Sexually Transmitted Infections In Developing Countries

Current concepts and strategies on improving STI prevention, treatment, and control

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Acronyms and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
CDC	U.S. Centers for Disease Control and Prevention
DALY	Disability-adjusted life year
HBV	Hepatitis B Vaccine
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSV-2	Herpes Simplex Virus-2
STD	Sexually transmitted disease
STI	Sexually transmitted infection
USD	United States dollars
WHO	World Health Organization

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Executive Summary

The Global Burden of STIs on Health and Development

The global burden of sexually-transmitted infections (STIs) to health and development is often overlooked as a public health priority. The majority of STIs worldwide are caused by eight infections: syphilis, gonorrhea, chlamydia, trichomoniasis, genital herpes, hepatitis B virus (HBV), and human papillomavirus (HPV). These infections, often silent and without symptoms, can result in serious or fatal health consequences. Cervical cancer, caused by HPV, is the largest single cause of years of life lost to cancer in the developing world and, because it affects women in their most productive years, has a devastating effect on the well-being of families. Syphilis among pregnant women still results in up to 1.5 million perinatal deaths each year. Damage to the fallopian tubes from gonorrhea and chlamydia can lead to infertility, as well as tubal pregnancy, an important cause of maternal death in developing countries. Hepatitis B, most frequently transmitted from mother-to-child in endemic areas, can result in chronic infection, liver cancer and liver failure. Genital herpes and other genital ulcer diseases increase risk of HIV transmission.

STIs are among the world's most common diseases, with an annual incidence exceeded only by diarrheal diseases, malaria, and lower repiratory infections. The burden on the health care system and healthcare expenditure is great. STIs, even without including HIV, are consistently among the most common conditions leading to health care visits regardless of national resources. Due to their high prevalence, particularly in developing country settings, STIs result in substantial productivity losses for individuals and communities, particularly where the majority of the population is under 40 years of age. In developing country settings, STIs are among the leading causes of disability adjusted life years (DALYs) lost for women of reproductive age, exceeded only by maternal causes and HIV.

Effective, Affordable Solutions

The tragedy of the health and economic burden of STIs is that they are preventable and often treatable, frequently with simple, inexpensive interventions. For example, stillbirths due to syphilis can be prevented with routine screening of pregnant women and treatment with a single injection of penicillin. A number of evidence-based and effective strategies have emerged and become widely accepted over the past two decades:

Prevention through Treatment: Prompt identification and treatment of bacterial STIs remains a cornerstone of STI control. Treating STIs reduces prevalence and breaks the chain of transmission in the community, and is therefore the most effective form of prevention in the absence of a vaccine. However, facility-based case management alone is not enough to control STIs. Core components of STI control involves a series of interventions working together:

- Clinic-based management of symptomatic STIs. Syndromic management has been demonstrated to be effective in the absence of laboratory capacity.
- Identification and treatment of sex partners
- Screening asymptomatic persons (particularly women) at risk for adverse outcomes, such as universal screening of pregnant women and routine cervical cancer screening
- Targeted control measures among "core" high risk groups (e.g. sex workers) and populations that "bridge" to the general population (e.g. clients of sex workers, truckers, and other mobile populations).

Primary Prevention through Vaccines
Safe and effective vaccines against HBV and HPV hold the promise of eliminating a substantial proportion of the world's STI-related cancers and chronic liver disease and have been added as a core program element. Although inexpensive HBV vaccines are now widely available, they are still not included in infant immunization schedules in some of the most affected countries.

Other Supporting Elements for Prevention and Control
In addition to the core components of STI prevention and control, six additional supporting elements have proven important in ensuring the core programs can be effectively provided:

- *Leadership and advocacy* to ensure an environment supporting STI control and prevention
- *STI surveillance* to track burden of disease and track program impact
- *STI laboratory capacity* that is sufficient to monitor critical diseases and support programs
- *Training* around STI clinical management and prevention
- *Monitoring and evaluation* of STI programs to assess progress and make needed changes
- *Community education* around STI risks and prevention, especially important for youth

World Bank STI Technical Note
Although an increasingly large array of effective STI interventions exists, limited implementation and quality of STI management occurs in some of the world's poorest nations. Prevention and control of STIs can mitigate health costs, morbidity and mortality and help support poverty reduction efforts in developing world settings, particularly among women, infants, and adolescents. STI control programs are increasingly under-funded in many developing world settings. Some of the nations most affected by STIs still lack the basic surveillance needed to establish burden of disease, monitor implementation of programs and evaluate their impact. Many cost-effective strategies to prevent and control STIs are inadequately implemented where they could provide the greatest good. In addition, newer strategies that can prevent non-HIV morbidity and mortality need attention now to ensure systems are in place for their adoption in the future. Better use of existing, effective STI prevention and control strategies, including integration of systems when possible, could greatly assist many nations in reaching UN Millennium Development Goals, particularly targets focusing on women, infants and children, and youth of reproductive age.

This technical note was developed to provide World Bank technical staff a background in STI burden, economic costs, evidenced-based STI programmatic interventions. New research findings and future directions are also discussed, such as new point-of-care diagnostics, HSV treatment to prevent HIV and male circumcision. Globally, the populations most vulnerable to STIs are those who are disproportionately affected by other health and social issues: adolescents, pregnant women and their unborn children, migrant populations and other economically or socially marginalized groups. Accordingly, the technical note has emphasized STIs in these vulnerable populations, describing the health and social consequences of STIs in women, adolescents and infants; how stigmatization and gender inequities can affect health seeking and care and increase burden of disease; and the role that STIs play on poverty and economic burden. Descriptions are provided about key STI prevention and control strategies, available empiric data on their expected costs, and potential new strategies on the horizon.

I. The Global Burden of Sexually Transmitted Infections (STIs) and their Consequences

STIs are among the world's most common diseases, with an annual incidence exceeded only by diarrheal diseases, malaria, and lower respiratory diseases. Due to their high prevalence, particularly in developing settings, STIs result in substantial productivity losses for individuals and communities, particularly where the majority of the population is under 40 years of age. In developing countries, STIs are among the leading causes of disability-adjusted life years (DALYs) lost for women of reproductive age.

A. Overview: The Effects of STIs on Health and Development[1]

Among the most common infectious diseases. Sexually transmitted infections are among the most common of all infectious diseases. Every day nearly 1 million people acquire a new STI, and more than 340 million new cases of *curable* STIs occur throughout the world each year. Adolescents and young adults have the highest rates of curable STIs -- up to 1 in 20 adolescents develop a new STI each year.

Infertility, tubal pregnancy, and maternal mortality. Untreated bacterial STIs in women result in pelvic inflammatory disease in up to 40% of infections; and 1 in every 3 of these will result in infertility. Tubal damage from STIs can lead to ectopic (tubal) pregnancy, the cause of up to 10% of maternal mortality in settings with high STI prevalence. Chronic pelvic pain from untreated bacterial STIs is an important cause of health care visits among women.

Infant blindness. Up to 4000 newborn babies become blind every year because of eye infections that are attributable to untreated maternal STIs, and that could be easily prevented with topical infant eye medications.

Perinatal deaths. Syphilis is one of the most important causes of adverse pregnancy outcomes globally, estimated to account for up to 1,500,000 perinatal deaths each year – equal or exceeding the perinatal mortality associated with either HIV or malaria. In Africa and Latin America, 2 to 15% of all pregnancies are in women with untreated syphilis. Infected women will experience an overall perinatal mortality of 40% -- including stillborn infants and early neonatal deaths.

Inexpensive, cost-effective solutions. Syphilis screening and treatment (a penicillin injection) can cost as little as 1 USD, and is among the most cost-effective all public health interventions -- but is still not effectively applied in many nations. Universal syphilis screening and treatment in pregnant women would prevent up to half a million perinatal deaths each year in Africa alone.

Chronic liver disease and death. Chronic infection with hepatitis B virus (HBV) is the most important cause of disability and death from liver disease in developing world settings – causing 1 in 40 deaths among adults globally each year. Most HBV is transmitted from mother to child at birth. Existing HBV vaccine series cost 3 USD or less and, if provided to neonates, could prevent 30 to 70% of all deaths related to liver cancers and cirrhosis among adults living in developing settings.

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[1] Adopted from World Health Organization (WHO). 2006. *Global Strategy for the Prevention and Control of Sexually Transmitted Infections, 2006-2015*. WHO: Geneva.

Cervical cancer and death. Cervical cancer is the most common cause of cancer mortality among African women, and its frequency and progression are increased with HIV infection. New vaccines against human papillomavirus (HPV) infection could stop the early death of approximately 240,000 women from cervical cancer every year in resource poor settings.

Effective strategies for prevention and treatment. Many viral STIs can be prevented with vaccines, and most STIs (including some caused by viruses) can be prevented with male latex condoms. Many common STIs can be cured with widely and affordable available antibiotic drugs, and symptoms and infectiousness of certain viral STIs (e.g., HIV and genital herpes) can be ameliorated with antiviral drugs.

B. STI Infections, Syndromes and Sequelae

Sexually transmitted infections (STIs) are among the world's most common diseases, with annual incidence exceeded only by diarrheal diseases, malaria, and lower respiratory infections More than thirty different bacterial, viral or parasitic agents are recognized as being transmitted sexually; however, the majority of new STIs worldwide are caused by eight infections (syphilis, gonorrhea, chlamydia, trichomoniasis, genital herpes, HIV, hepatitis B virus [HBV] and human papillomavirus [HPV]). The World Health Organization (WHO) estimates that each year more than 340 million new curable STIs occur in reproductive-aged men and women; this excludes the estimated 33 million new cases of HIV as well as estimated 100 million plus infections caused by other viral STIs each year (WHO, 2001)**.** Excluding HIV, STIs and other reproductive tract infections (RTIs) account for a substantial proportion of outpatient health care visits among adults of reproductive age**,** and in most nations are ranked among the top five leading causes that individuals seek health care (Dallabetta et al., 2006). In the United States, five of the 15 most commonly reported notifiable diseases are STIs (gonorrhea, chlamydia, HIV, syphilis and hepatitis B) including the first and second most commonly reported diseases, gonorrhea and chlamydia, respectively (Centers for Disease Control and Prevention, 2007).

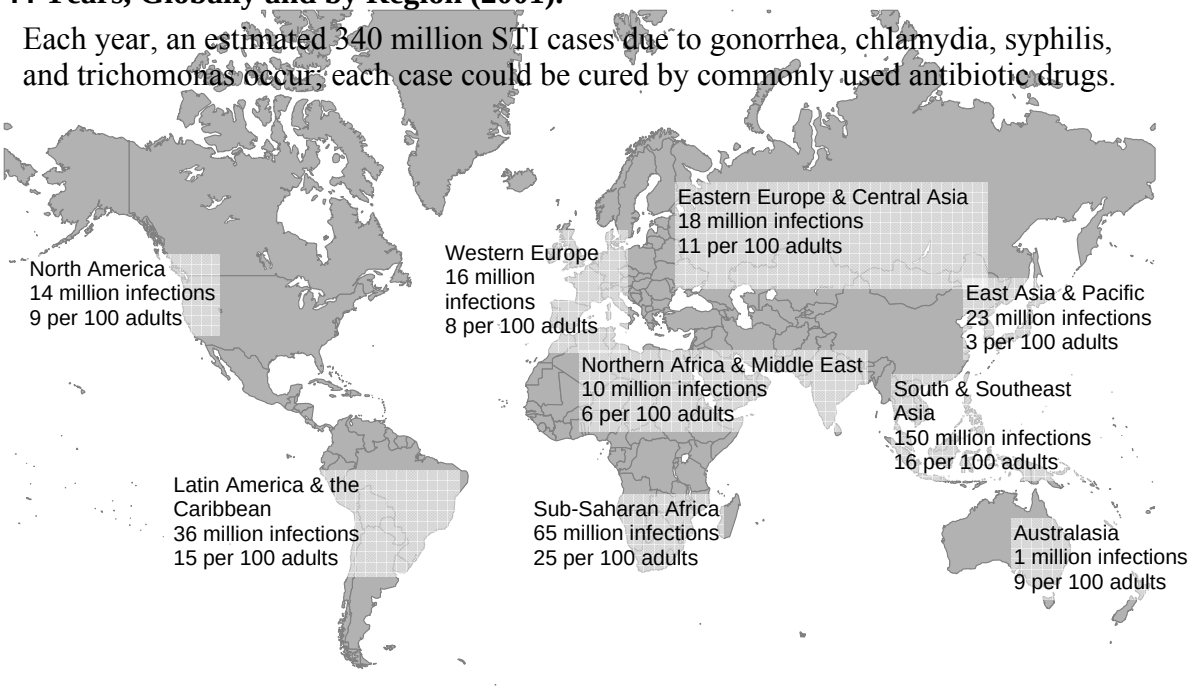
In fact, reported STIs represent only the "tip of the iceberg" because most infections—typically more than half of any specific diagnosis regardless of bacterial or viral etiology—are entirely asymptomatic or (if symptoms exist) unrecognized (Adler, 1996; Kamb et al., 2000; Peterman et al., 2006). This is especially true for women (Bolan et al., 1991; WHO, 2000; WHO, 2006a). Furthermore, adequate data are not available in developing countries to even analyze reporting rates in those settings. Even when symptoms exist, the social stigma associated with STIs in virtually every society contributes to their under-detection. Shame, stigmatization or both lead many affected individuals to seek treatment outside established health care systems, whether with traditional healers, self-treatment using alternative or over-the-counter remedies, or through other avenues -- or to not seek treatment at all. In almost all nations, more STIs are treated in the private than public health sector. Private (formal and informal) providers have been found to have wider access and provide more confidential and less judgmental services, but are also more likely to use unnecessary diagnostic tests, recommend outdated or ineffective treatment regimens, and not treat sex partners thus leading to re-infection in the index patient (Dallabetta et al., 2006). In most nations, a variety of challenges apply to both private and public sector STI management (see Box 1) (Wilkinson, 1999; Connolly et al., 1999; Schneider et al., 2001; Jacobs et al., 2004; Dallabetta et al., 2006; Nuwaha, 2006).

C. Human and financial costs

STIs impose costs on individuals and economies in several ways. Direct medical costs associated with acute STI diagnosis and treatment can be substantial. A recent review of direct STI treatment costs in low and middle income nations estimated the median cost for drugs alone for a single acute, bacterial STI episode to be USD $2.62 (range, $0.05 to $35.23) -- more than three times the average daily income for low income nations (Terris-Prestholt et al., 2006). Aside from acute care, the costs associated with medical treatment for adverse outcomes related to STIs (e.g., treatment for infertility) is substantial in industrialized nations, but has not been well documented in developing world settings. STIs can also impose costs related to lost productivity due to STI morbidity and mortality (Table 1). The STI-associated morbidity and mortality related to adverse pregnancy outcomes (stillbirth and early neonatal deaths), reproductive morbidity and mortality (e.g., maternal deaths related to ectopic pregnancy), anogenital cancers and chronic liver disease or cancer have been documented in industrialized nations, but less so in low and middle-income settings. Similarly, the lost productivity related to STIs themselves or unintended negative aspects of STI management (e.g., partner violence associated with poorly implemented partner notification, divorce or family breakdown related to infertility, depression related to stillbirth or neonatal death) are generally undocumented in developing world settings. Another way that STIs could impose costs is through the impact of STI prevalence and associated adverse outcomes on economic growth, whether locally or regionally. With the exception of HIV, this STI cost has also not been well documented in either developed or developing world settings.

Figure 1. Estimated Prevalence and Incidence of Curable STIs among Men and Women Age 15–44 Years, Globally and by Region (2001).

Each year, an estimated 340 million STI cases due to gonorrhea, chlamydia, syphilis, and trichomonas occur; each case could be cured by commonly used antibiotic drugs.



Source: World Health Organization (WHO). 1995. An Overview of Selected Curable Sexually Transmitted Diseases, Geneva: WHO, Global Programme on AIDS.

D. Prevention and Control of STIs

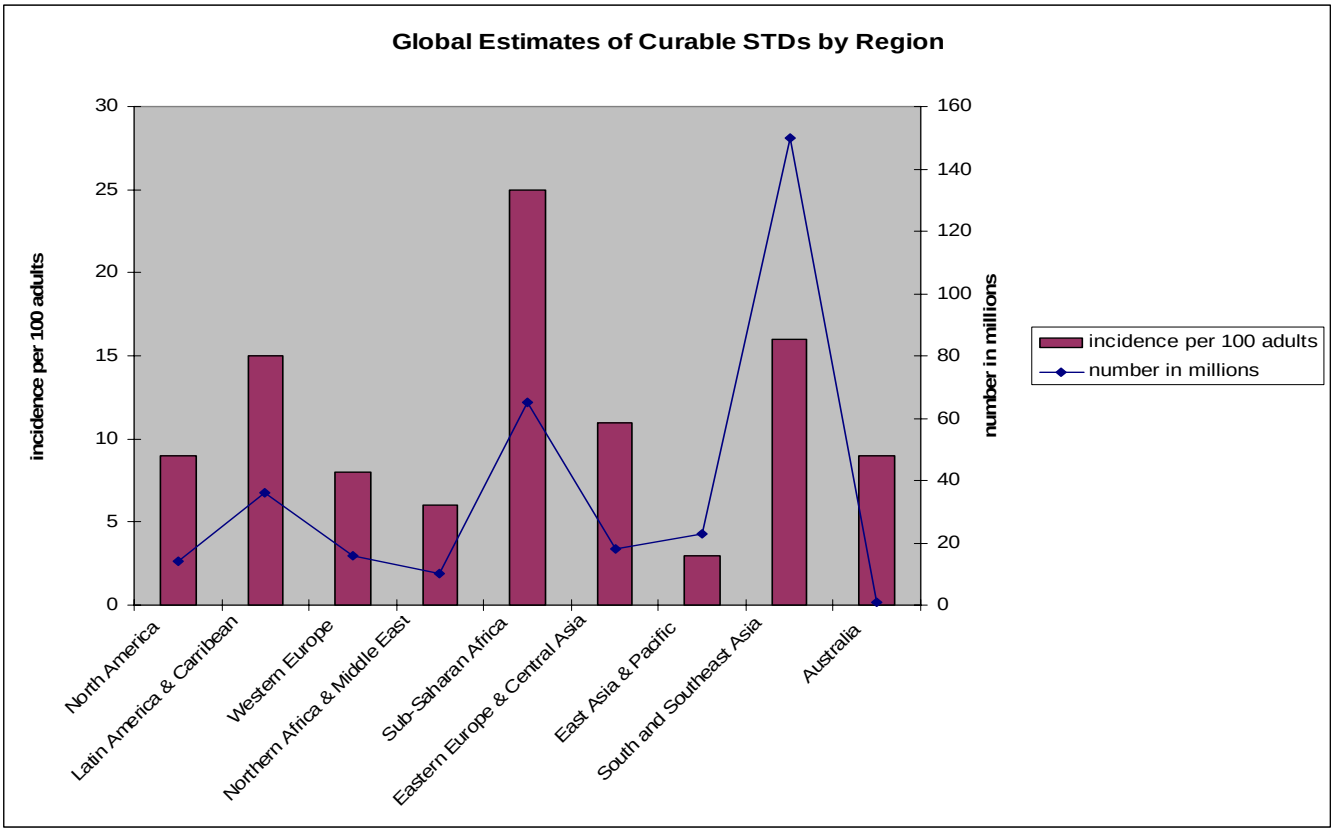
Strategies for prevention and control vary according to whether STIs can be cured with antibiotic drugs or are caused by a virus and may result in long-term or even life-long infection (i.e., are non-curable). The WHO estimation that 340 million new STIs occur globally each year among men and women aged 15 – 49 years refers specifically to *curable* STIs caused by common bacteria (i.e., gonorrhea, chlamydia, syphilis, trichomoniasis) (Gerbase et al., 1998; WHO, 2001). If identified, each of these infections can be effectively treated and cured using antibiotics that exist on the Essential Drug formularies of most nations. However, if not appropriately treated or treated too late, these STIs can cause a number of serious health consequences (Table 1). The most important consequences fall under the general categories of *reproductive morbidity and mortality* (e.g., infertility), *adverse pregnancy outcomes* (e.g., perinatal death, stillbirth), or *enhanced acquisition or transmission of HIV infection* (e.g., from a genital ulcer or inflamed urethra or cervix) (Meheus, 1992; Gutman L.T., 1999; Watson-Jones et al., 2002; Goyaux et al., 2003; WHO, 2006a). For a number of biologic and behavioral reasons, curable STIs are most common in younger populations in their reproductive years, particularly adolescents and young adults under age 24 (see Box 1).

Of all curable STIs, syphilis may cause the most substantial mortality and be the most easily preventable disease**.** WHO estimates syphilis accounts for 750,000 to 1,500,000 perinatal deaths each year (personal communication, Dr. George Schmid, WHO), and that prevalence rates among pregnant women attending antenatal care clinics range from 2 to 10% in Latin America and 4 to 15% in Africa (WHO, 2006a)**.** Research studies indicate that 22 to 51% of all pregnancies among women with untreated early syphilis will result in stillbirth, a further 14% of pregnancies result in neonatal death**,** and that the least common (but most recognized) result of untreated maternal syphilis is congenital syphilis in a live born infant (Ratnam et al., 1982; Aiken, 1992; McDermott et al., 1993; Watson-Jones et al., 2002; WHO, 2006a).

E. Curative Treatment and Control of Transmission

Adverse health outcomes related to curable STIs are especially regrettable because they are unnecessary; these infections can be effectively treated using affordable antibiotic drugs that are already available in most nations (often as a single dose, thus able to be provided on-the-spot and directly observed). Furthermore, most nations with intact health care infrastructure have already demonstrated declines if not community control of syphilis and gonorrhea through use of straight-forward public health control programs (e.g., effective STI management; asymptomatic screening of vulnerable populations) (Berman and Kamb, 2007) (See Section IV). Curable STIs remain problematic in settings lacking established health care systems, drug distribution systems, or adequate surveillance (WHO, 2007) , and high prevalence of STIs such as syphilis as gonorrhea (particularly among pregnant women) could be considered a marker of poor health care infrastructure. WHO estimates that currently 80 to 90% of the global burden of curable STIs occurs in developing countries (WHO, 2006b), with incidence and prevalence rates of these infections up to 20 times higher in developing settings compared with Western Europe or North America (Adler, 1996), and with this gap increasing over time (WHO, 2006b). As of 2006, the highest prevalence rates (i.e., population-based burden) of curable STIs occurred in the sub-Saharan Africa nations, followed by Latin America and the Caribbean, and South and Southeast Asia (Figure 1). However, because of large populations with distributions skewed under 40 years, the largest numbers of curable STIs occurred in Asian nations (Figures 1 and 2).

Figure 2. Global Estimates: Numbers and Incidence of Curable STIs per 100 Adults, by Region



F. Primary Prevention of Chronic Infections and Sequelae of Viral STI

The common viral STIs -- HIV, hepatitis B virus (HBV]) human papillomavirus (HPV), and herpes simplex virus type-2 (HSV-2) -- are not included in the WHO global STI estimates, but are estimated to account for the overwhelming majority of new (as well as prevalent) STIs (Agacfidan and Kohl, 1999). Viruses are not cured by antibiotics, and if not cleared by the body's immune system can lead to latent infections, chronic infectiousness and/or serious sequelae, most notably primary cancers. While not curable, two of the most important viral STIs -- HBV and HPV -- can now be prevented through vaccination, and both HIV and HSV-2 can be treated with antiviral drugs that diminish their infectiousness and long term complications.

HPV and Cervical Cancer: Common and Preventable

HPV is the most common STI. A recent U.S. study, using sensitive detection techniques, estimated that 27% of sexually active women aged 14 to 59 years were infected with at least one HPV subtype – and other countries likely have similar prevalence. Most HPV infections are asymptomatic or cause minimal morbidity (e.g., genital warts); however, certain HPV subtypes are established as the causal agents of anogenital cancers including cervical, penile and anal carcinomas (zur Hausen, 1996). Two carcinogenic HPV subtypes (16 and 18) are believed responsible for 70% of all cervical cancers and 80% to 90% of anal and penile cancers worldwide (Munoz et al., 2003; Daling et al., 2004; Daling et al., 2005). For women, cervical cancer is the second most frequent cancer worldwide and the leading cause of cancer deaths in the developing world, leading to up to 240,000 deaths per year (WHO, 2006a). In industrialized nations, cervical cancer has been associated with substantial morbidity but decreasing mortality as cervical cancer screening increases. The enormous disparity in cervical cancer

deaths between industrialized and developing nations is largely attributed to availability of cervical screening, standard-of-care in high-income (using Pap smears) and many moderate income (using direct cervical visualization) nations. But in Africa it has been estimated that less than 5% of eligible women have had cervical screening during the past 5 years (WHO, 2002a). HPV-related anogenital cancers occur more frequently and progress more rapidly in HIV-infected individuals, and with the advent of effective antiretroviral therapies against HIV have been an increasingly important cause of HIV-related death. One of the most exciting new developments in STI research has been the development of new HPV vaccines (discussed in Section V), which have the potential to essentially eliminate cervical cancer and other anogenital cancers caused by HPV.

Prevention of Hepatitis B Virus and Resultant Chronic Liver Disease

HBV is another virus for which an effective vaccine exists (Section V). Common in developing world settings, particularly in Asia, chronic HBV infection often results in serious, long-term complications including primary liver cancer, cirrhosis, end stage liver disease and death (O'Farrell, 1999; Perz et al., 2006). Primary liver cancer, called hepatocellular carcinoma, is the fifth leading cause of cancer death in adults worldwide and third most common cancer in developing world settings (Pisani et al., 1999; Parkin et al., 2001). Globally, at least half of all primary liver cancers are attributable to HBV, although regional estimates vary (North America, 16%; Africa, 47%; Southeast Asia, 47%; Eastern Mediterranean, 59%; East Asia, 65%) (Perz et al., 2006). Most HBV in developing settings is transmitted from mother to child at birth, followed by parenteral transmission through tainted blood products, organs, or medical or illicit drug injecting equipment; however, HBV is a sturdy virus that is easily transmitted through unprotected sex (sex without a condom). Men who have sex with men are a group at particularly high risk for sexual HBV transmission. Vaccination, preferably shortly after birth, is the most cost-effective and practical approach to eliminating the adverse consequences of HBV. Since the development of the first effective vaccine against HPV in the 1980s, several very low-cost options have become available (See Section V). Serological tests can detect early cirrhosis and liver cancers, but are not useful for disease prevention and are seldom available in developing world settings.

Prevention of Genital Herpes Infections

Another common viral STI is HSV-2, the cause of genital herpes infection, which is often asymptomatic but when associated with symptoms causes a genital ulcer syndrome. Genital herpes has become the most common cause of the genital ulcer syndrome, in part due to program successes in eliminating bacterial causes of genital ulcers (syphilis and chancroid) but also because of increasing HIV prevalence in many countries. HSV and HIV are synergistic viruses: genital ulcers can enhance HIV acquisition and transmission, and HIV results in increased shedding of HSV, thus more HSV infections (WHO, 2006a). Treatment of genital herpes with specific antiviral agents can effectively reduce the duration and frequency of ulcer episodes related to genital herpes, and thus reduce the medical costs related to health care visits, the psychological costs of a chronic disease associated with frequent outbreaks, as well as new infections in partners (Centers for Disease Control and Prevention, 2006).

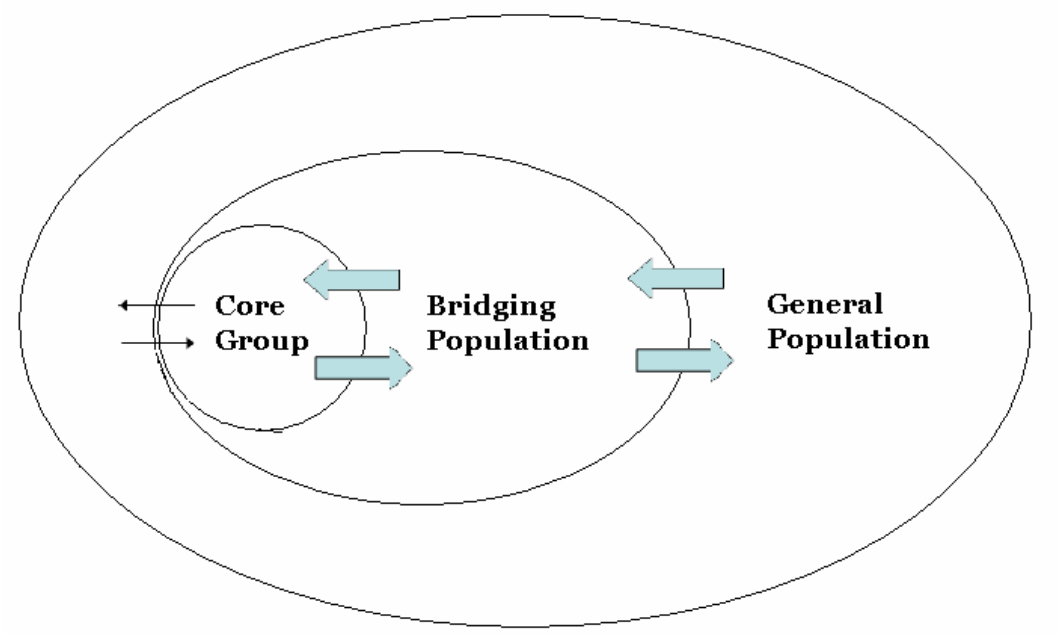
II. STI Transmission Dynamics

A. Determinants of STI Transmission

As with other communicable diseases, the distribution of STIs in a given population is not static; epidemics evolve through different phases characterized by changing patterns in the transmission (and

distribution) of STIs between and within various subpopulations (WHO, 2006a). Three factors are believed to govern STI rates: (1) an agent's infectiousness (i.e., transmission efficiency per sexual contact), (2) its duration of infectiousness, and (3) the rate of sex partner change among infected persons. In early or well-controlled epidemics STIs are generally transmitted among high risk persons with high STI prevalence and multiple and frequent changes in sex partners ("core groups"). As epidemics evolve, STIs are spread from higher to lower risk individuals through individuals who have sexual contact with both ("bridging groups") (WHO, 2006a) (Figure 3). Bridging groups vary from society to society, but are often clients of sex workers or mobile men (e.g., truckers, miners, migrant workers) who may transmit infections from higher risk partners to their wives or girlfriends. Thus, targeted prevention programs aimed at core and bridging groups have been identified as important priorities for interruption of transmission and disease control (see Table 2 in Annex A).

Figure 3: STI Transmission Dynamics in a Population (adapted from WHO 2006)



B. Biologic Factors Affecting STI Transmission

Individual biologic, behavioral, social and environmental factors can all determine a person's risk for acquiring STIs (Dallabetta et al., 2006). Biologically, the "host's" anatomy, microbiology (e.g., vaginal flora), and hormonal and immunologic status may enhance likelihood of acquiring an STI. Many STIs initially infect mucosal surfaces, such as the lining of the penile urethra in men, vaginal walls and cervix in women, and oral pharynx and rectum. The relatively large surface area of the female vagina confers particular risk for women for those STIs (e.g., syphilis, chancroid, trichomonas, most viral STIs) that infect mucosal surfaces. Some STIs are attracted to specific target cells. For example, the bacteria causing gonorrhea and chlamydia prefer the specialized columnar epithelial cells lining of the female cervix. These cells are more exposed in young women, helping explain why adolescent girls are at particular risk for these STIs. Viral STIs may have other targets; HIV selectively attaches to specialized receptors common in the vaginal wall, rectal mucosa, and foreskin of uncircumcised men. Other biologic factors can affect STI acquisition. Many STIs are inactivated by acidic environments, and thus substances that increase vaginal pH (e.g., sperm, menstrual blood, or chemical douching agents [liquids used to flush out the vaginal after sex or menstruation]) may

increase a woman's STI risk. The skin itself is an important protective barrier, and even small breaks in the skin may enhance the likelihood of infection. Traumatic sex, caustic douching agents, or herbal preparations used to dry out the vagina (practiced in some cultures to enhance sexual pleasure for males) can all increase a woman's chance of acquiring STIs including HIV. Hormonal and immunologic factors (e.g., pregnancy, use of oral contraceptives) can also enhance a woman's risk for certain STIs.

C. Behavioral Factors Affecting STI Transmission

Not every encounter with an infected partner will automatically result in an STI. Some pathogens appear to be highly infectious: For example, exposure to the bacteria causing gonorrhea results in transmission to a sex partner in up to 50% of sexual exposures (i.e., 1 in 2 exposures). Other pathogens, such as HIV, are much less infectious. In prospectively observed discordant couples (one partner HIV infected and the other uninfected), only 0.002 to 0.0001% of sexual exposures led to a new HIV infection (i.e., between 1 in 500 to 1 in 10,000 exposures) (Varghese et al., 2002). This observation has supported the notion that HIV transmission or acquisition may require additional "help" through means of an underlying co-infection (e.g., with an STI causing an ulcer or inflammation), a break in the skin, a partner with a particularly high HIV viral load or some other factor. In fact, laboratory and clinical research supports that new HIV infections are strongly associated with STIs causing genital ulcers, and to a lesser extent those causing inflammatory urethral and cervical responses.

Behavioral factors affecting STIs can be divided into personal risk behaviors and broader community norms. Regarding personal risk behaviors, although abstinence is the only certain way to avoid STIs, certain sexual practices (e.g., unprotected sex [without a condom], penetrative vaginal or anal sex) with an infected partner are more likely to result in an STI or HIV than others (Varghese et al., 2002). Furthermore, STIs are communicable diseases that, regardless of the riskiness of a particular sexual practice, require an infected partner who is infectious enough to transmit the agent. Not surprisingly, there is a direct relationship between higher number of sex partners and likelihood of acquiring an STI; larger numbers of partners mean greater likelihood of contacting someone who is infected with an STI. However, in communities with low STI prevalence, partner number may not be as strongly associated with new STI as partner risk factors (i.e., a partner who has sex with other high risk people). Sex with several low risk partners who themselves have sex with only a few low risk partners may be less risky than sex with a single high risk partner (e.g., a sex worker, a client of a sex worker). As STI prevalence decreases in a community, other partner characteristics such as prior STI, younger age and lower education (perhaps resulting in fewer prior protective behaviors) appear to predict STI risk more accurately than partner number (Peterman et al., 2000).

Mutually monogamy (both members of a partnership faithful to each other) is universally promoted as an effective means of reducing risk for STIs including HIV, but obviously requires both partners to be uninfected. However, STI status is not always known and may be difficult to ascertain in settings where specific STI laboratory testing is not attainable or affordable. The effectiveness of mutual monogamy also depends on both partners being faithful. This can be challenging in cultures that expect women to be faithful to their husbands while allowing men to have overt or tacit access to other partners (e.g., commercial sex workers). In such situations, relying on faithfulness alone may be very risky for women, especially women who perceive themselves to have low STI and HIV risk and thus not needing to employ protective measures such as negotiating condom use(Padian et al., 2007) (see Box 3).

D. Social and Environmental Factors Affecting STI Transmission

While individual biologic and personal protective behaviors are important, the socio-cultural "macro-environment" may affect STI patterns even more dramatically. Socio-demographic factors such as younger age structures, sex ratio imbalances in either direction, urbanization and rural to urban migration have all been observed to have large effects on STI prevalence (Dallabetta et al., 2006). Younger age structures, by definition, means that a larger proportion of the population is susceptible to STIs. Economic reforms, political unrest, natural disasters, or societal stigma around personal partner choice have been observed to affect STIs as individuals (often young people) move from more rural communities to cities in search of employment, safe shelter, or mates (Dallabetta et al., 2006). If economic conditions require, some individuals – generally young women -- may choose or be forced to provide transactional sex (i.e., exchanging sex for goods in order to sustain themselves or their families at home), and young men from rural areas may move to cities for further schooling, to obtain jobs or to serve in the army. Urban environments providing mobile young adults access to larger numbers of available sex partners (including higher risk partners), and thus to STIs. The movement away from traditional communities and family structures can also be associated with a loosening of societal norms around sex and increased STIs (Dallabetta et al., 2006). Although rural-to-urban migration may seem to pose most STI risk for city-dwellers, rural communities can also be infected if young people (typically young men) return home and transmit STIs to friends, fiancés and spouses. Paradoxically, some countries have found higher HIV prevalence among rural than urban antenatal clinic attendees, perhaps reflecting that rural women perceive themselves to be at lower STI risk or are less knowledgeable about STIs and how to prevent them than their urban counterparts (O'neil et al., 2004; Blanchard et al., 2005).

Literacy, educational levels and community health beliefs related to STIs (e.g., a community's willingness to support dissemination of information about STI/HIV risk and preventive strategies) also affect STI acquisition, particularly for women. Results from Demographic and Health Surveys (DHS) conducted from 2000 through 2005 indicated that among 15-49 year olds, 22 to 61% of women in Africa, 58 to 72% of women in Central Asia, and 34 to 73% of women in South and Southeast Asia did not know that "people can protect themselves from contracting HIV by using condoms". (Demographic Health Surveys (DHS), 2007) (Website: www.measuredhs.com). As recently as the late 1990s, surveys of female sex workers in India found that in 12 states fewer than half of participants had ever heard of HIV/AIDS (Over, 1999). Aside from basic information, factors such as societal stigma around STIs or certain other cultural practices (e.g., practice of male infant circumcision) can affect prevalence of STI in a community (although in the case of circumcision, probably in opposite directions.) (Male circumcision is discussed further in Section V). The HIV epidemic itself has had an impact on the epidemiologic patterns of other STIs. In nations with high HIV prevalence, HIV may enhance expression and transmission of certain STIs (most notably genital herpes) which enhance HIV transmission and acquisition – creating a vicious cycle (Paz-Bailey et al., 2006). Additionally, stigma or fear around HIV may lead people with STI symptoms to avoid or delay health seeking, increasing the chance that STI infections are missed and resulting in more long term consequences and further spread of STIs in the community.

E. Special Case: The Interaction between HIV and Other STIs

Individuals infected with STIs causing genital ulcers (e.g., syphilis, chancroid, genital herpes) or urethral or cervical inflammation (e.g., gonorrhea, chlamydia, trichomonas) are more susceptible to

acquiring HIV infection, probably because of disruption of mucosal integrity, increased prevalence of HIV receptor cells or both (Wasserheit, 1992). Additionally, people co-infected with HIV and STIs have been found to shed HIV virus more efficiently, and thus more likely to transmit HIV to an uninfected partner. (Wasserheit, 1992; Fleming and Wasserheit, 1999). Furthermore, effective STI treatment has been shown to reduce HIV viral shedding**.** Among high risk individuals such as female sex workers, routine STI clinical services and condom promotion has been documented to reduce HIV incidence or prevent HIV prevalence from increasing (Plummer et al., 1991; Wasserheit, 1992; Laga et al., 1994; Levine et al., 1998). In the 1990s, one well-done community randomized trial in Mwanza, Tanzania documented that communities receiving improved management of symptomatic STIs had about 40% fewer new HIV infections compared with communities with typical STI management – supporting the benefit of high quality STD management for HIV prevention at the community level. However, at least two subsequent, well-conducted community-level trials did not find the same HIV prevention benefit. The lack of a similar effect in the later community level intervention trials has caused experts to question whether a community-level HIV benefit to STD control could be expected in all circumstances or all populations. A 2006 WHO Technical Consultation of experts concluded that (1) the benefits of STD control for HIV prevention at the *community level* likely depends on several factors including prevalence of curable STIs (i.e., syphilis, chancroid, gonorrhea), the coverage of effective STI management, the phase of the HIV epidemic (with low level epidemics more amenable to beneficial effect of STD control) and possibly other factors; (2) compelling evidence supports that prompt identification and treatment of curable STIs among HIV-infected and HIV susceptible *individuals* should be prioritized; and (3) effective STI management should include, in addition to use of validated syndromic algorithms and availability of effective drugs in developing settings, other prevention elements such as partner management, condom promotion, risk reduction counseling or education, and HIV testing and counseling.

The association of the genital ulcer disease syndrome with HIV transmission has led many experts to wonder whether HSV-2 viral therapy might reduce the likelihood of transmitting or acquiring HIV infection (Weiss, 2004; Paz-Bailey et al., 2006). Multiple randomized trails of herpes therapy are rigorously evaluating this theory. Several antiviral agents effective against genital herpes are widely marketed, and some (e.g., acyclovir) are affordably priced for most nations. However, many nations have not yet incorporated acyclovir into their national Essential Drug formularies (Paz-Bailey et al., 2006; WHO, 2006a) and, given the well-documented benefit of this drug for genital herpes prevention, and probably benefit for HIV prevention, this situation should be addressed – particularly in nations with high HIV prevalence. Similarly, the HPV vaccine may have implications for HIV transmission, but research on this interaction is ongoing and is, to date, inconclusive.

III. STI Prevention & Control Strategies

A. The Basis for Effective STI control -- "Treatment is Prevention"

For communicable diseases such as STIs, case identification and treatment is the most effective form of prevention in the absence of a vaccine. Treating STIs in individuals breaks the chain of transmission, and thus reduces STI prevalence in the greater community (Parran, 1937). Many industrialized nations have already effectively greatly reduced syphilis and gonorrhea prevalence through a combination of basic ("core") program components, including:

(1) **Clinic-based symptomatic STI case management.** Effective case management assumes etiologic or syndromic diagnosis of STIs, choice and availability of effective drug therapies,

education about compliance, counseling about STI risk reduction and provision of condoms with instructions on their correct use (WHO, 2006a).

(2) **Partner management.** Because STIs are communicable diseases, sex partners must be treated to eliminate chance for re-infection of the index patient. Partner management also helps break the chain of STI transmission in the community (Centers for Disease Control and Prevention, 2006).

(3) **Asymptomatic screening.** Screening asymptomatic individuals (typically women) who are at high risk for certain STIs reduces the most serious STI-related consequences (e.g., syphilis screening among pregnant women to reduce adverse pregnancy outcomes, routine Pap smear screening to reduce cervical cancer) (Berman and Kamb, 2007).

(4) **Targeted STI control interventions.** Interventions focused on core groups (e.g., sex workers) or bridge populations (e.g., clients of sex workers, mobile men) prevent STI spread into the general population and reduce subsequent morbidity (WHO, 2006a). Earlier STI control efforts have been primarily aimed at curable STIs, but the development of vaccines against two common viral STIs can substantially reduce the incidence and subsequent mortality of these infections.

(5) **Vaccines.** Safe and effective vaccines against HBV and HPV, although not yet well implemented into basic public health programs, hold the promise of eliminating a substantial proportion of the world's STI-related cancers and chronic diseases.

Besides the five core components to STD prevention and control, six supportive elements have proven important in ensuring the core program can be effectively provided (WHO, 2006a):

(1) **Leadership and advocacy.** When leaders are aware of the magnitude and importance of STIs and associated morbidity, they can effectively advocate for high quality, sustainable programs.

(2) **STI surveillance.** Adequate surveillance is important to clarify burden of STIs and serious STI-associated consequences to allow policy makers to make informed choices and to help ensure sufficient quality of implementation of STI program elements. Surveillance can also help monitor program successes and challenges.

(3) **STI laboratory capacity.** Sufficient – although not necessarily excessive -- laboratory capacity is needed to support local programs, including disease surveillance.

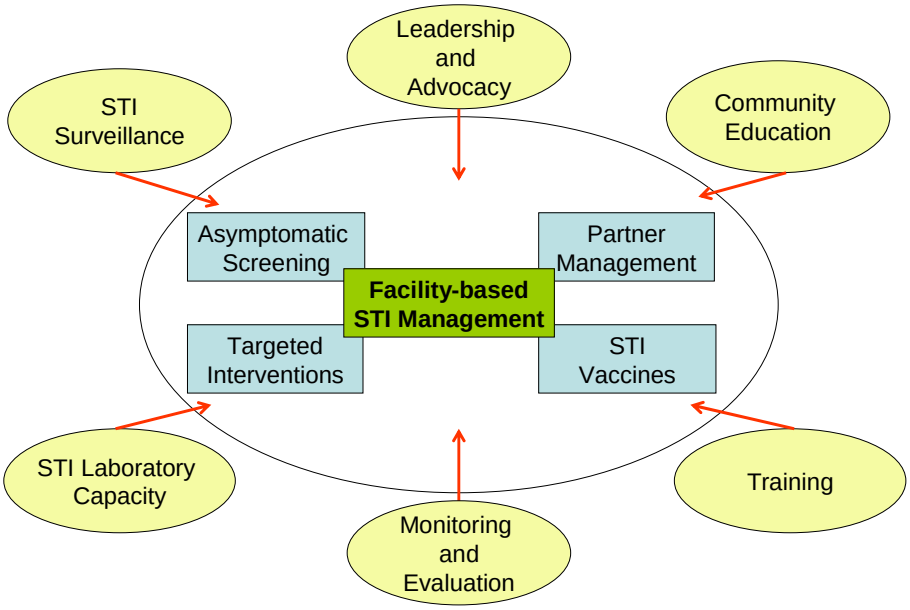
(4) **Training.** Appropriate training of health care providers (formal and informal) ensures core STI prevention and control programs are provided efficiently and effectively.

(5) **Monitoring and evaluation.** Routine, periodic monitoring of program quality and evaluation of program effectiveness through on-site visits, data review and operational research ensures program quality, but requires effective program management.

(6) **Community education.** In addition to focus on facility-based STI management and treatment and targeted interventions aimed at highly vulnerable populations, broad-based community education around STIs including HIV, and how to prevent them, is important for primary

prevention. Education is particularly for adolescents and young adults as they have highest STI rates, regardless of nation or community setting.

Figure 3. STI Prevention and Control:
Five core components and supportive elements



An in-depth description of the core program elements for STI prevention and control follows:

Core component #1: Effective STI Management

STI management is aimed at symptomatic individuals who seek health care, and thus is generally facility-based whether provided in the public or private sector, or by formal or informal (e.g., traditional healers) providers. Case management based on etiologic diagnosis employs laboratory diagnostic tests in combination with clinical presentation; management based on syndromic diagnosis relies on patient symptoms, clinical presentation and examination. Regardless of diagnostic approach, high quality STI management requires effective drug treatment, and is most successful if coupled with prevention services including education on drug compliance, counseling on personal behavior change, and provision of condoms and skills around correct and consistent condom use and, if appropriate, contraception (WHO, 1991; Ryan, 1999; WHO, 2006a). Because HIV is behaviorally and biologically linked to other STIs, any clinical encounter involving STI management is recommended to always include offering of HIV testing and counseling (WHO, 2006b).

In many settings, reliable diagnostic tests are unaffordable or unavailable. Additionally, providers who are not familiar with prevalent STI trends in the community may miss co-infections for which testing was not done. Furthermore, the drug options preferred by health practitioners may be ineffective against the organisms being treated, or may be unaffordable to patients. To address these problems, in the early 1990s WHO began advocating that resource-limited settings encourage health providers to use syndromic approaches for clinic-based STI/RTI management of symptomatic patients (Ryan, 1999; Schmid et al., 2005; WHO, 2006a).

Syndromic Management Approaches. Syndromic approaches base treatment on patient-reported symptoms and reported or observed clinical signs, using a series of flow charts (clinical algorithms) that allow provision of standardized therapeutic regimens for specific syndromes. WHO recommends that national STI control programs in developing countries incorporate syndromic flowcharts into their STI/RTI management guidelines after validating and adapting them based on local epidemiology (Over and Piot, 1993; Dallabetta et al., 2006; WHO, 2006a) . In most settings, there are benefits and limitations to syndromic approaches (see Box 4).

Evaluation studies from low income settings support that syndromic approaches have been most effective for management of certain syndromes, particularly genital ulcer syndrome in men and women, urethritis and epididymitis in men and neonatatal conjunctivitis in infants (WHO, 2006). Repeated cross-sectional studies in several nations with high STI prevalence indicate that bacterial causes of genital ulcer syndrome (particularly chancroid, but also syphilis) have markedly declined in parts of Africa over the past decade (WHO, 2006a). Although possibly related to other factors, these observations suggest that adoption of syndromic management approaches can substantially reduce prevalence of important bacterial STIs (especially those most highly associated with HIV transmission and acquisition) in certain settings. With declining bacterial causes of genital ulcer syndrome, and increasing prevalence of HSV-2, it will be important that national STI/HIV programs include acyclovir or other HSV antiviral drug therapies routinely in their syndromic algorithms (WHO 2006 Report on Technical Consultation on STI and HIV interaction).

Considerable debate has focused on the fact that syndromic approaches are less effective in managing vaginitis, a common reason women seek health care, than other syndromes. Considered as an STI control strategy, success of syndromic management is highly dependent on prevalence of inflammatory STIs among women attending the primary care or family planning clinics and, not surprisingly, is least effective in settings with lower prevalence of these STIs (as other factors can cause vaginitis). This situation is particularly common in family planning and reproductive health clinics in many moderate income settings, especially those with low HIV prevalence and in parts of Asia. On the other hand, even when STI prevalence is low, syndromic approaches can be cost-effective and beneficial for women if the primary objective is to treat all-cause vaginitis (caused by other reproductive tract infections such as bacterial vaginosis or candidiasis) as well as STIs (Vuylsteke, 2004; WHO, 2006a).

Drug Availability and Antimicrobial Resistance. Effective STI management requires availability of appropriate drugs, preferably those with acceptably low toxicity, for which microbial resistance is unlikely to develop (or will be delayed), that can be administered orally – preferably as a single dose – and that are not contraindicated in pregnant or lactating women (WHO, 2006b). An ongoing problem for many nations is that the most desirable drugs are not included on the national essential drug lists. While availability of STI drugs depends on a number of factors, the most immediately pressing is often affordability, which often depends on national, regional and international considerations such as patents, limited volume or limited competition, import duties and tariffs, and local taxes and mark-ups for wholesaling. Local availability also depends on the efficient distribution of STI drugs and other commodities to all levels of the health care system before product expiration dates. Drug distribution is important for all diseases, but particularly important for STIs because of antibiotic resistance. Worldwide, the effective treatment of gonorrhea, chancroid and to some extent syphilis has been complicated by the spread of antimicrobial resistant strains. Currently, almost all gonorrhea strains worldwide are resistant to first-line therapies including tetracycline, still often recommended by STI providers. Furthermore, most gonorrhea strains in Asia and increasingly more in other developing settings (including East Africa) are no longer susceptible to fluoroquinolone antibiotics. The loss of this class of drugs has essentially eliminated the possibility of using oral antibiotics against gonorrhea

in many settings; communities must resort to injectable drugs such as ceftriaxone. When effective STI drugs are not included on essential drug formularies, a "two tiered" system of drug availability often results, with provision of less effective drugs at the peripheral health care levels and the most effective (and generally more expensive drugs) only at the referral levels (Dallabetta et al., 2006; WHO, 2006a). This, in turn, leads to an unacceptable rate of treatment failures, unnecessary referrals for patients, further drug resistance and eroded confidence in the STI management program (WHO, 2006a).

Service Delivery. Effective STI management also requires symptomatic individuals have access to sufficient quality services. Access to STI services is complex in most societies, as health seeking is a function of attitudes around disease and sex as well as the availability, affordability and acceptability of the services (Dallabetta et al., 2006). STIs are associated with substantial stigmatization and prejudice, and tend to be viewed as "social diseases" that are dirty, shameful and somehow deserved. This is a particularly difficult situation for many women (and infants) whose STI exposure is related to partner rather than personal risk. STI service availability involves easy-to-reach locations, convenient hours of operation, and providers trained in effective STI management approaches. Services must also be affordable, and a number of personal and societal factors affect this. In some nations, public clinics provide services free of charge, but individuals are required to pay for drugs. Prescribed drugs are often expensive, exceeding many patients' daily income (Terris-Prestholt et al., 2006). Services must also be acceptable to clients, but this can be affected by the shame and stigmatization that surrounds STIs as well as judgmental or unsympathetic attitudes of some providers. Perceived empathy and acceptance by service providers can have a profound impact on patients' opinions of services; "(p)roviders should not scold" (Dallabetta et al., 2006). Factors such as privacy of setting and confidentiality of services are also important to service acceptability. Adolescents and poorer or marginalized groups (e.g., sex workers, men who have sex with men) most vulnerable to STIs who may contribute most importantly to STI transmission dynamics in a community (Figure 3) may be least likely to seek services in official settings. Effective STI control programs will ensure that acceptable STI clinical services are available to these groups, often through specialized, targeted interventions (See Core Component #4).

Core Component #2: Partner Management

Notifying partners that they have been exposed to an STI, and providing them (or encouraging they seek) treatment is important to ensure that index patients are not re-infected with the STI. Partner management also reduces further spread of the STI in the community. Although well recognized as a core STI control strategy, effective partner management is not always implemented even in nations with good resources. Effective strategies in developing settings with limited resources have not been well studied.

Partner Management Can Be Difficult. Effective partner management can be difficult for several reasons. Partner notification can be labor-intensive, costly and difficult (e.g., if public health outreach is used). The social stigma surrounding STI diagnosis may lead patients to be reluctant to notify partners or providers to recommend treatment. This may be particularly true for women who are in a situation where partner violence may occur. Although research from the United States and Europe suggests partner management does not lead to an overall increase in partner conflict or violence, this may not be applicable to other societies or settings where cultural norms and gender power balances differ. Many providers are reluctant to promote partner management without a clearly defined etiologic diagnosis, as is the case for most syndromic STI management approaches. In certain settings serving high risk patients who have anonymous or casual sexual encounters (e.g., sex workers, men who have sex with men, itinerant workers), notifying partners can be impractical. Another reason that

partner management is poorly implemented is that established systematic approaches are often not employed.

Effective Partner Management Approaches. At least three general partner management approaches have been applied with apparent effectiveness in different parts of the world, provider notification (e.g., through outreach), patient notification (e.g., giving partner(s) a card notifying about STI exposure), and expedited partner treatment (i.e., patients provide partners effective STI drugs, or a pharmacy card that allows partners to get drugs) (WHO, 2006b). Regardless of the approach promoted, experts warn about the critical importance of avoiding coercion and observing confidentiality, and about the potential importance of gender power imbalances (WHO, 2006a). Strong evidence supporting one approach over the others in developing world settings does not yet exist (WHO, 2006a), and this is an area where further research on best practices and cost-effectiveness is warranted.

Core Component #3: Asymptomatic Screening

The objective of STI screening is to identify individuals who have asymptomatic or unrecognized STIs that are associated with serious sequelae, and treat them before complications arise. Syphilis, gonorrhea, chlamydia and HPV-related anogenital cancers are examples of STIs associated with serious long term complications. European and North American nations have adopted asymptomatic screening for most of these STIs, and in many cases have experienced notable reductions in the STIs and their long term complications. Examples include maternal syphilis screening to reduce adverse pregnancy outcomes, and Pap smear screening to reduce cervical cancers related to HPV. North America and some European nations are also conducting chlamydia screening for young women in order to reduce STI-related infertility; however, the success of this program is yet to be determined. Asymptomatic screening appears to be most successful when attached to existing, facility-based programs (e.g., as part of routine antenatal care, or part of routine family planning services).

For developing world settings, at least two situations exist in which asymptomatic screening may avert substantial STI-related morbidity and mortality among women or infants, syphilis screening in pregnant women and cervical cancer screening.

Syphilis screening in pregnant women. As noted earlier, maternal syphilis often leads to fetal loss, stillbirth, neonatal death or debility, or congenital syphilis. Screening for pregnant women is a highly cost-effective intervention (Table 2) supported by numerous research studies (Hira et al., 1990; Jenniskens et al., 1995; Fonck et al., 2001; Walker et al., 2002; Terris-Prestholt et al., 2003; Peeling et al., 2004; Vickerman et al., 2006a). Some experts have pointed out the irony of the widespread adoption of other, more costly child-survival programs in settings where maternal syphilis still leads to substantial morbidity and mortality (Dallabetta et al., 2006); Peeling et al; 2004). Although integration of child survival programs to allow economies of scale seems to be an obvious solution, integrating programs is not always simple. Most nations already recommend universal syphilis screening in pregnant women; however, such screening is not always implemented or is done too late in pregnancy to prevent adverse outcomes. Among the chief problems in the past has been the lack of affordable and sufficiently accurate point-of-care diagnostic tests to allow infected women to be identified and treated at the time of their clinic visit (and not lost to follow up). This situation has changed. Several affordable, single antigen rapid syphilis test already exist, but are not yet widely used in settings where they could make the greatest difference (Peeling et al., 2004). The WHO STD Diagnostic Initiative (SDI) provides opportunities for nations to purchase rapid diagnostics such as these in bulk at very low

cost (www.who.int/std_diagnostics). At least two new dual antigen diagnostic tests are currently being field-tested, and preliminary data suggests these will be reliable and affordable.

Cervical Cancer Screening. Cervical cancer continues to account for an estimated 250,000 deaths annually of which most (80%) are in developing world settings. Cervical screening allows early detection of cervical cancer precursors, and thus treatment of these lesions before they progress into invasive cancers. Pap smear screening programs have resulted in precipitous drops in cervical cancer in nations, most notably in Europe and North America. However, Pap smear screening programs are costly, requiring trained cytopathologists to reliably read smears, intact transport services, high levels of follow-up and health referral networks to ensure effective treatment of suspicious lesions before they develop into cancers. In many developing world settings, none of these systems are in place. While an estimated 50 million Pap smears are done each year in the United States alone, in poor nations the majority of women do not have a single Pap smear during their lifetimes (Schmiedeskamp and Kockler, 2006). In light of this problem, cancer experts are discussing the feasibility and potential impact of more affordable screening options such as direct cervical visualization on cervical cancer in developing world settings. Such options may have an important impact on disease, but they will still require infrastructure that allows women to be referred for curative treatment. The recent development of safe and effective vaccines against carcinogenic HPV subtypes has enormous potential for reducing the incidence of cervical and other anogenital cancers – but its impact in developing settings is still unknown (See Core Component #5, Vaccines).

Core Component #4: Targeted STI Interventions for High Risk Populations

Targeted interventions refer to special STI prevention and treatment approaches directed toward vulnerable populations, core groups, bridging groups or other sub-populations with high STI prevalence, high rates of partner change or both and who do not access available STI management services. Some of the groups most vulnerable to STIs are also those who may be highly stigmatized or discriminated against (e.g., sex workers, men who have sex with men, sexually active adolescents). These sub-populations may also avoid STI management provided at official health care systems, because of real or perceived stigmatization, lack of trust in official systems, prior negative experiences or other reasons (Dallabetta et al., 2006). Other vulnerable groups (e.g., prisoners, detained populations, undocumented workers from other nations) do not have access to official health-care systems. Some groups, such as men and women engaged in transactional sex, adolescents, itinerant workers (miners, agricultural workers, truckers), refugees and other displaced populations may not seek health care services because they do not recognize they are infected with STIs, or because they lack the financial or other resources. The goal of targeted interventions is to expand the numbers of STI-infected individuals who receive high quality STI management services (Dallabetta et al., 2006). In most settings, and especially in low level epidemics where STI prevalence is concentrated among certain core groups rather than the general population, targeting prevention, diagnosis and treatment can have a strong impact on spread of STIs. The recent WHO Global Strategy for STI Control and Prevention notes that targeted interventions should be a priority in settings where HIV and other STIs are concentrated in high risk populations, although not to the exclusion of education and other prevention and care services for the general population (WHO, 2006a).

Targeting Core Groups. It has been noted that "the labeling groups as 'core' can produce stigma, [however] the concept is intended to be epidemiological rather than moral or social" (Mayaud et al., 1998b). In settings where core groups are not easily identifiable or approachable certain types of targeting could further stigmatize them (e.g., street-based outreach for sex workers). One approach to address this concern has been the use of peer-educators to conduct the outreach programs, either

providing services themselves, or referring their contacts to specialized services. Another approach has been to develop specialized services (e.g., dedicated sex worker clinics; adolescent clinics). The distinctive aspects of such targeted interventions may include dedicated, user-friendly clinical services, with specially trained providers who provide professional and confidential services that are conveniently located (perhaps even using mobile units).

Efficacy of Targeted Interventions. Evaluations studies have suggested mixed results about the efficacy targeted STI intervention approaches; however, true evaluation can be difficult because of the complexity of various approaches and the difficulties of ensuring the integrity and quality of the interventions (Manhart and Holmes, 2005). An early example of an effective, targeted intervention for sex workers was Thailand's 100% condom use program for brothel-based sex workers, which resulted in significant reductions in STDs as well as HIV in the 1990s. The success of this intervention on reduction of STIs and HIV may have been the result of the structural changes in laws and policies of brothel-owners, as these were rigorously enforced by police, as opposed to individual behavior changes among the sex workers. A number of other interventions aimed at sex workers, often using rights-based approaches, have shown reductions in STDs and in some cases declines or maintenance of low HIV prevalence (Vuylsteke et al., 2003).

Special Case of Adolescents. Adolescent women are at particularly high risk for STIs and are often unable or unwilling to access official health care for a variety of reasons (see Box 2). The 2006 WHO Strategy makes particular mention of the importance of developing and evaluating acceptability and effectiveness of specialized clinical and prevention services for adolescents, perhaps incorporated into other programs of interest (WHO, 2006a). Some recent examples of innovative services that seem acceptable to many adolescents have utilized skills building interventions around condom use or negotiating condom use with partners, sometimes using condom videos (Warner et al., 2006) or internet interventions (Rietmeijer et al., 2003).

High Risk Men. Men whose work requires them to be on the move (e.g., truckers) or work away from home (e.g., miners, migrant workers), or who are clients of sex workers are at high risk for contracting STIs including HIV and also at risk for transmitting disease to regular sex partners. Many men do not utilize public sector primary care systems for STI care, although they may seek treatment of symptoms with private sector or with alternative providers (e.g., traditional healers, pharmacists) (see Box 5). The recent WHO Global Strategy promotes "male involvement, male motivation and services for men" as one of five new technologies for a strengthened response (WHO, 2006a). Some examples of targeted interventions effective in providing STI prevention and treatment for high risk men include programs that train pharmacists in quality STI management strategies and use of pre-packaged STD kits. Facilities serving high risk men could also provide opportunities to support other prevention strategies, including STI treatment for symptomatic men and STI screening (e.g., if men are provided STI screening and treatment prior to surgery) as well as male circumcision. Additional prevention services that could be included at these health facilities aimed at accessing high risk men include on-site HIV testing and counseling, condom provision and education, specific behavior change interventions aimed at risky sexual practices – each of which would promote prevention and control of STIs in addition to HIV prevention.

Men Who Have Sex with Men (MSM). MSM are at behavioral and biologic risk for other STIs as well as HIV, but are often difficult to access for STI and HIV prevention or control. Depending on the national or local context, cultural or societal norms or laws may affect men's ability to be open about homosexual behavior, to access services or to socialize. MSM living in rural areas may be especially isolated. Some men may have female as well as male partners, and may not self-identify as

homosexual or bisexual. A number of targeted approaches have been effective in reaching MSM in various settings, including models that use popular opinion leaders, peer educators or role models, entertainment venues and (more recently) the internet (Mimiaga, 2006; Bowen et al., 2007).

HIV-Infected Persons. HIV-infected individuals have behavioral as well as biologic risk for other STIs and, if co-infected with other STIs, are at high risk of transmitting HIV to others. Individuals who are referred into HIV clinical care are an unusually accessible group because they are already participating in the established health care delivery system; it is important not to miss any opportunity to appropriately intervene. Several experts recommend all patients in HIV clinical care have initial (and possibly periodic) screening for those STIs most associated with HIV transmission (e.g., syphilis, gonorrhea, and in some settings chlamydia, trichomonas and HSV), and that women have cervical cancer screening (Centers for Disease Control and Prevention, 2003).

Core Component #5: Preventive Vaccines

Vaccines provide primary prevention against the specific agents targeted, preventing any of its long term sequelae and – if widely enough practiced – allowing the potential for reduction (or even elimination) of the agent in the community. In the last 2 decades, successful vaccines have been developed for HBV and HPV, and may be on the horizon for HSV-2.

HBV Vaccine. A HBV vaccine has been available since 1984, safety and efficacy rigorously documented, and since that time inexpensive recombinant hepatitis B vaccines are increasingly available in most of the world. Among those getting the full 3-dose series, about 95% of children and 90% of adults develop protective antibodies (Szmuness et al., 1980). The substantial morbidity and mortality associated with chronic HBV, described earlier, provides a compelling economic rationale for its widespread use – particularly given that the full series costs as little as USD 3 (Table 2). WHO has recommended since 1992 that all nations include HBV vaccine in their routine infant immunization schedules; however, in 2003 global coverage of eligible infants was estimated at 42% or less (WHO, 2004). The long latent period between infection (during birth) and adverse health outcomes is probably the critical factor leading to the underutilization of this important vaccine, and inclusion of the vaccine as part of routine infant immunization schedules has been recommended of high priority for any setting with substantially high HBV prevalence. *HPV Vaccines.* Two separate vaccine against the HPV subtypes most commonly associated with cervical cancer (3-dose bivalent vaccine against 2 subtypes) or cervical cancer and genital warts (3-dose quadrivalent vaccine against 4 subtypes) have recently been developed, and both rigorously studied and found to be safe and effective in preventing persistent infections and cervical dysplasia. (Szmuness et al., 1980; Koutsky et al., 2002; Villa et al., 2005). In 2006 the U.S. Advisory Committee on Immunization Practices recommended routine HPV vaccination for females 11-12 years of age and catch up vaccination for females 13-26 years of age who had not been vaccinated previously or who had not completed the full vaccine series, with other industrialized nations expected to follow. A full 3-dose vaccine series is still expensive (~ $350), and the utility of the vaccine among women with HIV-infection is still unclear. However, even expensive interventions have the potential to be cost-effective or even cost-savings in nations with very high rates of cervical cancer and where infrastructure for cervical cancer screening (also expensive) is not in place because of substantial prevention to premature mortality among women (Table 2). As vaccine prices fall, cost-effectiveness will improve in a number of settings and this intervention will need to be seriously considered in STI control program.

B. Supportive Elements for STI Prevention and Control

While not strictly core components, several additional elements should be in place to strengthen STI prevention and control programs, such as adaptation of normative guidelines, training and information networks, commodities logistics, laboratory support, surveillance and operations research. Additionally, a supportive social and political environment, brought about by supportive leadership and advocacy around STI prevention and control, although not strictly essential, goes far in ensuring STI programs persist despite the prejudices associated with sex and associated disease. Six supportive elements are:

Supportive Element #1: Leadership and Advocacy

Most societies have some prejudices associated with sex and associated disease. In many countries, restrictive policies or laws may adversely affect STI/RTI prevention and control efforts (Dallabetta et al., 2006). For example, some national or local policies restrict access of women or youth to services or require spousal or parental permission for exams and treatment. Some limit access to preventive measures such as condoms to adolescents or single women. In some settings, laws exist that prohibit diagnosis and treatment of STIs by health care providers other than physicians or that encourage clinic-based, laboratory-dependent or physician managed services exclusively, resulting in restrictive access to STI services for some highly vulnerable populations (e.g., women, adolescents, sex workers) (WHO, 2006a). Leaders may give low priority to STI control because they lack sufficient understanding of the magnitude of disease burden, associated sequelae or potential economic consequences related to STIs. Consequently, budget allocations for STI programs and drugs may be low relative to other diseases, even in settings experiencing high STI prevalence and substantial associated morbidity. Sector-wide approaches for donor aid to the whole health sector (rather than to specific projects) allow health ministries to determine national priorities, but also mean that countries which have accorded little importance to STI/RTIs in their health budgets in the past are likely to continue to do this (WHO, 2006a). Additionally, although most nations have developed broad, multi-sectoral responses to HIV, many have yet to develop formal strategies for the prevention and control of other STIs and RTIs. Insufficient attention to STIs because of prejudice or lack of information can also result in lack of a formalized, national control strategy, limited private (or even public) sector commitment to STI care, inadequate training of providers, exclusion of effective antibiotics on essential drug lists, or tariffs that make importation of essential drugs or commodities costly or difficult (Dallabetta et al., 2006). Developing a supportive social and political environment for STI prevention and control, despite the prejudices associated with sex and associated disease, can be an important means of ensuring program success and sustainability.

Commitment and Advocacy from Leaders around Sexual Health. As one of its four Prime Objectives, the most recent (2006) WHO Global Strategy for STI Prevention and Control calls for national leaders to ensure that "policies, law and initiatives related to provision of STI care are non-stigmatizing and gender-sensitive within the prevailing socio-cultural context" and enumerates as an "Essential Element in the Response" a review of policies, laws and regulations regarding STI control to ensure that they are non-punitive, non-coercive and contribute toward the aims of STI prevention and control services (WHO, 2006a). In settings with high STI prevalence, commitment of policy makers helps provide a foundation for a strong and effective national response. Coordination of representatives from related health sectors (i.e., reproductive health and family planning, maternal child health, and HIV/AIDS programs), along with stake-holders from public and private sectors within and outside the health systems can help ensure a multi-sectoral response towards STI prevention and control that is strong and sustainable. Ideally, these partners would be an integral part of a process developing a formal, comprehensive national STI prevention and control strategy with clearly defined, time-phased goals

and objectives, and that outlines responsibilities for carrying out different elements of the strategy and that covers all population groups for which interventions are required. Inclusion of all partners ensure that health programs with similar interests or clients (e.g., STI, HIV, Reproductive Health, Family Planning) promote mutually beneficial outcomes and develop program efficiencies, and that sectors outside health (e.g., finance, trade, justice) understand how STIs affect societies and economies and support the national program accordingly. Strong leadership and advocacy around sexual health also allows a supportive environment that allows communities the ability to educate young people about HIV and STIs and contraception, ways that that STIs and HIV are transmitted between partners, and effective ways that they can protect themselves against STIs/HIV and undesired pregnancies, whether through abstinence, delayed sexual debut, mutual monogamy or consistent and correct condom use.

Supportive Element #2: STI Surveillance

Surveillance systems allow clarification of disease burden, monitoring of STI trends useful in evaluating program impact over time, and help in projecting resource needs. WHO's 2006 Global Strategy for STI Prevention and Control indicates that many low-and moderate income nations lack sufficient surveillance infrastructure, clearly defined procedures, human and other capacity, or funding to effectively advocate for STI prevention and control or design and implement their national strategies (WHO, 2006a). The 2006 Strategy notes that the basic components of STI surveillance (that ought to be done in any country) include:

- *Case-reporting by syndrome or etiological report (per availability) disaggregated by age and sex*. Separate data among men and women, and among very young adults (15-24), other reproductive aged adults (25-44) and mature adults (older than 44 years) are important in understanding the dynamics of specific STI syndromes within the population and how well services are delivered and organized. As possible, the formal and informal private sector (e.g., private physicians, pharmacists) should be included in the reporting system (see Box 5). WHO notes that incentives to encourage reporting, such as accreditation or other strategies may aid in this effort (WHO, 2006a).
- *Prevalence assessments and monitoring to identify and track the burden of symptomatic and asymptomatic STIs in defined populations*. Useful assessments can be carried out by means of special surveys in targeted populations or by linking to routinely conducted (e.g., Demographic and Health Surveys, HIV surveillance) or other special surveys. Over the past decade nucleic acid amplification tests for STIs have become much less expensive, and use non-invasive samples (e.g., urine, self-administered vaginal swabs) that do not require difficult handling or transport procedures can be collected even in remote field settings. Because these tests are highly sensitive and specific, information from a relatively small samples from groups with high STD prevalence could provide meaningful information on STI trends and help guide treatment protocols (WHO, 2006a)
- *Linking of related program data*. Data from screening or case-finding programs conducted in other health divisions (e.g., syphilis screening in ANC clinics, stillbirth or cancer surveillance by hospitals, Pap smear screening in family planning clinics, HBV vaccine coverage by immunization programs) would ideally be linked to STI program data. Formal collaborations between programs ensure collection of critical program information (e.g., gestational age in maternal syphilis screening) and sharing of mutually beneficial information.
- *STI etiologic studies.* Periodic (e.g., every five years) assessment of STI etiologies (e.g., etiologies of genital ulcers) using reliable and quality-controlled laboratory testing allows updating of syndromic treatment algorithms or etiologic approaches recommended in national guidelines as well as selection of appropriate antibiotics to be included on essential drug lists.
- *Selected antimicrobial resistance monitoring*. Antimicrobial resistance monitoring for specific pathogens (e.g., gonorrhea, chancroid) ensures appropriate antibiotic selections in national

guidelines, planning around drug procurement, adaptation of provider training and treatment algorithms, and early warning about important trends that may affect prevalence and costs. Depending on available resources, this can be done locally, nationally or regionally or even international groups working on surveillance of antimicrobial resistant organisms.

Support Element #3. STI Laboratory Capacity

The importance of sufficient laboratory capacity to support core program components, even in low-income settings, is often overlooked; however, as noted in the above discussion of surveillance, is important in guiding effective national programs. Many settings have limited resources, or sufficiently trained staff, to allow strong STI laboratory capacity, and the promotion of syndromic case management approaches rather than diagnostic tests may have exacerbated this. Although extensive laboratory capacity is not strictly necessary at all local levels, capacity should exist at the national level to ensure quality of lower level services, support surveillance and ensure adequacy of treatment protocols. This may entail periodic isolation and antimicrobial resistance testing of N. gonorrhoeae or other pathogens. Reference facilities can provide quality control for lower level laboratories, and can aid programs in diagnosis and treatment decisions with difficult cases unresponsive to first courses of treatment at lower health care levels.

High quality laboratory systems require development of clearly defined procedures and appropriate training for laboratory personnel. Internal quality control guidelines for specific laboratory procedures must be established and adhered to, and laboratory participation in external quality assurance programs is encouraged. Laboratories should be established and strengthened at regional or national elvels, where feasible at local levels. Such a network of laboratories can work together to strengthen STI services nationally and regionally.

Supportive Element #4: Training

Training ensures that adequate STI management (including diagnosis, treatment and prevention) standards are met by all members of the health care team, whether they are clinicians, pharmacists, laboratory personnel, receptionists or supervisors located in the public or private, official or even informal sectors.

Beyond the Clinical Encounter. Adequate training does not involve only the biomedical aspects of STI diagnosis, treatment and prevention; it includes education about how provider attitudes and beliefs and social stigma affect STI prevalence, means of ensuring confidentiality of information and effective ways of interaction that do not alienate the patients (FHI, 2001). Basic training is ideally provided to every professional involved in any aspect of STI management – taking into account the role and responsibilities of the provider to ensure the training is pertinent. For example, if health care providers delivering antenatal care or family planning services are expected to provide STI care in some instances, their training should reflect this. Similarly if physicians are expected to provide prevention interventions such as personalized risk reduction counseling, training should be included in these areas. Training alternative providers (e.g., traditional healers) in risk reduction counseling, correct and consistent condom use and partner notification strategies may be a way to expand service provision to populations who do not access official health clinics. Training of supervisors is important to ensure they are familiar with the programs under their oversight and also, as needed, to reorient skills to being supportive and constructive in their feedback to providers, focused on constantly improving program quality rather than judgmental and fault finding. Although basic training provides a foundation for effective program provision, the need for refresher training or other continuing education should be based on results of program monitoring, evaluation or both (Dallabetta et al., 2006).

Innovative Training Models. Traditionally, training has involved on-site approaches. However, innovative models such as distance and computer assisted learning may be helpful in some settings. Professional associations can help promote training opportunities through continuing medical education, conferences, journal articles and newsletters. Since training requires time away from clinical work and involves substantial time and costs, some programs have tried to minimize costs by bundling of training programs when appropriate (e.g. training on syndromic management, confidentiality of services, respect, risk reduction counseling, condom demonstration).

Revising Professional Curricula and Other Strategies. Professional schools (e.g., medical, nursing, pharmacy schools) and other educational institutions can play an important role in furthering an effective national response against STIs. Syndromic STI/RTI management is often poorly implemented by physicians who were trained in etiologic diagnosis using laboratory testing and thus tend to view it as "unscientific." Inclusion of syndromic STI/RTI approaches in medical, nursing and other professional school curricula, including their overall rationale and utility and the use of flow charts, could go a long way in increasing its successful application by physicians and other clinical providers. Pharmacists can also be educated to provide effective syndromic management (Green et al., 1998; Garcia et al., 1998; Tuladhar et al., 1998). Inclusion of STI prevention and control strategies in professional school curricula may also help support partner management, which is often poorly understood by clinicians, and may help ensure that providers prescribe drugs that are available in the community, affordable for the patient, require the fewest doses for the shortest possible period of time and have the fewest side effects. (Dallabetta et al., 2006) Providing training on the burden of STIs and other RTIs as well as HIV, their significant morbidity and potential prevention and control strategies as a routine part of public health, laboratory and pharmacy school curricula is a structural intervention that may have much greater sustainability than the current strategy of repeated on-site training for clinicians involved in STI management. Incorporating routine, periodic updates on STI management as part of professional recertification or licensing programs is another structural intervention that has been successfully applied in some nations (Dallabetta et al., 2006) .

Supportive Element #5: Monitoring and Evaluation

Quality assurance monitoring and evaluation of ongoing programs, along with surveillance, are the basis for establishing and sustaining STI control programs and keeping them relevant and effective (Dallabetta et al., 2006)**.** This assumes effective program management.

Program Management. Effective program management assumes establishment of local STI program goals and objectives and development of needed protocols, standard performance targets or annual and semiannual review sessions. Ideally, these should be consistent with national protocols. Administrative structure outlined on paper, with clear lines of communication, supervision and responsibility clarify roles and responsibilities and help support a common goal. Similarly, at local levels, clearly defined procedures manuals should be developed for health service sites help clarifying responsibilities and procedures and ensure programs are conducted as planned. Periodic (e.g., semiannual) reviews that link referral centers and local programs are generally more meaningful and motivating to the health care team. Supportive supervision need not be confined to the public sector. Linking the private sector, including pharmacists and other medicine dispensers as well as clinicians, is helpful in supporting their engagement and commitment to providing good quality of services, and can facilitate reporting to surveillance system (see Box 5). Engagement of the private sector can often be achieved by including them in training opportunities (See Training).

Program decentralization and privatization in many nations have led to challenges in developing processes that ensure high quality care for the population in the private as well as public sector. Some successful strategies to support program standards and quality have been identified, including:

- National guidelines. Guidelines for STI case management can ideally be disseminated to all STI care providers – formal and informal, whether in the public or private sectors.
- Licensing, certification and accreditation. This strategy helps maintain quality, safety and geographical distribution of health-care systems – and could apply to pharmaceutical and health-insurance industries as well as health-service industry (WHO, 2006a). Professional associations and other self-regulatory bodies whether function outside of or in partnership with government can be an essential element of regulatory and quality control. Peer review and self-regulation (e.g., continuing education credits) can be useful, and may be particularly attractive to providers if linked to financial incentives or access to better working conditions (WHO, 2006a).
- Referral centers. Establishment of referral centers for complicated STI cases where diagnoses can be reviewed and confirmed or enhanced improves overall program quality. Ideally, efficient referral protocols should be included as part of standard management protocols, as drop outs of referred patients are common. Special care should be taken not to send patients to long and expensive journeys to centers that have little to offer the patient.

Program Monitoring. Several quality assurance monitoring strategies have been successfully applied to promote the goals of specific STI program (or core components) and many are appropriate for developing as well as developed world settings, such as:

- Collecting limited, critical program indicators or "data for action," evaluating it routinely providing timely, constructive feedback to lower levels: Local programs are more productive and goal-focused when they are sure they understand the important outcomes on which they will be judged, and are more open to suggestions if they also receive positive feedback for a job well done.
- Direct observation and immediate feedback: Although expensive and time consuming for managers, this is the only sure way of knowing that programs are implemented as conceived and is essential information in understanding overall program strengths and weaknesses. WHO program indicators PI-6 and PI-7 have been found to be excellent measures for evaluation, but are often not implemented by managers because of lack of funding for travel or lack of management staff. Some settings have had success using direct observation can also be done by simulated clients, staff posing as clients who evaluate service delivery.
- Ongoing training: Training is critical in ensuring providers are aware of up-to-date STI management issues, drug therapies, and management strategies and is described under Support Component #4.
- Other quality assurance strategies: Some STI programs have employed other means of ensuring high quality of program such as periodic client satisfaction surveys, case or "referral" conferences in which providers discuss difficult (or routine) cases and provide feedback to each other. Consultations and communication between health centers and referral centers by means of visits, radio or telephone links provides new information and also facilitates professional trust and confidence in the system and in peer professional networks.

Program Evaluation. Evaluating program strengths, weaknesses and impact is best done using a combination of strategies:

- Routinely collected data evaluating quality of STI programs and availability of essential STI drugs and commodities should be used to evaluate program adequacy and plan future needs.

- Special studies such as outbreak investigations for specific STIs (e.g., lymphogranuloma venereum [LGV] in men who have sex with men, highly resistant gonorrhea) can provide important new information.
- Behavioral and STI biologic surveillance data collected (for example) as part of second generation HIV surveillance can help clarify where prevention and control of other STIs is currently strong or weak, and specific population vulnerabilities in the future.
- The phase of the HIV epidemic locally has implications for STI priorities including surveillance activities, and existing HIV systems can provide STI programs information on determinants of HIV-STI epidemiology, the relationship of HIV to under-detection and underreporting of other STIs and identification of important core groups and bridging populations – as these populations are likely similar for HIV and other STIs.
- Special operational research studies are helpful to provide data on how programs, particularly core components are working in reality, how well they are maintaining existing standards and guidelines, and their impact on STI control and prevention in the community.

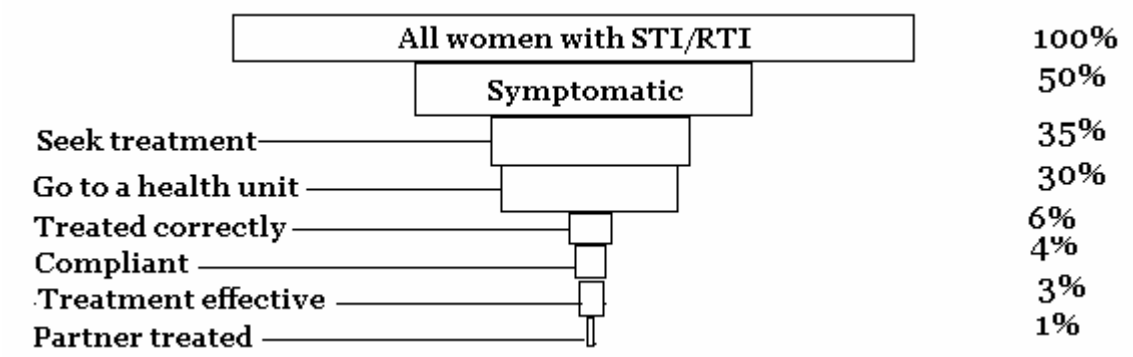
Supportive Element #6: Community Education

Educating communities, particularly young people at risk, about STIs and ways to prevent them is a primary prevention strategy, and an example of a structural or environmental change aimed at disease preventnion. Some noted experts believe that individual behavior change strategies for high risk persons (e.g., the risk reduction counseling and condom promotion employed during routine STI management or as part of targeted interventions for high risk groups) may not have as great an effect on reducing disease prevalence in a community as community-wide behavior change strategies that seek to change overall community norms (G. Rose). Such community-wide changes "shift the bell curve" (disease risk in the entire population) to the left, bringing large benefits to the community, although less benefit to individuals. Many examples of community education models exist, such as social marketing campaigns and school-based educational strategies for children or adolescents.

C. Beyond Clinic-Based Care: Expanding STI Control Efforts

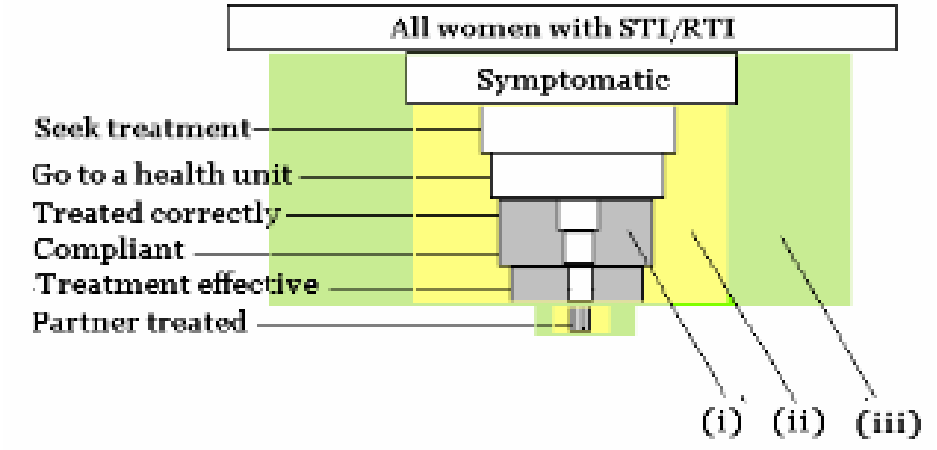
As noted earlier, for curable STIs, treatment is the most effective prevention method and thus high quality clinic-based STI management is a cornerstone for STI control. Effective diagnosis and treatment of curable STIs cures infections and minimizes adverse outcomes in the individual, and reduces further spread of STIs and subsequent STI-related morbidity in the community. However, case management alone has limitations that are graphically illustrated by an STI management model that was developed using real data from rural African nations. Figure 5a describes STI prevalence in the community, the series of steps needed to ensure effective treatment and the proportion of STIs that are missed (not effectively treated) at each step.

Figure 5a. Piot-Fransen Model of STI Prevalence and STI Case Management



The model illustrates that most individuals with STIs, even those with symptoms, never reach a health unit that could provide effective diagnosis and treatment. Even among those who reach a health unit, many are not treated correctly, do not use drugs correctly enough for cure, experience treatment failure, or are re-infected because sex partners were not treated. These issues can be addressed, however. Figure 5b shows the potential effects of (i) well conducted clinic-based case management, which requires symptomatic persons seek and obtain effective treatment, (ii) the additional benefits that asymptomatic screening, effective partner management and targeted outreach and community-based programs can provide, (Hudson, 2001) and (iii) yet additional benefits primary prevention, whether using an effective vaccine or widespread community education and promotion of abstinence or safe sex practices including condom use. Clinic-based STI management alone will not control STIs in a community. Rather, clinic-based management should be incorporated into an organized program involving the other essential public health elements.

Figure 5b. Potential Effects of Additional Control Strategies used with STI Case Management



D. Prioritizing Program Delivery Based on Resource Availability (Annex A; Table 2)

Nations will vary in terms of the resources and personnel available and – if resources are limited – may need to prioritize implementation of various elements of a national or local STI prevention and control program. Table 2 in Annex A summarizes priority activities and the appropriate level of intervention

for STI prevention and control in countries with limited resources as well as those with more resources available. Whenever possible, it is desirable for community-based programs to focus on local epidemiology and thus encourage STI surveillance. Surveillance could employ case reporting of key STIs (using either syndromic or etiologic reporting, based on local practices) and need not be extensive (e.g., could use sentinel sites or sentinel populations) or excessive (e.g., could be conducted every three to five years rather than annually).

Additionally, standard practices for STI management, whether using etiologic or syndromic diagnosis) should be addressed early. Syndromic approaches were specifically developed to address settings with limited resources, but must be locally validated in order to ensure drugs available and prescribed are effective in treating prevalent STIs. Because of their links to HIV, prompt identification and treatment of genital ulcers should be particularly promoted, and genital ulcer etiology evaluated (e.g., need to include therapies for chancroid, HSV-2 in treatment algorithms). When resources are scarce, interventions that take advantage of existing infrastructures are usually easiest to manage. Maternal syphilis screening at the first-antenatal visit, with prompt treatment of positives, for pregnant women in antenatal care is another limited and cost-effective intervention that for most resource-poor settings should be universally implemented. Similarly, scaling up STI prevention and treatment programs for HIV-infected persons in clinical care is an urgent priority as an STI-HIV co-infection is a marker of enhanced likelihood of HIV transmission biologically as well as behaviorally.

For nations or local settings with stronger resources, other core or support STI program components can be phased in as possible, including targeted interventions for high-risk and vulnerable populations, age-appropriate sexual health education and services, promotion of partner treatment and prevention of re-infection (which, while considered a core STI program component, can be difficult and costly to implement) and scaling up of effective STI vaccines. The recent WHO Global Strategy for STI Prevention and Control (2006) has recommended a strategy for prioritizing implementation of essential STI prevention and control components in resource limited settings, recommending a series of "Priority 1" strategies that should be implemented in all settings, regardless of resources, and "Priority 2" strategies that should be implemented if resources exist (Table 3) (WHO, 2006a).

IV. Integration of Services

The growing health and economic burden of STIs, HIV, and population growth in resource-poor countries have led many organizations to reconsider traditional vertical approaches to health programs. Men and women of reproductive age, even those living in stable couple relationships, are at risk for HIV, STIs, and unintended pregnancies. For example in Uganda, 60% of persons found to be HIV-positive in couples counseling and testing were in stable couple relationships with a seronegative partner. Studies in Kenya, Zimbabwe, Haiti, and Tanzania found that more than half of the women accessing HIV counseling and testing services did not want to get pregnant, and the majority were not using a contraceptive method. The interaction of these sexually-transmitted conditions has fuelled an interest in advancing integration of services at point-of-care to increase patient access, improve efficiencies, reduce missed opportunities for prevention, and improve health outcomes. Though vertical programs have the benefit of increased focus and expertise for a particular health issue, more often men and women presenting for specific services leave with important health risks left unaddressed. Integration of services holds the opportunity for HIV, STIs, and reproductive health services to be delivered at a variety of entry points into healthcare systems, including HIV counseling and testing centers, antenatal care, family planning, primary care services, and specialized STI treatment or HIV clinical care.

Integration of HIV, STI, and reproductive health services has been identified as a priority in a number of prominent forums. The 1994 International Conference on Population and Development in Cairo released a consensus statement supporting comprehensive reproductive health services, including HIV and STIs, with emphasis on the use of existing, mainstream, primary healthcare services of maternal and child health and family planning services (www.iisd.ca/Cairo.html). USAID issued technical guidance for field programs on family planning/HIV integration and has a website and workgroup dedicated to integration issues and case studies. A high-level congress of the international donor community held in Glion, Switzerland issued a call to action for integration of HIV and reproductive health. The Center for Strategic and International Studies (CSIS) issued a document outlining strategic opportunities for integration of reproductive health and HIV/AIDS programs in the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). A 2007 Technical Consultation on elimination of congenital syphilis as a public health problem encouraged that congenital syphilis elimination be approached through integration of the variety of antenatal services proven effective in reducing infant and maternal morbidity, and advised against a vertical programs that might shift emphasis away from other needed antenatal care components.

Other interactions exist between STIs, HIV, and reproductive health that lend themselves to a more integrated approach:

- HIV clinical care provides an important opportunity to screen for other STIs whose presence represents biological and behavioral risk for HIV transmission, and to promote effective contraceptive methods.
- STI syndromic management should include promotion of HIV testing, risk reduction counseling or education, and promotion of contraception when applicable.
- Although STI and HIV screening among women attending family planning services may not be cost-effective in low prevalence settings, in high prevalence settings, these services provide access to sexually active women at risk;
- Recent findings in three randomized trials indicate that there are substantial benefits to HIV prevention through male circumcision. This new research will lead to expansion of circumcision services for men and such services provide an excellent opportunity to promote sexual health among men through screening for HIV and other STIs, counseling and education on STIs, and effective contraceptive practices.

V. Future STI Prevention Initiatives and Opportunities

Several ongoing STI research areas hold promise for the future. In 2006 WHO released a new *Global Strategy for STI Prevention and Control* which outlined recommended program focus for the next 10 years. In the Strategy, two global initiatives -- the elimination of bacterial causes of genital ulcer disease and elimination of congenital syphilis as a public health problem – were prioritized for action now, given both are associated with serious health consequences that could be averted with generally readily available and affordable interventions. Additionally, evaluation research for the WHO STI Diagnostics Initiative continues to identify high quality and affordable rapid, point-of-care tests that will support STI control even in settings with limited infrastructure and resources. Recent prevention research around some biomedical interventions (e.g., HPV vaccines, male circumcision) has been remarkably fruitful and exciting, other areas (e.g., vaginal microbicides) are proving more difficult in identifying safe and effective interventions, and some areas (e.g., herpes treatment prevention of HIV transmission and acquisition) have yet to be clarified – but will in the next one to two years.

A. WHO Global Strategy (2006)

The recently published WHO report, *Global Strategy for the Prevention and Control of Sexually Transmitted Infections: 2006-2015 – Breaking the Chain of Transmission,* developed using an inclusive and broad consultative process within the WHO Secretariat and WHO Member States as well as external partners, moves beyond earlier reports to emphasize the action steps needed for an accelerated response to STI control (WHO, 2006a). Calling for improved sexual and reproductive health as defined in the UN International Conference on Population and Development (1994), the strategy has two broad components: technical and advocacy. The technical content of the report emphasizes a public health approach to STI control focusing on delivery in primary health care settings. New recommendations include the need for HIV and STI programs to integrate whenever possible (e.g., recommendation of HIV testing at every STI clinical encounter), the importance of focus on marginalized and vulnerable populations (e.g., adolescents) and the importance of monitoring and evaluating program quality. The advocacy section provides recommendations to program managers on mobilizing the political commitment necessary for an accelerated community response. Recognizing that nations vary in their ability to respond to the strategy, action steps for provision of interventions are prioritized, and national-level targets recommended (Table 3).

B. STI Diagnostics Initiative

The STI Diagnostics Initiative (SDI) is an externally funded program of diagnostic development, partnering with UNICEF, the United Nations Development Programme, and the World Bank and located in the WHO Special Programme for Research and Training in Tropical Diseases (TDR) (http://www.who.int/std_diagnostics). The SDI's mission is to promote the development, evaluation and application of diagnostic tests for STIs that are appropriate for use in primary health care settings in developing world setting. In describing desire test capabilities, the Initiative uses the acronym "ASSURED": tests should be *affordable* by those at risk for infection; *sensitive* (i.e., with few false negatives); *specific* (i.e., with few false positives); *user-friendly* and simple to perform, ideally able to done in four or fewer steps and with minimal training, *rapid and robust* to enable treatment at the first visit and not requiring refrigerated storage, *equipment-free* and *easy* to collect, preferably with non-invasive specimens such as urine or saliva, and with test results *delivered* at point-of-care to patients.

The current priorities for the SDI are the development and evaluation of rapid point-of-care tests for *N gonorrhoeae* and *C trachomatis* in order to improve treatment among women presenting with vaginal discharge and asymptomatic women at high risk (Mabey et al., 2001; Mabey et al., 2001; Mabey et al., 2004). Also prioritized are rapid POC tests for syphilis to aid in screening antenatal women at risk for congenital syphilis. Currently, the SDI website describes several high quality rapid treponemal tests for syphilis which are available at affordable rates (several under 1 USD) for developing nations through a WHO bulk purchasing mechanism. The initiative is also evaluating some new dual antigen, treponemal plus non-treponemal tests for syphilis, which would allow identification of infectious syphilis and add value to nations with current or recent high syphilis prevalence. SDI researchers observe that their biggest current challenge is to ensuring that adequate-quality, rapid tests are accessible to the developing country populations that need them most (Mabey et al., 2001).

C. Recent Prevention Research Findings

<u>HPV Vaccine</u>

One of the most exciting STI research developments in the past decade has been development of vaccines against HPV, the largest single cause of years of life lost to cancer in the developing world and a disease that, because it affects women in their most productive years, has a devastating effect on the well-being of families (Agosti, 2007). A new quadrivalent HPV vaccine has been proven safe and effective in preventing cervical cancer precursors associated with four common HPV subtypes, including the two most common carcinogenic HPV subtypes worldwide (HPV 16/18) (Future II Study Group, 2007). Earlier results from the bivalent vaccine (against HBV 16/18) demonstrated similar efficacy. The burden of HPV-associated disease has been well characterized globally, allowing policy makers from almost every nation to begin to consider the affordability and cost-effectiveness of HPV vaccine relative to other budgetary needs. Experts point out that the effectiveness of this vaccine in the field will require improved health systems for adolescents and environments that support government health care and vaccine initiatives – but this may be difficult given that programs targeting young women may be misconstrued as attempts to control fertility. With a current cost of $350 USD for the full 3 dose series, price is the greatest barrier to the introduction of the HPV, and subsidies will be needed for any role out of this vaccine in developing world nations. The Global Alliance for Vaccines and Immunization (GAVI Alliance) is a partnership of national ministries of health, WHO, the World Bank, donor agencies such as the Bill and Melinda Gates Foundation, the vaccine industry, non-governmental organizations and public health institutions that has provided technical assistance and monetary resources for vaccines in low-income countries. Although HPV vaccine is not yet part of GAVI's prioritized for support, it is hoped that with the help of this alliance HPV vaccines can begin to be rolled out in those countries that would most benefit (Agosti and Goldie, 2007).

Adult male circumcision. Particularly compelling recent HIV/STI prevention research has been the consistent findings from three randomized clinical trials in Africa (2006) that adult male circumcision can reduce new HIV infections by approximately 40-60% (Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007; US National Institutes of Health, 2006a; US National Institutes of Health, 2006b). The multiple observational studies showing a benefit of circumcision for heterosexual men in reducing their risk of HIV acquisition through sex with women were, clearly, correct. Communities are already implementing or scaling up mechanisms that would allow safe and affordable adult circumcision for interested men, often through use of specialized clinics.

As was the case with earlier observational studies, the circumcision trials also showed modest benefits of circumcision in reducing risk for bacterial STIs (although not HSV-2). Preparatory work is already underway to establish male circumcision programs as "male health" programs, in Africa. Adult men seeking circumcision will be or at least perceive themselves to be at high risk for HIV (and through the same risk, for other STIs), and thus such clinics have an opportunity of accessing the very men who are most difficult to access in current primary care settings and who have tended to seek care outside established health infrastructures. Integrated services could include STI and HIV screening, education and counseling around STIs and risk reduction (including promotion of correct and consistent condom use), contraception and other health issues (e.g., anemia, hypertension screening). Men identified as HIV positive could be offered on enrollment into HIV clinical care programs.

Vaginal Microbicides. Microbicides, chemical substances developed for topical use inside vagina (or rectum) to protect against HIV/STI, have been under study for several years. Although primarily targeted at preventing HIV, an "ideal" microbicide would also protect against other STIs and would help protect male partners as well as women (Minnis and Padian, 2005). Finding an effective agent has proven elusive for several reasons. For one, ensuring safety of the microbicide in the doses required to confer efficacy is problematic, and at candidate agents may actually confer risk if used in

certain formulations with very high doses. Additionally, evaluation can be difficult: ethically run clinical trials require the control intervention to include strong promotion of all available effective strategies, including provision and promotion of male latex condoms and risk reduction counseling. Under study conditions, high risk "control" populations who are consistently provided prevention support have often proven willing and able to apply these methods, reducing power to detect a meaningful prevention benefit for any new microbicidal candidate. Consequently, while these trials have greatly increased our knowledge about the risks and benefits of potential candidate agents and about the potential for personal behavior change and condom use among high risk women sanctioned to protect themselves as much as they can, as yet no microbicidal agent safe and effective against HIV and other STIs is available. Several candidate agents are still under investigation, and efficacy studies that are currently underway will be reporting results in the next several years (Alliance for Microbicide Development, 2006). Acceptable female controlled methods to prevent against HIV/STI are important because negotiation around use of the male latex condom is difficult for many women, particularly women outside the sex industry whose greatest HIV/STI risk is through their regular partner. Other methods besides microbicides are, such as the female condom (and possibly also diaphragms, cervical caps and sponges – although these appear to be most effective if used with a microbicidal agent) can also be useful for some women and are as efficacious as the male condom in protecting against HIV/STI (Minnis and Padian, 2005). Advantages to these barriers over the male condom are that they can be inserted before and left in place for up to 24 hours after intercourse, and thus offer protection for multiple coital acts, and they can be used without a partner's knowledge and may not require negotiation. The female condom is substantially more expensive than male condoms (pennies), however it is made out of a stronger material (polyurethane) that appears to be able to be safely reused if appropriately washed dried and stored (WHO, 2002b). A number of small studies from around the world have demonstrated reasonable acceptability of the female condom, especially among highly vulnerable women such as commercial sex workers (Elias and Coggins, 2001) and STD clinic patients (Artz et al., 2000).

Herpes treatment for HIV prevention. As noted earlier, clinical and research studies indicate that herpes antiviral therapy suppresses genital HSV-2 shedding, and that there is a strong link between HSV and HIV. Several clinical trials have recently or are currently investigating whether drugs that suppress genital herpes infection can reduce HIV transmission, including one large multi-national trial; and at least one large trial is evaluating whether HSV suppression can reduce HIV acquisition (Celum et al., 2005; Paz-Bailey et al., 2007b) (Weiss, 2004). The largest study evaluating the impact of genital herpes suppression on HIV infectiousness among discordant heterosexual couples is enrolling 3000 couples in which the HIV-infected partner is co-infected with HSV-2, hypothesizing that use of standard doses of twice daily acyclovir by the co-infected partner will decrease the frequency and extent of genital HIV shedding and thus, substantially reduce HIV transmission to the HIV-uninfected sex partner. Trial results are expected within the next 12 – 24 months. A partner study is evaluating effectiveness of similar, standard doses of acyclovir in preventing new HIV infection in HSV-infected, heterosexual women and men who have sex with men. This study is enrolling a similar number of participants, and is expected in 2010. Earlier, smaller trials have already reported a benefit of HSV suppressive therapy on reducing HIV shedding in co-infected individuals, and that episodic therapy reduces ulcer duration and HIV shedding from genital ulcers of symptomatic co-infected patients (Nagot et al., 2007; Paz-Bailey et al., 2007a). HSV vaccine trials are also underway with efficacy results expected in upcoming years.

Annex A. Tables: Table 1: Adverse Outcomes of STIs Occurring during Pregnancy and in Infants and Adult Women and Men

Adverse Pregnancy/Infant Outcomes	
Syphilis	**Infant:** Spontaneous abortion, stillbirth, preterm delivery, low infant birth weight, congenital syphilis
Chlamydia	**Maternal:** Ectopic pregnancy, maternal death, preterm rupture of membranes; **Infant:** Neonatal conjunctivitus, pneumonia, premature birth, low birth weight
Gonorrhea	**Maternal:** Ectopic pregnancy, maternal death, preterm rupture of membranes; **Infant:** Neonatal conjunctivitis, corneal scarring, blindness, premature birth, low infant birth weight
Trichomonas vaginalis	**Infant:** Low infant birth weight, preterm delivery
Cytomegalovirus	**Infant:** Primary infection of the newborn, hepatitis, sepsis, deafness, mental retardation, infant death
Genital Herpes Infection	**Infant:** Primary infection of the newborn, hepatitis, sepsis, infant death
Human papillomavirus (HPV)	**Infant:** Laryngeal papilloma
Hepatitis B virus (HBV)	**Maternal:** Vertical transmission to infants; **Infant:** Cirrhosis, end stage liver disease, primary liver cancer
Conditions in Adults	
Chlamydia	**Women:** Cervicitis, Bartholinitis, endometritis, salpingitis, pelvic inflammatory disease, chronic pelvic pain. **Men:** Orchitis, epididymitis, perihepatitis, urethral stricture, prostatitis. **Both Men and Women:** Infertility, proctitis, pharyngitis, Reiters syndrome, urethritis, perihepatitis (Fitz-Hugh-Curtis Syndrome), enhanced HIV risk – asymptomatic in up to 2/3 of cases, (LGV) ulcer or inguinal swelling
Gonorrhea	**Women:** Cervicitis, Bartholinitis, endometritis, salpingitis, pelvic inflammatory disease, chronic pelvic pain **Men:** Orchitis, epididymitis, urethral stricture, prostatitis **Both Men and Women:** Infertility, proctitis, pharyngitis, Reiters syndrome, urethritis, perihepatitis (Fitz-Hugh-Curtis Syndrome), disseminated gonococcal infection, enhanced HIV risk – asymptomatic in 2/3 (women) and 1/3 (men) of cases.
Syphilis	**Both Men and Women:** Primary ulcer (chancre), local adenopathy, skin rashes, condyloma lata, enhanced HIV risk; bone, cardiovascular (e.g., aortic disease) and central nervous system disease (e.g., optic atrophy, tabes dorsalis), death
Chancroid	**Both Men and Women:** Painful ulcers, inguinal adenitis, disfiguring lesions, tissue destruction, enhanced HIV risk
Trichomoniasis	**Women:** Cervicitis, vaginitis, vaginal discharge, vulvar itching, endometritis, salpingitis, probably enhanced HIV risk **Men:** Prostatitis, urethritis, urethral strictures, epididymitis, genital inflammation, infertility **Both Men and Women:** Asymptomatic infection
Granuloma Inguinale (Donovanosis)	**Both Men and Women:** Nodular swellings and ulcerative lesions of inguinal and anogenital areas
Other bacteria (e.g., Mycoplasma, Ureaplasma)	**Women:** Bacterial vaginosis, pelvic inflammatory disease, possibly enhanced HIV risk **Men:** Urethral discharge
Genital Herpes Infection	**Both Men and Women:** Anogenital vesicular lesions and ulcerations, recurrent genital ulcers, cervicitis, proctitis, chronic pain, arthritis, central nervous system involvement, hepatitis, meningitis, enhanced HIV risk
Human papillomavirus	**Women:** Vulval and cervical warts, cervical dysplasia and carcinoma, vulval carcinoma **Men:** Penile warts, penile carcinoma **Both Men and Women:** Anal warts, anal carcinoma
Hepatitis B virus	**Both Men and Women:** Acute hepatitis, liver cirrhosis, end stage liver disease, hepatocellular cancer
Kaposi's Sarcoma associated herpes virus (HHV type 8)	**Both Men and Women:** Aggressive type of cancer in immunosuppressed persons
HIV	**Both Men and Women:** HIV-related disease, opportunistic infections, AIDS, death

Table 2: Operational Guidance for Implementation of Essential STI Prevention and Control Activities in Resource-Limited Settings

Priority 1: Should be implemented in all nations
Priority 2: Should be implemented if resources exist

Priority 1 Activities and [Level of Intervention]	Indicators	Suggested National-Level Targets[2]
1. Build on success. Scale up STI diagnosis and treatment (Use syndromic management where diagnostic resources are limited.) [Any clinic providing family planning and HIV services, including STIs.]	1a). Proportion of primary point-of-care sites providing comprehensive case management for symptomatic STIs. 1b). Proportion of patients with STIs at selected health facilities who are appropriately diagnosed, treated and counselled according to national guidelines.	1a). 90% of primary point-of-care sites provide comprehensive STI care by 2015. 1b). By 2015, 90% of women and men with STIs at health-care facilities are appropriately diagnosed, treated and counselled.
2. Control congenital syphilis as a step towards elimination. [Antenatal and PMTCT clinics.]	2. Proportion of pregnant women aged 15-24 years attending antenatal clinics with a positive serology for syphilis.	2a). More than 90% of first time antenatal care attendees aged 15-24 years screened for syphilis. 2b). More than 90% of syphilis sero-positive women treated adequately by 2015.
3. Scale up STI prevention strategies and programmes for HIV-positive persons. [Antenatal and PMTCT clinics or any clinic where SRH and HIV are linked.]	3. Proportion of HIV-positive patients with STIs who are given comprehensive care including advice on condom use and partner notification.	3a). Strategies and guidelines for HIV positive persons with STIs interventions in place by 2010. 3b). 90% of primary point-of-care sites provide effective STI care for HIV infected persons.
4. Upgrade STI surveillance within the context of second generation HIV surveillance. [MoH and National AIDS Commissions.]	4a). Number of prevalence studies regularly conducted (at sentinel sites or in sentinel populations) every three to five years. 4b). Annual incidence of reported STIs (syndromic or etiologic reporting).	4a). At least two rounds of prevalence surveys conducted by 2015. 4b). Routine STI reporting established and sustained over at least 5 consecutive years by 2015.
5. Control bacterial genital ulcer disease (GUD).[3] [Antenatal and HIV clinics.]	5a). Proportion of confirmed bacterial GUD cases among patients with genital ulcerative diseases. 5b). Percentage of pregnant women aged 15-24 years attending antenatal clinics with a positive serology for syphilis.	5a). Zero cases of chancroid identified in GUD patients by 2015. 5b). Reduction to below two percent of positive syphilis serology among antenatal care attendees age 15-24 years.
6. Build on success. Implement	6a). Health needs identified and	6a). By 2010, health needs, policies, legislation and regulations

[2] National targets must be tailored to the country context, need, and availability of resources.
[3] Critical activity for pregnant women who are HIV-positive.

Priority 1 Activities and [Level of Intervention]	Indicators	Suggested National-Level Targets[2]
targeted interventions in high-risk and vulnerable populations.	national plans for STI control, including HIV, for key high-risk and vulnerable populations developed and implemented. 6b). Proportion of young people (age 15-24 years) with STIs that were detected during diagnostic testing for STIs.	reviewed; plans in place and appropriately selected country-specific targeted interventions implemented. 6b). At least two rounds of prevalence surveys conducted among groups with high-risk behaviour and among young people by 2015.
7. Implemented age-appropriate comprehensive sexual health education and services. [Ministry of Education and Ministry of Health.]	7. Percentage of schools with at least one teacher who can provide life-skills-based HIV and other STI prevention education.	7a). Review of policies and development of age-appropriate training and information materials for schools completed by 2007. 7b). Increased number of teachers trained in participatory life-skills-based HIV education that includes other STIs by 2015.
8. Promote partner treatment and prevention of reinfection. [All levels of primary and secondary care.]	8a). Proportion of patients with STIs whose partner(s) are referred for treatment.	8a). Plans and support materials for partner notification developed, and health-care provider training in place by 2010. 8b). Double the proportion of patients who bring in or provide treatment to their partner(s).

Priority 2 Activities and [Level of Intervention]	**Indicators**	**Suggested National-Level Targets[4]**
9. Build on success. Implement targeted interventions in high-risk and vulnerable populations.	6a). Health needs identified and national plans for STI control, including HIV, for key high-risk and vulnerable populations developed and implemented. 6b). Proportion of young people (age 15-24 years) with STIs that were detected during diagnostic testing for STIs.	6a). By 2010, health needs, policies, legislation and regulations reviewed; plans in place and appropriately selected country-specific targeted interventions implemented. 6b). At least two rounds of prevalence surveys conducted among groups with high-risk behaviour and among young people by 2015.
10. Support roll out of effective vaccines (HBV, HPV and eventually HSV). [Ministry of Health and Ministry of Finance.]	9a). Policy and plans for universal vaccination for hepatitis B. 9b). Plans and policy reviews and strategies for implementation of HPV and potential HS-2 vaccines.	9a). Plans in place regarding vaccination for hepatitis B and HPV by 2008. 9b). Pilot vaccination programmes initiated and scaling up in progress by 2010.
11. Facilitate development and implementation of universal opt-out voluntary counseling and testing for HIV among STI patients. [Ministry of Health.]	10. Proportion of patients assessed for STIs who are routinely counselled and offered confidential testing for HIV.	10a). HIV testing and counselling available in all settings providing care for STIs by 2015. 10b). Double the proportion of STI patients who receive voluntary counseling and testing for HIV.

[4] National targets must be tailored to the country context, need, and availability of resources.

Table 3. Costs and Cost Benefits of Major STI Control Strategies[5]

STI Control Strategy, Target Audience	Country	Unit cost (Total Cost/N)	Cost/ treatment	Cost/outcome averted	Measure of health-adjusted life year saved	Comment
Syndromic STI management **Symptomatic adults**	**Indonesia** Symptomatic males 19-50 yrs (Djajakusumah et al., 1998)	$3 per male urethritis case	$3 per correctly treated confirmed inflammatory STI	Not reported	Not reported	1998 USD Lab confirmed GC/CT prevalence= 75%
	China Symptomatic men (age not reported) (Liu et al., 2003)	$2 per male urethritis case $3 per GUD case	$3 per correctly treated confirmed inflammatory STI $14 per correctly treated confirmed genital ulcer/STI	Not reported	Not reported	2002 USD Lab confirmed GC/CT prevalence=69% Lab confimed GU (syphilis) prevalence=25%
	Tanzania Symptomatic men and women (discharge & ulcers) (Mayaud et al., 1998)	Not reported	$10 per syndrome treated (genital ulcer or discharge syndrome)	$218 per HIV infection averted (based on study of HIV incidence)	$9 – 10 per DALY saved (based on HIV-1 morbidity)	1993 USD Community STI prevalence: Syphilis = 6% HIV = 4% Urethritis symptoms = 10%
	South Africa Male and female STI patients (age not reported)—pre-packaged syndromic STI packets (Harrison et al., 2000)	$2 per packet (drugs, info sheet, condoms, partner card)	$7 per correctly treated confirmed inflammatory STI	Not reported	Not reported	1997 USD Estimated STI prevalence among women in region ($\geq$ 1 STI) = 25% HIV prevalence among pregnant women in region = 30%

[5] All costs in US dollars unless otherwise noted; all costs include intervention and programmatic costs.

STI Control Strategy, Target Audience	Country	Unit cost (Total Cost/N)	Cost/ treatment	Cost/outcome averted	Measure of health-adjusted life year saved	Comment
Syphilis Screening in pregnant women	**Kenya** (Terris-Prestholt et al 2003 based on Jenniskens et al., 1995)	$2 per woman screened	$34 per woman treated $22 per person treated (including partners)	$280 per perinatal outcome averted	$17 per DALY saved	2001 USD Maternal syphilis prevalence=7%
	Kenya (Terris-Prestholt et al 2003 based on Fonck et al., 2001)	$1 per woman screened	$40 per woman treated $26 per person treated (including partners)	$300 per perinatal outcome averted	$19 per DALY saved	2001 USD Maternal syphilis prevalence=3%
	Tanzania (Terris-Prestholt et al., 2003)	$1 per woman screened	$20 per woman treated $15 per person treated (partners)	$187 per perinatal outcome averted	$11 per DALY saved	2001 USD Maternal syphilis prevalence=7%
	Zambia (Terris-Prestholt et al 2003 based on Hira et al., 1990)	$1 per woman screened	$22 per woman treated $12 per person treated (partners)	$181 per perinatal outcome averted	$11 per DALY saved	2001 USD Maternal syphilis prevalence=9%
Hepatitis B vaccine (3 dose series) for infants	**High Endemicity** (Beutels 2001 based on Liu 1995)	$3 per person	$4.2	$30 - 40 per carrier case averted	Not reported	1998 USD Population Hep B prevalence = 70 - 90%
	Medium Endemicity (Beutels 2001 based on Antonanzas 1995, Ginsberg 1996, Garuz 1997)	Not reported	$13 - 30 per person	$385 - 2,108 per infection averted	Not reported	1998 USD Population Hep B prevalence = 20 - 55%
	Low Endemicity (Beutels 2001 based on Margolis 1995, Wiebe 1993, Szucs 1998, Mangtani 1995, Fenn 1996, Williams 1996)	Not reported	$31 - 127 per person	$57 – 43,264 per infection averted	$5,499 per QALY gained $5,615 – 14,271 per life-year gained	1998 USD Population Hep B prevalence = 5 - 20%

STI Control Strategy, Target Audience	Country	Unit cost (Total Cost/N)	Cost/ treatment	Cost/outcome averted	Measure of health-adjusted life year saved	Comment
Homosexual men (ages 15 – 40)	**France** (Beutels, 2001 based on Kerleau et al 1995)	Not reported	$161 per vaccinated person	$ 765 per case prevented	Not reported	1998 USD Population Hep B prevalence =
HPV vaccine (coupled with cytologic screening) (3 dose series) Pre-adolescent girls	**United States** (Goldie et al., 2004)	$377 per woman	Not reported		$20,600 per QALY gained (compared to screening alone)	2002 USD HPV Prevalence = (modeled) 1% - 3% age<35 yrs
Adolescent girls	**Brazil** (Goldie, et al., 2007)	I$25 – I$450 per woman	Not reported		I$700 - I$9,600/YL saved (not quality-adjusted) compared to screening alone	2000 International Dollars (I$) HPV Prevalence = (modeled) 41.5% age 12-14 yrs
Targeted outreach (syndromic STI management, condoms, and periodic presumptive treatment) **Female sex workers**	**South Africa** (Vickerman et al., 2006)	$44 per clinic visit	$102 per syndrome treated	$2,093 per HIV infection averted	$78 per DALY saved (full intervention) $31 per DALY saved (incremental cost of adding periodic presumptive treatment to others	2001 USD Prevalence HIV= 45% - 54% Prevalence CT or GC= 39%

Annex B. Boxes

Box 1: Benefits and Challenges to Private and Public Sector STI Management

	Private Sector	Public Sector
Benefits	- Much wider access - Greater confidentiality - Less judgmental attitudes - More highly valued by clients, including at-risk populations - More respectful provider attitudes - More efficient services	- Easier provision of standardized accountable services (e.g., syndromic) - Greater opportunity for oversight - Lower costs to patient (e.g., subsidized) - Greater likelihood of including prevention elements (counseling, condoms, HIV test) - Partner treatment more likely
Challenges	- Higher costs related to testing - Greater likelihood of inadequate reatment choices - Partner treatment less likely - Lower accountability - Quality of care may depend on client's ability to pay	- Limited access, long waiting times - Lower acceptability, especially for men and vulnerable groups (e.g., adolescents, sex workers) - Provider tendency to scold patients, disrespectful attitudes towards clients - Quality dependent on intact health care system (e.g., supplies depend on distribution system)

Based on operational research studies from Uganda, Ghana, South Africa and India. (Schneider, 2001; Jacobs 2005; Conolly 1999; Wilkinson 1999; Nuwaha, 2006; Dallabetta, 2006).

Box 2: Why Adolescents are at Particularly High Risk for STIs

In many developing countries, more than half of the population is 15 years old or younger, and in some countries three quarters of all people are younger than age of 25. Throughout the world, adolescents and young adults under age 25 have the highest STI rates. Each year 1 in every 20 adolescents will develop a new STI. Why are young people at such high STI risk?

- Adolescents and young adults are more likely to have multiple partners (sequential or concurrent partnerships) rather than long-term relationships. Higher partner numbers and concurrent partnerships increase the chance of exposure to an STI. Adolescents are more likely to choose sex partners who are also adolescents and who may already have an STI (Dallabetta et al., 2006).
- Early age at first sex increases the chance of exposure to an STI. Biologically, young women appear to be at even greater risk than young men.
- Many young people have difficulty using effective preventive strategies. They may be unable to refuse sex with partners, or unaware that condoms are effective against STDs including HIV if used consistently and correctly. Adolescents are less able to negotiate with partners about using condoms and often lack experience in using them correctly. They may also lack the resources to buy condoms.
- Adolescents have less access to healthcare and fewer resources for health services or effective treatment. Some communities or health facilities have restrictive policies requiring parental approval before treatment. Late or lack of treatment for curable STIs increases the likelihood of adverse consequences. Avoiding treatment also increases the likelihood that partners will not be treated, and further STI spread.

While young men and women both have increased STI risk, young women are most affected -- adolescent girls have six times the STD and HIV risk of boys.

- Girls tend to have earlier onset of sexual activity and more biologic factors that enhance their risk for certain STIs
- Girls tend to have older partners who may have already contracted non-curable (often silent) STIs such as HIV. In many cultures, the median age of first marriage for women is well under 20 years.
- Young women may have more difficulty negotiating around sex, especially with older, more experienced partners.

The WHO Global Strategy for STI Prevention and Control (WHO, 2006a) recommends making clinical and prevention services as responsive and acceptable to adolescents as possible, and lists scaling up of "user-friendly services" for adolescents among its five recommended new technologies for strengthened response to STI prevention and control (WHO, 2006a). Important prevention strategies for adolescents in that document include:

- Promotion of sexual abstinence, delaying sexual debut, and reducing number of sex partners
- Providing education about STIs and how they are transmitted
- Providing condoms (male and female) along with information and demonstrations on their correct use

Box 3: How STIs Can Affect Women's Gender Power Balances*

For all women – and especially those living in the developing world – STIs or their adverse outcomes can extend beyond health complications alone, and may involve serious, negative social consequences, stigma or personal harm. For example:

- Youth surveys indicate that one third or more of sexually experienced girls in South Africa are afraid to "say no to sex," or had been "forced to have sex." Most reported there were times they did not want to have sex but did so because a "boyfriend insisted." (Kaiser Family Foundation, ;Pettifor et al., 2004)
- A vicious cycle can be set up in which relationships outside marriage lead to STIs and thus to infertility, and infertility leads to relationships outside marriage and to further spread of STIs (Dallabetta et al., 2006).
- Syndromic STI management, which does not identify a specific pathogen, can make partner management difficult and possibly harmful if the male partner is asymptomatic or does not perceive himself to be infected with an STI. For women with STIs, lack of partner treatment will likely lead to re-infection. For women with vaginitis that is unrelated to an STI (e.g., caused by bacterial vaginosis), treatment of a male sex partner who knows he has been faithful may lead to mistrust, conflict, or physical harm to the woman (Ryan, 1999;Dallabetta et al., 2006).
- STI diagnosis, pregnancy loss, neonatal death, or infertility can lead to conflicts in marital and larger family relationships, status in the family, partner or other violence, divorce or abandonment. In some societies, a husband can return an infertile woman to her parents or request return of her bride price (Dallabetta et al., 2006).
- Infertile women may resort to expensive or risky therapies in a desperate attempt to become pregnant. Studies in several African nations (e.g., Niger, Uganda and the Central African Republic) have documented the movement of abandoned or rejected barren women to urban areas where, due to economic need, they practice prostitution (Frank, 1983).
- In low-income communities, commercial sex (sex in exchange for money) or transactional sex (sex in exchange for goods) work may be common. Risk behavior surveys indicate that 3 to 30% of women and 10 to 45% of men in some African settings exchanged sex for money or goods during the past year. All women who sex for money or goods as a means of survival are susceptible to STIs including HIV; however, studies suggest that the poorest and least educated women also the least likely to be able to negotiate safer sex practices as sex without a condom is usually perceived to be worth a higher price (Dallabetta et al., 2006).

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The WHO Global Strategy for STI Prevention and Control (2006) includes as a guiding principle that "gender inequalities must be addressed through interventions that influence political will as well as societal norms and attitudes concerning sexual behavior and the status of women. Active promotion of male responsibility and the empowerment of women in the prevention and control of STIs are crucial elements in an effective gender-sensitive response" (WHO, 2006a).

*Based on studies from Mali, Niger, Uganda, Senegal, Ghana, Central African Republic, Botswana and South Africa.

Box 4. Benefits and Limitations to Syndromic Management of STIs

The syndromic approach is based on the identification of "syndrome" -- a constellation of easily elicited symptoms and recognizable clinical signs associated with a limited number of well-defined STI or RTI etiologies. The approach is pragmatic in that it can be effectively carried out in almost any setting. The approach has many benefits (Dallabetta et al., 2006):

- It does not require laboratory facilities (often lacking or unreliable in developing settings).
- Patients are treated at the initial clinical visit. Early treatment minimizes the chance for complications to develop because of inadequate follow up, shortens duration of disease and thus reduces opportunities for further transmission to partners.
- Patient costs are less because laboratory tests are avoided, simplified drug regimens are part of the algorithms, and use of standardized management increases likelihood of effective STI treatment and need for repeated visits or referrals to other centers
- The major curable STIs are treated without concern of false negative lab results.
- Patient compliance is higher because drugs are available and education is provided in a standardized manner
- Patient satisfaction is higher, because drugs are more likely to work and services are provided in a respectful, non-judgmental and confidential manner
- Standardized training on flowcharts and therapeutic regimens allows providers to also be better trained on critical ancillary prevention strategies (including educational messages, condom provision, partner notification and referral) as part of routine care
- Standardized regimens allow for improved case-reporting for surveillance, and thus more information for program management (Ryan, 1999;Dallabetta et al., 2006).
- The approach seems to be particularly successful in treating the STI syndromes most strongly associated with HIV, genital ulcer and urethral discharge syndromes.

The syndromic approach also has some important limitations (Ryan, 1999;Dallabetta et al., 2006;WHO, 2006a).

- Syndromic management is not useful for asymptomatic patients, who account for at least half of all STIs. Asymptomatic women with cervical infections are at risk for serious adverse outcomes including infertility but are not covered by the approach.
- Since genitourinary symptoms are common even in the absence of an STI, the syndromic approach can lead to false positive diagnoses and thus unnecessary drugs and associated costs, and also raises the risk of causing drug resistance to certain antibiotics.
- Partner management can be complicated, particularly for women with vaginitis. Many providers are hesitant to treat sex partners of individuals treated without a specific STI etiology even though reinfection of the patient would be very likely if an infected steady partner were not treated.
- The most common presenting syndrome, vaginal discharge syndrome in women, is more likely to be caused by non-STI related reproductive tract infections (e.g., bacterial vaginosis, candidiasis) or other factors, and vaginitis can be complicated to treat, often requiring multiple visits and repeated presumptive treatment trials which can be costly.
- Many health care providers, especially physicians, are reluctant to use the syndromic approach because they were trained in treatment based on etiologic diagnosis.
- In the case of re-focused health workers to specialize in syndromic management of STIs, there is a risk of "de-skilling" or losing the multidimensional breadth of the health workers due to a limitation in the services they provide.

Box 5. Involving Private Sector Providers in STI Management

In all nations, most STIs are managed by private sector providers, whether formal (e.g., private physicians) or informal (e.g., traditional healers). Strategies to support the private sector in providing high quality STI care can greatly improve STI prevention and control in a community.

In Madagascar:

- The government has developed national STI management guidelines that employ locally validated syndromic STI and RTI management approaches
- National STI program trainers have conducted training courses for private as well as public sector clinicians, encouraging private physician attendance through a variety of incentives.
- Because of the high prevalence of genital ulcer disease related to bacterial STIs, a pre-packaged STI management kit for genital ulcer disease including adequate doses of medications against syphilis and chancroid, prevention messages and male latex condoms, and partner notification cards describing free treatment (both in local languages) is being marketed to private providers – including pharmacists – at subsidized cost using a social marketing strategy.
- High use of the pre-packaged kit by individuals with genital ulcer disease is expected to minimize likelihood that infected individuals use ineffective drugs, encourage treatment for exposed sex partners, reduce prevalence of genital ulcer disease in the community and possibly limit HIV transmission (personal communication, USAID, Madagascar).

In Peru:

- Rates of STIs among symptomatic pharmacy clients were similar to symptomatic patients attending primary care clinics.
- Pharmacy workers were offered training on STD-HIV management and prevention, especially improved recognition of syndromes, applying the national syndromic management approach, referral to physicians for management of STDs and counseling on risk reduction, partner referral, condom promotion and compliance with and abstinence during treatment (Garcia et al., 1998).
- 56% of pharmacies had staff receiving additional training. After training, counseling for PID and genital ulcers was more frequent in pharmacies that received specialized training.
- A cost analysis estimated provision of STI care through pharmacies saved 2 USD per case adequately managed (societal perspective) (Garcia and Holmes, 2003).

Annex C. Website links

1. Millennium Development- Goals -- http://www.undp.org/mdg
2. Demographic and Health Surveys – http://www.measuredhs.com
3. Centers for Disease Control and Prevention
    - Program Operations Tools -- http://www.cdc.gov/std/program
    - CDC 2005 STD Treatment Guidelines -- http://www.cdc.gov/std/treatment/
4. World Health Organization (WHO)
    - Guidelines for STI management: http://www.who.int/reproductive-health/publications/rhr_01_10_mngt_STDs
    - Fact Sheet, STDs and young people: http://www.who.int/mediacentre/factsheets/fs186
    - Fact Sheet, Women and STIs: http://www.who.int/mediacentre/factsheets/fs249
    - STI Diagnostics Initiative (SDI): http://www.who.int/std_diagnostics
    - Vaccine Preventable Diseases (VPD): http://www.afro.who.int/ddc/vpd
5. Other
    - HIV/AIDS Integration Partners Working Group: http://www.fpandhiv.org
    - UN, 1994 Conference on Population Development, Cairo: http://www.iisd.ca/Cairo.html
    - Alliance for Microbicide Development: http://www.microbicide.org

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