (LET) urine test analysis.

The tally of the socio-demographic risk factors coupled with the results of the swab or urine test indicated whether or not the patient should be treated for *N. gonorrhoea* and *C. trachomatis*. For pregnant women, this tally of socio-demographic risk factors had to equal or exceed 28 in order to receive treatment. On the other hand, CSWs could have a risk score plus medical exam score of no greater than 8 in order to be treated. When the risk score chart plus exam was applied to the women at the antenatal clinic and those at the health care clinic for CSWs, there was very little difference in the sensitivity results. Gold standard diagnosis for comparison was isolation of *N. gonorrhoea* and EIA for *C. trachomatis*. The sensitivity levels were 71% for the CSWs population and 72% for the pregnant women. The specificity levels, on the other hand, revealed a larger gap in efficacy: 73.5% in the antenatal clinic and 55.8% in the women's health care clinic for CSWs. PPV was 15.8% for pregnant women and 41.9% for CSWs.

The use of risk scores plus medical exams is significant, especially when the results are compared to other models. We see that the sensitivity levels of the risk scores plus exams are far greater among both the high- and low-risk populations than when the WHO algorithm for vaginal discharge with medical exam was applied to the same populations. Whereas the algorithm plus exam only yielded sensitivity levels of 48% (pregnant women) and 54.9% (CSWs), the risk score charts without exam yielded a moderate sensitivity of 71-72%. These higher sensitivity levels are crucial in the development of methods to treat women with STDs indicated by vaginal discharge. The increased sensitivity of these risk scores plus exams do not effect the levels of specificity. When a model is applied to low-risk populations, there is generally a higher specificity than when the model is applied to high-risk populations.

In the family planning clinic in Dar-es-Salaam, Tanzania, the risk score approach for gonorrhoea was developed by Vuylesteke et al. (1983) was used by Gertig *et al.* (1997). With clinical examination, sensitivity was 98% and specificity was 15%. Without clinical examination, the sensitivity only decreased to 97% and the specificity only increased to 17%. The PPV remained at 5% in each case. The gold standard for comparison in this case was Gram staining and culture for *N. gonorrhoea*. Testing for chlamydia was not performed. These results indicate that the addition of the clinical diagnosis to the risk score charts added little to the sensitivity and specificity.

In 1994, a study was done whereby risk score charts were coupled with leukocyte esterase tests (LET) and applied to 645 women attending antenatal clinics in Ouagadougou and Bobo-Dioulasso, Burkina-Faso (Meda *et al.* 1997). The risk score charts, designed for the diagnosis and treatment of gonorrhoea and/or chlamydia, only asked the women about their partner status (whether they had been with their current partner for less three years), and then the physician performed an LET test. If the women were considered high-risk (i.e. had been with her partner less than three years) and had a positive LET test, she was treated for gonorrhoea and chlamydia. The results of this study are good. The reference used was culture and Gram staining for *N. gonorrhoea* and EIA for *C. trachomatis*. With these parameters, 80% sensitivity and 50.6% specificity was obtained. An important factor to note is that this sensitivity is again higher than the WHO algorithm plus exams for vaginal discharge.

In the population-based survey held in Cobancesme, Turkey, 690 asymptomatic women who reported the use of contraceptive methods were measured by the risk score chart and were evaluated on the following risk factors: partner is symptomatic, age (less than 21), single status, more than one partner, and new partner within the last three months (Ronsmans *et al.* 1996). The results of these risk score charts alone are discussed in the above section. In this case, physicians administered the risk score charts followed by medical examinations. If during a speculum examination, the physician found either endocervical mucopus or induced endocervical bleeding and the patient had a high risk score, she would be treated for a cervical infection (*C. trachomatis* and *N. gonorrhoea*). The addition of the medical examination to the risk score greatly increased the sensitivity of this study from 8.82% to 47% but decreased the specificity from 96% to 56%. The gold standard was EIA detection for chlamydia. As before, no techniques were used to isolate *N. gonorrhoea*.

In Libreville, Gabon, one arm of the study charting the risk factors of 646 pregnant women attending three different antenatal clinics (see above section) was extended so that women who were at medium risk (risk score equal to 2) were taken through a series of clinical exams (Bourgeois *et al.* 1998). These exams, although useful in distinguishing between vaginitis and cervicitis, were only effectively used to treat cervicitis. In this study, vaginitis was mostly treated for those women who had a risk score less than 2. When women with a risk score equal to 2 were taken through a CT/Ag detection, the detection of cervicitis had an 83.6% sensitivity and a 63.4% specificity. When the risk score flow chart was couple with a leukocyte count, both the sensitivity and specificity for the diagnosis of cervicitis dropped, yielding a 67% sensitivity and a 57% specificity.

The study in Cité Soleil, Haiti shantytowns coupled pregnant women's risk scores of less than 2 with speculum examinations (Behets *et al.* 1995). If the result of a speculum examination was a profuse, runny, or malodorous discharge, the patient was treated for trichomonas; if the discharge was white and curdlike, she was treated for a yeast infection; if there was cervical discharge present, she was treated for gonorrhoea and chlamydia. Additionally, factors such as cervical friability, vaginal and cervical ulcers, findings on bimanual exam, vaginal fluid pH, and a whiff test with 10% KOH were performed. These methods as performed by the study nurses combined with the risk score yielded an 89% sensitivity and a 43% specificity, as compared to isolation of *N. gonorrhoea* and antigen detection of *C. trachomatis*. PPV was 18.8%.

In the study done by Mayaud *et al.* (1995) in Mwanza, Tanzania, a cohort of 964 women who scored greater than 3 on the risk score chart were given a medical exam. Gonococcal cultures, gram stain tests for intracellular diplococci, and swab tests were performed. If a patient had abnormal vaginal discharge according to these tests (>10 PMN/high power field), she was diagnosed as having *N. gonorrhoea* and *C. trachomatis* and treated accordingly. This method yielded a very low sensitivity of 31% but a high specificity of 88%.

A recent study in Manila and Cebu City in the Philippines used risk assessment in conjunction with medical examination (Wi *et al.* 1998). The study population included 273 CSWs from Manila at Philippine General Hospital and 300 CSWs from Cebu at a CSW clinic. Gonorrhoea was diagnosed by culture, and chlamydial infection was determined by antigen detection. Gonococcal and/or chlamydial infection was found in 23.3% of study participants in Manila and 37% of participants in Cebu. In Manila, a flow chart using age less than 25 and/or being an unregistered sex worker, was followed by an examination for mucopus, cervical motion, adnexal or uterine tenderness. This yielded a 42.1% sensitivity, 91.5% specificity, and 60% PPV. In Cebu, the same flow chart provided a 14% sensitivity, 98.8% specificity, and 80% PPV. The differences in outcome seen in these two cities may partially be accounted for by training and personnel differences at the two sites (Wi *et al.* 1998). The

study's authors acknowledge that clinicians in Cebu had less specialized training and therefore may have been less proficient at performing physical exams and identifying abnormalities. They are quite right to point out that the level of training and proficiency of implementation in Cebu are more like that of other developing countries, thus indicating that this algorithm would more likely perform as it did in Cebu. Therefore, as a risk score/exam algorithm, it probably would not be worthwhile to pursue any further.

Finally, in a more recent study conducted in Cape Town, South Africa and presented as an abstract, 161 consecutive symptomatic women were sampled and interviewed for demographic and other risk factors (Coetzee, 1997). Details were not given regarding what type of clinicians performed the study or the type of training that was given to them. The risk factors for cervicitis include being single, having a discharge that was smelly, and cervical motion tenderness. These women were then clinically examined. Culture for gonorrhea, antigen EIA plus LCR for chlamydia were performed as the gold standard comparison. The score-based algorithm plus exam yielded a 56.4% sensitivity and a 29.7% specificity for the treatment of cervicitis.

c. Other Uses of the Risk Score Chart

In another study conducted in Washington State, women who were at high risk for cervical chlamydial infection were identified by a means of a questionnaire sent to women who were enrollees of a health maintenance organization and who were 18 to 34 years of age (Scholes *et al.* 1996). Women were considered to be at high risk if they were less than 24 years old, were black, had douched in the last twelve months, or were nulligravid. (See Risk Score Charts, Section 10.) Based on their answers, about 40% (1009/2607) of these women were tested for chlamydia, and the other 60% were assigned to usual care. Seven percent of those women tested for chlamydia were positive and were then treated. In one year's time, it was found that the incidence of pelvic inflammatory diseases was remarkably different among these two groups. Of the group that had been tested and treated for chlamydia, only nine women had pelvic inflammatory disease. On the other hand, 33 women receiving usual care had pelvic inflammatory disease (Scholes *et al.* 1996). In point to the strong correlation between chlamydia and pelvic inflammatory disease, these results clearly indicate the importance of developing a strategy for identifying and treating women who are at increased risk for cervical chlamydial infection

d. Conclusions about Risk Scores

Overall, these results show that when risk scores are coupled with medical exams, there is a higher specificity but a lower sensitivity than the risk scores used alone, and a higher specificity but lower sensitivity compared to the algorithm plus exam. In other words, risk scores plus exams yield the highest levels of specificity. Additionally, the difference in specificity indicates that risk profiles are more useful in low-risk populations than in high-risk populations.

IV. PROBLEMS IN IMPLEMENTING STD TREATMENT

Published and unpublished studies of syndromic treatment offer insights into more than just the sensitivity and specificity of particular algorithms. They reveal problems related to quality of care, ranging from drug and equipment supplies to the training of providers and problems with clients. Furthermore, these studies highlight the differences in implementation based on type of health care system and health care setting, as well as the need to include traditional healers in syndromic management. By sharing knowledge of what has and has not worked in syndromic treatment trials, the unpublished studies are important in providing information to improve existing programs and to create new ones.

A. Supply of Drugs and Equipment in Syndromic Management

STDs can not be successfully treated without adequate drugs and supplies. Unless this obstacle is surmounted, STD diagnosis and treatment will remain a charade in many clinics. A case in point: Harrison *et al.* (1997) used supply checklists in KwaZulu/Natal, South Africa and found two of ten clinics with inadequate drug supplies and 50% of the clinics without specula for pelvic exams.

B. Incorrect Use of Syndromic Diagnosis and Treatment by Providers

Vuylsteke *et al.* (1997) studied the quality of STD case management after a one-week training course in syndromic management. They found that syndromic treatment was prescribed for 50% of men and only 2.6% of women who came to 33 different primary health care centers in Rio de Janeiro and Santos in 1996. Only 51% of those diagnosed with STDs were prescribed the drugs recommended by the Ministry of Health. Information regarding treatment of partners was given to 90% of men and 50% of women. The study concluded that the acceptance of syndromic management is very low among health care workers. This could be partially attributed to the short training period, but it is also likely to involve other unidentified factors. Further exploration of the differences in treatment and counseling of men and women could prove to be worthwhile.

In Bangladesh, paramedical staff running the rural primary health care clinics rarely asked women about sexual behavior, sometimes gave factually incorrect information, and tended to be judgmental when giving messages urging behavior change (Hawkes *et al.* 1997). From this, study authors concluded that hands-on clinical training as opposed to purely theoretical training would be beneficial. Lowndes *et al.* (1997) found that doctors in Brazil have difficulty discussing STDs with women because of societal norms regarding male infidelity. This type of information can be used to develop training programs for health care workers. In both of these cases, it would seem that part of the problem is embarrassment that health care providers feel in talking to women about STDs. Such barriers have a negative impact on treatment of women and must be overcome.

Similarly, qualitative data in the South African study by Harrison *et al.* (1997) shows that there is low morale and confusion over syndromic management procedures among treatment providers. The abstract does not detail the type of providers that were studied. Only 45% of patients were even told that they had a sexually transmitted disease. Appropriate treatment was given to 55% of patients, while only 40% received condoms. Perhaps most surprising was that only 19% were given a partner notification card. In response to these findings, the group recommends formation of a peer training group, with

monthly training sessions and the development of syndrome packets containing treatment, condoms, partner cards, and STD information (Harrison *et al.* 1997). These modifications would probably be relevant for syndromic treatment programs in other countries.

Many of the health care providers in Cape Town, South Africa felt unchallenged by a syndromic approach (Karpika *et al.* 1997). Clinicians said that they were not given the chance to utilize their skills and thus lost interest in examining patients. This led to minimal interaction between patients and clinicians and created a barrier to effective care (Karpika *et al.* 1997).

C. Patients and Syndromic Management

Many patients do not understand that their symptoms are abnormal and caused by an STD. Lack of understanding can lead to poor treatment compliance, likely re-infection, and poor partner notification. Karpika *et al.* (1997) found in South Africa that most patients did not comply with a full course of antibiotics. This group also found that condoms were not considered to be an option to men, even while they were being treated. Similarly in Uganda, only 71% of men and 49% of women would accept condoms from the health care provider (Kengeya-Kayondo *et al.* 1997; Nalweyiso *et al.* 1997).

Karpika *et al.* (1997) also report that syphilis screening was perceived as an HIV test by many patients, which caused great fear. Such misunderstanding could lead to test refusal or even clinic avoidance. Another factor leading to clinic avoidance is the perceived shamefulness of STDs. Treatment is therefore postponed or sought from traditional healers or pharmacies to ensure maximum confidentiality and that partners are not notified (Rajani *et al.* 1997). Kengeya-Kayondo *et al.* (1997) report that approximately half of all peripheral health unit (PHU) clinic attenders in Masaka, Uganda seek STD treatment from other sources before attending the PHU clinic. 14% attempt self-medication; 13% visit private practitioners; and 11% first visit other PHUs. Rajani *et al.* (1997) found that in Mwanza, Tanzania, 28% of men first sought treatment from a health center; 23% attempted self-medication; and 4% visited a traditional healer. In an educational program targeting pharmacies in Tanzania, Garcia *et al.* (1997) found that pharmacists who underwent training provided counseling and referral more often than those who did not.

The above factors illustrate the need for training pharmacists, traditional healers, and other “peripheral” health workers in syndromic management in order to identify and treat as many STD cases as possible.

D. Clinic Populations and Syndromic Management

The clinic setting is a factor that influences the success of syndromic treatment algorithms. Because, depending on their needs, different types of people go to different clinics, there is wide variability in the performance of syndromic treatment. This variation is most obvious in women. For example, at family planning clinics, algorithms are generally poorly predictive of gonorrhea and chlamydia infections. In a review of studies done by Coggins *et al.* (1997), it was found that the positive predictive value ranged from 5% to 22% in this population but that in a “higher-risk” population (this population is not defined), the PPV ranged from 34% to 44%. In high-risk populations, syndromic treatment is more successful because there are more infected individuals, so they are more likely to be identified. Thus, sensitivities are higher, but specificities remain low.

In Dakar, Senegal, 540 antenatal clinic patients were studied. They were seen by midwives, who applied the algorithm, and then by physicians, who conducted an examination (Seck *et*

al. 1997). Diagnosis was compared to laboratory tests, which are not detailed in the abstract. In this case, the diagnostic value of the flow chart for cervicitis was low with a sensitivity of 35.9%, a specificity of 70.9%, and a PPV of 8.8%. These examples illustrate that the usefulness of syndromic treatment algorithms alone may be limited in women considered low-risk for STDs. Coggins, *et al.* (1997) observed that the addition of risk scores improved predictive ability, although the improvement was small. It is tempting to suggest that syndromic treatment be targeted to high-risk women, but until alternative measures are implemented for identifying STDs in low-risk women, this may not be prudent.

V. CONCLUSIONS ABOUT IMPLEMENTING SYNDROMIC MANAGEMENT FOR STDs

These studies pinpoint problems with the implementation of syndromic management strategies and make the likelihood of acceptable sensitivity and specificity measures, and effective treatment even less than demonstrated in the studies reviewed above. Areas highlighted by the studies reviewed as contributing to the decreased efficacy of algorithms include: 1) lack of supplies; 2) poor provider knowledge of syndromic diagnosis and treatment; 3) patients' lack of understanding of STDs and symptoms; and 4) differences between clinic populations. One step that would address many of these problems is increased provider and patient training and education. Potential solutions include giving hands-on as well as theoretical training in syndromic management (Hawkes, et al. 1997), formation of peer training teams, and regular monthly training sessions (Harrison et al. 1997).

Better counseling by more highly trained clinicians would lead patients to understand the importance of treatment compliance, partner notification, and condom usage, as well as allay fears of testing. Training of other health workers, such as pharmacists, leads to increased counseling and referral (Garcia, 1997). Likewise, Nalweyiso *et al.* (1997) suggest that by training clinicians from the private sector, an additional 10% of STDs can be treated. Collaboration with traditional healers might also increase coverage, since so many people first seek treatment in the informal sector.

Even with good drugs and trained personnel, communities still need better information to understand when to visit clinics and the importance of treatment compliance and partner notification. As shown by Piot and Fransen, there are several steps necessary to effectively treat an STD, and each of these steps is successful at a different rate. For instance, if 50% of women in a region have an RTI at any point in time, only half will be symptomatic. Only half of the symptomatic women will seek treatment, and not all go to trained medical providers. Further, only one in five women who present for treatment may get appropriate treatment, and of these women, not all will complete treatment or be cured. Therefore, only 3% of infected women will be cured, and many may be quickly re-infected by their partners (Hayes, *et al.* 1997).

More challenging issues also exist. It is important that problems of infrastructure are addressed. Drugs and supplies for STD treatment should be readily available, and patients should have privacy during their visits. Methods should also be found to target high-risk populations without neglecting the needs of populations at low risk for STDs. Although solutions to these problems are not readily apparent, work needs to be done to confront them.

Perhaps because of the problems inherent in the implementation and effectiveness of syndromic management, mass treatment of STDs has long been talked about as an alternative STD treatment approach but has only recently begun to be tested. Ongoing research in the Rakai District of Uganda may help to determine the effectiveness of mass treatment. Mass treatment is potentially more expensive than syndromic treatment and could lead to increased antibiotic resistance but offers the benefit of treating all infected individuals, symptomatic or not. It is important to continue to explore alternatives such as this in order to search for better treatment options.

Cost-effectiveness issues could play an important role in helping to decide at what levels of performance syndromic treatment regimens should be used. Few studies have been done on the cost-effectiveness of syndromic treatment. Two of the trials that we reviewed included cost data in their analyses:

- A.) In Mwanza, Tanzania, cost-effectiveness was evaluated as cost per DALY saved by averting HIV infection. Gilson *et al.* (1997) found this number to be US\$9.45 per DALY saved. Although this number was not compared to gold standard treatment costs, it was compared to other health programs in developing countries, including childhood immunization programs, which cost between US\$12-17 per DALY saved. Thus, it would seem that syndromic treatment—in relation to other health care programs already in place—is cost-effective in Mwanza, Tanzania at the levels of sensitivity and specificity observed in the trial (Gilson *et al.* 1997)
- B.) Likewise, in a cost comparison of syndromic treatment and the current methods (mostly clinical diagnosis with some laboratory testing) used in Malawi (Costello Daly *et al.* 1998), it was found that the cost of treatment per patient was nearly identical (US\$1.06 for current practice and US\$1.07 for syndromic treatment). Costello Daly *et al.* (1988) conclude that since syndromic management would substantially reduce the proportion of patients treated ineffectively under current Malawian practice, while drug costs would remain the same, cost-effectiveness would actually increase.

Effective STD control programs are essential in developing countries, both for the prevention of HIV transmission and the limitation of STD transmission and sequelae. Currently, gold standard STD diagnosis and treatment are neither practical nor possible in most clinics in developing countries. Syndromic treatment regimens offer an alternative to standard care by treating more individuals than can be identified through conventional methods (Ryan & Holmes, 1995; Wilkinson, 1997).

VI. SUMMARY OF FINDINGS:

1. Syndromic treatment algorithms for men with urethral discharge are more than 90% sensitive for identifying and treating patients. The specificity in the one study that reported was 40%. Such a low specificity will lead to over-treatment and potentially increase the rate of development of antibiotic resistance due to overuse (Ryan & Holmes, 1995). However, the benefits of treatment probably outweigh the costs of developing resistance.
2. Syndromic treatment algorithms for genital ulcer disease showed a range in cure rates, from 100% in Côte d'Ivoire to 67.4% in men in Zambia. GUD algorithms were not effective in identifying herpes, as demonstrated by a 4.5% sensitivity rate in both cases where it was measured. However, for syphilis and chancroid, the approach was effective. The WHO algorithm for GUD without clinical support fared better than the algorithm with clinical support, and clinical diagnosis alone was not found to be effective.
3. **The sensitivity of** syndromic treatment for vaginal discharge in women varies greatly, ranging from 29.3% for low-risk women visiting an antenatal clinic in Kinshasa, Zaire using speculum exam and swab test, to 89.9% in an antenatal clinic with clinical support in Burkina Faso.
 - A. An increase in sensitivity is almost always associated with a decline in specificity. (See Figure 2.)
 - B. When clinical examination was added to vaginal discharge algorithms, specificity increased, but sensitivity decreased.
 - C. Risk scores showed the highest sensitivities when used alone but as such showed low specificities.
4. Because syndromic treatment algorithms often show low sensitivities and/or specificities, the question arises as to what combination of the two is considered acceptable. For example, the algorithm for vaginal discharge as implemented in Kingston, Jamaica showed a moderate sensitivity of 72.8% and a moderate specificity of 55.5%. Nearly 30% of symptomatic STDs are missed, and almost 50% of the individuals being treated do not have the STDs they are being treated for. In situations where treatment options are *all* less than ideal, it seems worthwhile to continue using strategies that yield high rates of sensitivity.
5. Another conclusion that can be drawn from this analysis is that vaginal discharge is not an adequate indicator of any particular STD. **This makes the presence of vaginal discharge a poor algorithm entry point.** Although risk score studies have shown relatively high sensitivities (69-97%), they often show unacceptably low specificities. However, combining the WHO vaginal discharge algorithm with a risk score seems to improve the specificity without drastically affecting sensitivity (Behets, *et al.* 1995). Risk scores also offer the opportunity to tailor questions in a culturally relevant way. Factors placing a woman at elevated risk in a particular location are then better identified. Unfortunately, risk scores could also contribute to stigmatization by identifying individuals as "high-risk."

6. Syndromic treatment studies indicate that algorithms are most effective when targeted to high-risk populations. The highest sensitivities for the CDC algorithms for vaginal discharge are seen in high-risk women. This is due, in part, to the fact that more of these women are infected with STDs and therefore more identified. Since the core group bears a larger proportion of disease burden, it plays an important role in maintaining the prevalence rate of disease. Because the core group has sexual interaction with the non-core group, STD prevalence in the non-core group is maintained at levels higher than if there were no interaction (Jamison, 1993). While treatment of high-risk groups should remain a priority, it is also important to note that in areas of high STD prevalence, large numbers of low-risk individuals will still be infected. Therefore, it is important to continue to develop strategies to identify and treat low-risk women within the population, as well as target women of high risk.
7. Syndromic treatment algorithms only identify and treat symptomatic individuals. A large proportion of STD infections remain asymptomatic and therefore will not be identified. If the goal of syndromic treatment is to reduce the prevalence of STDs, it becomes crucial to
 - a. identify and treat a high proportion of the core transmitting group;
 - b. achieve a high enough success rate so that the average number of secondary cases produced from one infectious case is less than one; or
 - c. find alternative ways to identify asymptomatic individuals within the population. Risk scores could potentially bridge this gap.
8. These syndromic treatment trials were obtained under clinical trial conditions. How well will syndromic treatment algorithms perform when the appropriate drugs are not available, training is not recent, and supervision decreases? As seen in the meta-analysis of the vaginal discharge studies, those trials that obtained higher rigor scores were better able to identify infected individuals. Sensitivities and specificities will decline even more under non-trial conditions. This is particularly worrisome for vaginal discharge algorithms, which already perform at a less than optimum level.
9. A final issue that should be discussed is antibiotic resistance. As mentioned in conjunction with low specificities seen in men with urethral discharge, there is concern about over-treatment of people who do not have STDs. Chromosomal resistance to penicillin, tetracycline, and thiamphenicol is now common. Plasmid-mediated resistance has also been observed and is increasing rapidly. Although antibiotic resistance to the currently recommended drugs for gonorrhea infection has not yet been observed in sub-Saharan Africa, emerging resistance in Southeast Asia indicates that Africa might not be far behind. Inappropriate use of antibiotics, uncontrolled sale, and self-medication have all contributed to the development of antibiotic resistance (Van Dyck, *et al.* 1997). It is plausible that syndromic treatment could worsen the situation by exposing even more people to unnecessary antibiotics. Presently, we are unable to quantify what level of over-treatment is likely to contribute to antibiotic resistance, so although the risk may be overstated, it is prudent to be conservative in approach.

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