Interventions against sexually transmitted infections (STI) to prevent HIV infection

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STIs have taken on a more important role with the advent of the HIV/AIDS epidemic, and there is good evidence that their control can reduce HIV transmission. The challenge is not just to develop new interventions, but to identify barriers to the effective implementation of existing tools, and to devise ways to overcome these barriers. This ‘scaling-up’ of effective strategies will require an international and a multisectoral approach. It will require the formation of new partnerships between the private and public sectors and between governments and the communities they represent.

Towards the end of the 15th century, a devastating epidemic of infectious syphilis swept Western Europe. Observers at that time quickly perceived the disease to be transmitted sexually, but this group of ‘venereal diseases’ was subsequently regarded as unproblematic until it was noted to be a severe problem among military personnel in the 19th and 20th centuries. Interest in sexually transmitted infections (STIs) was further fuelled in the early 1980s by the advent of the HIV/AIDS epidemic and recognition of the role of STI in facilitating the sexual transmission of HIV. Interest in STI control has reached a peak recently when it was shown that many interventions to control STIs can help reduce the spread of HIV. Furthermore, this can be achieved through the use of low technology in sustainable and cost-effective control programmes.

However, despite decades of control efforts, STIs still thrive today. There are problems in the effective implementation of control programmes because STIs are not just biological and medical problems, but also behavioural, social, political and economic problems – many facets that have not been adequately addressed in the past. This realisation is slowly translating into more comprehensive approaches to STI control involving several disciplines. Yet, there is growing evidence that the epidemiology of STIs and HIV is changing, and control efforts may be severely challenged once again.
Public health importance of sexually transmitted infections

Sexually transmitted infections (STIs) constitute an important public health problem for the following reasons: (i) STIs are frequent with high prevalence and incidence; (ii) STIs can result in serious complications and sequelae; (iii) STIs have social and economic consequences; and (iv) a number of STIs have been identified as facilitating the spread of HIV.

Epidemiology of STIs

STIs are caused by over 30 pathogens, including bacteria, viruses, protozoal agents, fungal agents and ecto-parasites. The World Health Organization (WHO) estimates that approximately 340 million incident cases of the four main curable STIs (gonorrhoea, *Chlamydia* spp, syphilis and *Trichomonas vaginalis*) occur every year, with 85% in non-industrialised countries. There are, however, substantial geographical variations in estimated prevalence and incidence. Sub-Saharan Africa, whilst accounting for 20% of the global STI estimates, has the highest prevalence and incidence rates. The overall yearly incidence rate of curable STIs in Africa is estimated at 2.54 per 1000 people in reproductive ages (15–49 years), but is only 77–91 per 1000 in industrialised countries. The second highest rates are found in South and South-East Asia. This is not surprising given the large at-risk populations of young people in these countries, and – in the case of China – the recent opening of its borders to free trade, quickly followed by increases in prostitution and STI, which were once believed to have been controlled. Similarly, in the early 1990s, major political and economic transitions took place in the Newly Independent States (NIS) of the former Soviet Union. Since that time, there have been unprecedented epidemics of syphilis and gonorrhoea with annual increases of 100–300%. The reasons for the increase of STIs in many non-industrialised countries are multifactorial but relate to a great extent to the lack of access to effective and affordable STI services in many settings, or to the collapse of once relatively performant health systems in countries undergoing harsh economic and health reforms.

STIs impose an enormous burden of morbidity and mortality, both directly through their impact on reproductive and child health, and indirectly through their role in facilitating the sexual transmission of HIV infection. The greatest impact can be seen among women in whom severe complications include pelvic inflammatory disease, chronic pain, and adverse pregnancy outcomes (ectopic pregnancies, endometritis, spontaneous abortions, stillbirths and low birth weight). In both men and women, STIs play a major role in infertility. A growing number of
malignancies are also attributed to STIs, notably cervical, anal and penile cancers as well as hepatocellular carcinoma. Congenital infections in the new-born include congenital syphilis, ophthalmia neonatorum and pneumonia.

The World Bank has estimated that STIs, excluding HIV, are the second commonest cause of healthy life years lost by women in the 15–44 year age group, responsible for some 17% of the total burden of disease in women of reproductive ages, outranked only by causes of maternal morbidity. Yet it is only in recent years that STIs have been accorded any priority by national ministries of health or by the international community, mainly because of their potential interaction with HIV.

**HIV–STI interactions**

HIV and other STIs may interact with each other in the following ways (Fig. 1):

- HIV, by causing immunosuppression, can modify the natural history (duration), clinical presentation (severity), and response to treatment of certain STIs, notably other viral infections such as genital herpes simplex virus infection or human papillomavirus

- STIs, by causing ulceration or inflammation of the genital tract, may enhance the transmission of HIV by increasing infectiousness of HIV-positive individuals and/or the susceptibility of HIV-negative persons

Since the late 1980s, it had been noted that HIV-positive patients frequently gave a history of past STI or had serological evidence of past STI (e.g. increased prevalence of treponemal, chlamydial or herpes antibodies).
These studies suggested the existence of an ‘epidemiological synergy’ between HIV and other STIs. However, one of the major hurdles in understanding this relationship was that HIV and other STIs share a common sexual transmissibility, driven by common sexual behaviours; thus, the observed association could be the result of a ‘confounding’ effect. This could only be overcome at the analytical stage through statistical methods for ‘controlling’ for the effect of behaviour, or in study design, by conducting prospective randomised-controlled intervention trials.

In a recent comprehensive review, Fleming and Wasserheit group the evidence that STIs facilitate the transmission of HIV into three categories: (i) biological plausibility studies; (ii) HIV seroconversion studies; and (iii) randomised intervention studies.

**Biological plausibility or mechanism studies**

During sexual intercourse genital ulcers may bleed, leading to the increased risk of HIV transmission via the blood route. Studies of HIV infected people with genital ulcer disease (GUD) suggest that these ulcers may increase infectiousness as HIV virions have been detected in genital ulcer exudates among patients with chancroid or syphilis. Similarly, HIV proviral DNA was found in herpes-associated GUD among men in Seattle. Treatment or healing of GUD among HIV-seropositive individuals is accompanied by a decrease in HIV shedding. Among HIV-seronegative individuals, GUD may increase susceptibility by disrupting mucosal integrity, by the recruitment and activation of HIV target cells, such as lymphocytes, and possibly by HIV taking advantage of CCR5 and chemokine receptors.

The effects of STI on excretion of HIV-1 in genital secretions have been investigated. There is evidence that among HSV-2 infected women, even in the absence of an ulcer, HSV-2 genital shedding is increased in HIV-seropositive individuals and that both HIV-RNA and HSV-2 DNA shedding are increased in the presence of the other virus. The biological basis for the ‘promotion’ of HIV infection is not entirely elucidated but it has been suggested that, in the presence of HSV, HIV can infect keratinocytes that lack CD4 receptors.

Non-ulcerative STIs such as gonococcal or chlamydial infections have also been shown to increase the frequency of HIV-DNA shedding in cervico-vaginal secretions among HIV-seropositive female sex workers in Ivory Coast, and Kenya. A study among male patients in Malawi observed an 8-fold increase in secretion of HIV-1 RNA in semen compared with a control group. The effect was marked for men having either gonorrhoea or *T. vaginalis* infections. In both men and women, successful treatment of patients with STI resulted in decreased frequency or quantity of HIV shedding.

Changes in the vaginal flora, such as seen in bacterial vaginosis, appear to be increasing the risk of HIV acquisition. However,
properly randomised intervention studies are still required to determine the real causal role of this frequent condition.

**HIV seroconversion studies**
Several studies have demonstrated that prior presence of an STI will enhance HIV acquisition. In Kenya, HIV-seronegative men attending a STI clinic with a chancroid ulcer were 4 times more likely than their counterparts without an ulcer to seroconvert in the few weeks of follow-up\textsuperscript{23}. Other independent factors of HIV seroconversion included the lack of circumcision and a sexual contact with a sex worker. In a cohort study of Thai military conscripts, a significant 4-fold increase in the relative risk of HIV seroconversion was found among the men who were HSV seropositive at baseline, and a 2-fold significant increase among men who seroconverted for HSV in the intervening follow-up\textsuperscript{24}.

**Randomised intervention studies**
A large community-randomised controlled trial conducted in the Mwanza region of Tanzania showed that improved management of STIs in rural health centres and dispensaries, reduced the incidence of HIV infection by approximately 40\% over a 2-year period\textsuperscript{25} mediated by a decrease in the duration of symptomatic STIs\textsuperscript{26}. This study has provided the clearest evidence to date of the impact of a feasible and cost-effective STI intervention in preventing HIV transmission.

It has now been realised that the prevention and care of STIs are interventions which improve the health status of the population and are also important strategies for the prevention of HIV transmission. Consequently, UNAIDS and WHO have recommended that high priority be given to the development of STI control programmes\textsuperscript{4}.

**Approaches to STI control**

*Theoretical control models*

STI control strategies have long been influenced by the ‘transmission dynamics model’ described by Anderson\textsuperscript{27}. In this model, the transmission of a STI is expressed in terms of its basic reproductive number ($R_0$), *i.e.* the average number of new (or secondary) STI cases generated by an index (or primary) case in a defined population over a period of time. It has been demonstrated that $R_0$ is a function of the rate of partner change ($c$), the probability of transmission of the STI during sexual intercourse ($\beta$) and the duration of the infection ($D$)\textsuperscript{27} – summarized in the formula $R_0 = \beta \times c \times D$.

STI control programmes should, therefore, aim to reduce the basic reproductive rate by a combination of strategies, including behaviour...
change aiming at decreasing the number of sexual partners, increased condom use and treatment of patients with STI. The latter component of STI control programmes aims to reduce the duration of infectivity of individuals with an STD.

This model has also highlighted the importance of groups of individuals who have much higher rates of sexual partnerships. These ‘core groups’ and their sexual partners – who may form ‘bridge populations’ between the core groups and the general populations (Fig. 2) – have been shown to be epidemiologically important in driving the STI and HIV epidemics in many parts of the world28.

Other models have been developed to conceptualise the strategies needed to control STI. The ‘operational model’ identifies the many different steps that patients with an STI pass through before they can be considered cured by health services (Fig. 3). At each step, a proportion of patients will drop out. By multiplying the percentages of patients taking each step, one obtains an estimate of the cure rate achieved by the health services of interest. This model shows how, in most non-industrialised countries, only a fraction of STI cases are successfully treated29. In this way,
it clarifies the four main reasons for failure to control STIs: (i) failure to prevent unsafe sexual behaviour; (ii) failure of people with symptoms to access health services; (iii) failure to identify and treat patients with symptoms; and (iv) failure of health services to provide adequate treatment.

Each of these steps, in turn, suggests points for potential medical, health promotion, and service delivery interventions. Starting from the bottom of the model, broad options for STI control, therefore, include: (i) improving STI case management, including partner notification; (ii) improving treatment-seeking behaviour; (iii) case finding or screening for neglected or asymptomatic STIs; (iv) mass treatment of the general population and/or presumptive treatment of high-risk groups; and (v) primary prevention (information education and communication [IEC] strategies, condoms, microbicides, vaccines).

This paper will review the main strategies used under each of these approaches as a means to control STI, and prevent HIV.

**STI interventions**

**STI case management**

Early diagnosis and effective treatment of STIs is an essential component of STI control programmes. The traditional method for STI diagnosis has been through laboratory diagnosis of the aetiological agent. Whilst this is still the method of choice in many parts of the industrialised world, this approach is expensive both in terms of diagnostics, infrastructure, and maintenance. Additionally, it often results in delays in diagnosis and treatment. Moreover, most health centres and dispensaries in non-industrialised countries do not have access to reliable laboratory facilities. Consequently, clinicians either need to refer their patients to specialist centres, resulting in further delays, or they attempt to make a presumptive clinical diagnosis through the identification of particular clinical features related to various agents. This method has often proven inaccurate or incomplete³⁰.

To address the limitations of both aetiological and clinical diagnosis in the management of STIs, particularly for patients who attend the first level of primary health care, the WHO has developed and advocated the syndromic management approach. STI-associated syndromes are easily identifiable groups of symptoms and clinical findings on which the healthcare providers can base their presumptive diagnosis. Management is simplified by the use of clinical flowcharts, and allows time in the consultation to provide simple education messages, discuss partner notification and promote condoms. Antimicrobial therapy is provided at once to cover the majority of pathogens presumed responsible for that syndrome, in that specific geographical area⁷.
Syndromic management is simple and lends itself to use in a variety of outlets such as STI clinics, primary healthcare (PHC) facilities, pharmacies, family planning/maternal and child health (FP/MCH) services and private practitioners clinics. The sensitivity and specificity of the approach for the diagnosis and management of urethral discharge syndrome and genital ulcer syndrome in various settings have been very satisfactory. Other advantages include cost-effectiveness, diagnosis and treatment at first visit and increased patient satisfaction.

There are two main limitations to syndromic management. Firstly, the cost of over-diagnosis and treatment of patients with no or only one infection. This includes the direct costs of the antimicrobials as well as the indirect costs in terms of adverse drug reactions, alteration in normal gut flora (e.g. shigella) and potential domestic violence. Over treatment is particularly a problem in areas of low STI prevalence. A study conducted in Matlab, Bangladesh, found that cervical infections were present in only 3 out of 320 women complaining of abnormal vaginal discharge while the prevalence of endogenous infection was 30%31. In this setting, the WHO algorithm had a sensitivity of 100% but a very low specificity (56%) while a locally-adapted speculum-based algorithm had sensitivity ranging between 0–59% depending on the pathogens to be identified with a specificity of 80% up to 97%. Clearly syndromic management in this setting did not deal adequately with the management of vaginal discharge and it was calculated that between 36% and 87% of costs would have been spent on uninfected women.

The second limitation is the poor sensitivity and specificity of the syndromic approach for the detection of cervical infections in women, even in settings with higher STI prevalence. The WHO has recommended a risk assessment score to be added to the vaginal discharge syndrome in order to increase the effectiveness of algorithms7. Evaluation of this approach has taken place in several countries, but has yielded disappointing results: scores need to be setting-specific, with tremendous variations even within the same country; the performance of algorithms was not vastly improved; and, as in the case of the Matlab study, risk score was also found to be inadequate in societies where most women will not admit to extramarital or premarital sexual activity for threat of social sanctions31.

**Partner notification**

Partner notification (PN) is a strategy consisting of contacting sexual partners of STI patients to offer them screening and treatment. PN aims to reduce asymptomatic disease in the community and shorten the average period of infectiousness. This, in turn, is expected to reduce disease transmission in the population32. However, while bacterial STIs can be
identified and cured, thus breaking the chain of transmission, viral STIs such as HSV-2 and HIV have no cure and the rationale for PN is less obvious. In the context of syndromic management, it is even less clear which STI should be treated. The most practical approach has been to give the same treatment as for the index case, but this will clearly result in over-prescription of antibiotics. Very little work has been done to demonstrate the impact of PN on reducing the prevalence and incidence of STI in the population.

There has been more research to determine the best way to implement PN. There is strong evidence that simple PN forms given to the index patient ('patient referral') can be effective, and less labour intensive and costly than 'provider referral', where the services take responsibility of tracing contacts. Overall, it seems that PN is relatively ineffective in situations where there is low motivation of health providers, where sex with anonymous partners (e.g. sex workers) is common, where there is a high rate of sexual partner change and where resources are scarce and addresses unreliable. Acceptability of PN depends upon confidentiality and availability of treatment, but strategies should take into account the sexual practices and ethnicity of the population as well as potential negative impacts such as violence against the index case (especially women).

Promotion of treatment seeking behaviour and the role of the private sector

A key step where many STI patients can be lost in the operational model is 'attendance to services'. Surveys of health-seeking behaviour in non-industrialised countries indicate that a substantial proportion of people with symptomatic STI seek treatment in the informal or private sector, from traditional healers, unqualified practitioners, street drug vendors, and from pharmacists and private practitioners and will only attend formal public health services after alternative treatments have failed. Self-medication is also very popular in many settings, where up to 65% of men with symptoms of urethritis self treat.

Patients seek care in the private sector for many reasons. Public services often have restricted and inconvenient opening hours while private services tend to tailor their opening times to suit their clients. Moreover, provider-to-client ratios vary greatly between sectors in many countries. For example in Lagos State, Nigeria, Green found a ratio of one traditional healer per 200 population, whereas in Mozambique, the physician to population ratio was 1:50,000. In addition, private sector services are often seen as providing a more personalised and confidential service with less social and cultural distance between client and provider. An additional barrier to public services utilisation is sometimes the cost of services, as was evidenced in Nairobi, Kenya: when user fees were introduced, a huge decrease in monthly attendances of the largest STI clinic in the city were recorded. Lifting of the
fees a few months later resulted in increased attendances, although this never reached the same levels\(^{38}\).

Quality of care in the private sector is difficult to assess due to the range of services offered and the difficulty in accessing practitioners. A study of private doctors in South Africa showed that fewer than one in ten patients received adequate doses of antibiotics and in 75% of cases an incorrect drug was prescribed\(^{39}\). In private practice there is a financial incentive which can affect the quality of care. In some cases, private practitioners may provide a sub-optimal dose of antibiotics in order that the client can afford treatment and in other cases, for example in China, practitioners may increase their income through over investigation and over prescription (Mabey D, personal communication).

There has been a number of interventions to improve private sector management of STIs. In Jamaica, seminars were provided for public and private physicians and nurses and post-training tests showed an increase in knowledge with regard to STI diagnosis, and most practitioners reported an increase in risk reduction counselling\(^{40}\). Similarly, training for pharmacists in Nepal showed an increase of 45% in the correct syndromic treatment of urethritis\(^{41}\). This figure dropped to 26% nine months after the training, indicating the need for continued training and supervision\(^{42}\). A study in Thailand using ‘mystery shoppers’ again showed improved treatment of STIs by drugstore staff after training\(^{43}\).

Another strategy to increase effective treatment of STIs is the use of pre-packaged therapy (PPT) for syndromic treatment. A team in Uganda developed the ‘Clear Seven’ kit for patients with urethral discharge, which contains ciprofloxacin, doxycycline, condoms, partner referral cards and a clear instruction leaflet. The kit was socially marketed in clinics, pharmacies and retail drug shops. The study found that ‘Clear Seven’ users versus controls had significantly higher cure rates (84% versus 47%, \(P > 0.001\)), greater compliance (93% versus 87%) and increased condom use during treatment. Partner referral rates were similar for both groups\(^{44}\). Similar PPT kits have been used in Cameroon and South Africa with varying levels of acceptability by both health service staff and patients\(^{45,46}\).

In general, the private sector should be viewed as a complement to, and not a replacement for, effective and accessible public services. Furthermore, the views of government health authorities and the medical community should be considered when attempting to stimulate effective collaboration between the sectors.

**Screening and case finding**

Case finding is the testing for STI in individuals seeking health care for reasons other than STI, and screening is defined as testing for STI in
individuals not directly seeking health care (e.g. blood donors). Both strategies have an important role in the detection and treatment of asymptomatic STIs in the community. They should be principally directed towards ANC, FP and MCH clinic attendees as well as high-risk groups such as adolescents and sex workers.

Universal serological testing of ANC attendees for syphilis is recommended by WHO and is one of the most cost-effective health interventions available although programmes are poorly implemented in many countries. Donors of blood, tissue and semen should be screened for at least syphilis, HIV and hepatitis B in order to protect recipients, and the potential exists for screening of populations such as military recruits and company employees. In all cases, careful attention should be paid to patient confidentiality, and if necessary counselling and treatment.

There is an urgent need for simple and cheap methods of identifying asymptomatic women with cervical infections in antenatal, family planning and maternal child health clinics. A simple sociodemographic risk score which identifies women at greater risk of infection has been tried but it has a poor sensitivity and predictive value.

**Mass treatment**

Mass treatment involves the single or periodic administration of effective drugs to a whole population in order to treat, reduce the reservoir, and prevent continued transmission of a specific infection. Mass treatment of STI has many potential advantages: asymptomatic patients are covered, no screening tests are needed, it can be combined with syndromic treatment services and may be highly cost-effective. However, there are concerns about the ethics of treating healthy subjects, adverse effects of treatment, development of drug resistance, logistical difficulties and expense. It has also been suggested that mass treatment may create a false sense of security and result in risk compensation behaviour.

Between 1994 and 1998, a community randomised trial was conducted in Rakai, Uganda, to test the hypothesis that repeated rounds of mass treatment for STI would reduce STI rates and HIV transmission. The intervention comprised single dose oral treatment of all individuals with very effective antibiotics (azithromycin and ciprofloxacin) in the study areas and a single intramuscular penicillin injection for all patients with serological syphilis. Results showed significant reductions in the prevalence of some STIs, particularly among pregnant women in the intervention group. However, in contrast to the Mwanza study mentioned above, there was no effect on HIV incidence.

Reasons postulated for this paradoxical result include differences in the stage of the epidemic (mature epidemic in Rakai versus an earlier
stage in Mwanza), differences in accessibility to STI services for patients with re-infection (continuous availability in Mwanza, intermittent in Rakai) and differences in the prevalences of treatable STI (higher proportion of GUD due to HSV-2 in Rakai than in Mwanza). It was concluded that the proportion of HIV infections attributable to the enhancing effect of STIs seems to decrease with the progression of the HIV epidemic. The results of a third community randomised trial conducted in Masaka – adjacent district to Rakai, with the same epidemiological setting sharing the same epidemiological features but based on a similar intervention to the one used in Mwanza – are awaited with great anticipation.

It may be that single or multiple rounds of mass treatment combined with continuous availability of syndromic management could be an effective control strategy for many countries. In the face of looming epidemics in Asia and elsewhere, this option needs to be fully explored. However, the comparative advantages of mass treatment and continuous provision of syndromic treatment should be determined through RCTs with STI services as standard provision in the control group.

Targeted periodic presumptive treatment

Targeted interventions are based on the concept of core groups, which play a key role in the epidemiology of HIV-1. The ‘epidemiological synergy’ between STI and HIV is particularly important in core groups with a high incidence of STI and HIV. Moreover, Plummer showed in Kenya that progression to HIV disease is more rapid in prostitutes and it is likely that this rapid progression is related to concurrent STI infection. This could have an important effect on accelerating the epidemic as frequent episodes of STI would accelerate the development of lowered immunity and increased HIV infectiousness while also increasing susceptibility to STIs.

Core groups are context specific and, when designing interventions, it is important to take account of the social and economic forces creating these groups and to balance disease control measures against the potential for victimisation. Interventions need to be designed in partnership with core group members they should be context specific and emphasise common goals and interests.

An example of a successful core group intervention took place in a South African mining community. The Lesedi project provided STI treatment services including periodic presumptive treatment and prevention education to a core group of sex workers living around the mine. The study found that the intervention significantly reduced the prevalence of gonococcal and chlamydia infections (NG/CT: Neisseria gonorrhoeae/Chlamydia trachomatis) and GUD among women. Moreover symptomatic STIs were also reduced among the miners in the intervention area as compared to
miners living further away. The results of this study suggest that periodic presumptive treatment coupled with health education is a feasible approach to providing STI services to core groups.

Primary prevention

Primary prevention can be directed at changing the behaviour of individuals and these are particularly effective at reaching areas of need, especially when implemented in a clinical setting. These interventions often rely on the ‘rational health model’, which is based on the assumption that an individual has the power to make necessary changes. However, in many instances drugs/poverty/gender can diminish an individual’s ability to act on his/her intentions. Behavioural interventions are particularly important in adolescents as they have high rates of STI and are more susceptible to behaviour change intervention such as mutual monogamy, safer sexual practices and condom use. Many behavioural interventions for primary prevention of STI are similar to those for the prevention of HIV transmission. As these are discussed elsewhere in this volume, this paper will focus on those interventions specific to STIs.

Condoms

When used properly and consistently, condoms are one of the most effective methods of protection for individuals against STI. They are relatively cheap and free from side effects. They can be made readily available on a large scale through free distribution or social marketing – the promotion and use of marketing techniques to make products available at an affordable price.

However, in many countries only a small proportion of the sexually active population use condoms and those who do may do so irregularly and only with selected partners. Barriers to consistent use of condoms include high price in some settings, low availability and inadequate social marketing but above all, lack of appeal to potential users. Women may also be forced into unprotected intercourse as a result of unequal power relations between men and women.

In Thailand, the 100% Condom Programme overcame many of these barriers and the programme has been linked to the decrease in the numbers of cases of STI and HIV. However, similar declines in disease prevalence have been observed in Uganda where condom uptake is low. It has been suggested that a large increase in condom use could fail to affect disease transmission at a population level due to a ‘risk-compensation’ mechanism. This would imply that condom users switch from inherently safer strategies of partner selection and low rates of partner change, to a riskier strategy of maintaining higher rates of partner change plus reliance on intermittent condom use.
UNAIDS recommended best practice for condom programmes include campaigns to improve information, education and empowerment of individuals so that they can make informed decisions about condom use; ensuring easy access to high quality condoms; and conducting context specific research into behaviour and preferences as regards condom use.\(^5^6^6\)

**Female controlled methods of STI prevention**

STIs disproportionately affect women, and adolescent women are at increased risk of STI due to ignorance of appropriate preventative measures, unplanned or coercive sexual intercourse, where it may be difficult or impractical to negotiate safer sex. Female-controlled methods of protection against HIV and STIs are, therefore, taking on increased importance.

The female condom has important advantages such as efficacy, little reported disruption of sexual enjoyment, safety and in some areas increasing acceptance by women.\(^5^9^6\) However, disadvantages include high cost, lack of visual and auditory appeal, difficulty of use, pre-planning of intercourse and mixed reactions among male partners. A randomised study conducted among sex workers in Thailand has demonstrated that women who were trained on using female condoms in addition to male condoms became more consistent users of either method and had, therefore, higher rates of protected intercourse, compared to women to whom only male condoms were promoted and provided.\(^5^9^6\)

Vaginal microbicides potentially offer a female-controlled means of protection from both infection and conception and have been under development since the early 1990s. Currently, there are about 36 compounds under development.\(^6^0^6\) These compounds can have advantages over the female condom in that they can be developed with options for surreptitious use.

A detergent based chemical nonoxynol-9 (N-9) kills STI and HIV in vitro but while clinical trials suggest that the product provides some protection against gonococcus and chlamydia, results are disappointing for HIV.\(^6^1^6\) There is also concern that repeated use of these compounds can disrupt the vaginal and rectal epithelium and actually make users more susceptible to pathogens.\(^6^0^6\) This is a problem especially for female sex workers who would want to use it a lot.

New compounds are under development and evaluation. Studies using BufferGel (ReProtect) have shown positive spermicidal effects and also a decrease in symptoms of bacterial vaginosis, a condition which is highly prevalent in some areas and which increases susceptibility to HIV infection.\(^2^0^–^2^2^6\) Other studies have shown that an antibody-based microbicide that persists in the vaginal tract for 2–3 days may be feasible. This would be useful for women who have multiple sexual contacts in a setting where it is difficult to re-apply a microbicide.
It is possible that anti-retroviral agents already approved for systemic treatment may be used intravaginally and in fact many researchers predict that 'intravaginal chemoprophylaxis' may require a combination of agents to be optimally effective.

**Vaccines**

Vaccines have enormous potential in the prevention and control of STIs and some are currently under development for *Neisseria gonorrhoeae, Chlamydia trachomatis*, herpes simplex virus, human papilloma virus and HIV. However, there are difficulties in making effective vaccines available for use by those in need.

Firstly, many STI agents do not evoke lasting immunity even subsequent to natural infection. Agents such as *N. gonorrhoeae* and HIV are constantly evolving and this makes it difficult to create a reliable and widely applicable vaccine. Secondly, there are problems with the logistics of vaccine delivery. A vaccine against hepatitis B has been available for about 20 years but most sexually active adults remain unprotected today. The practicalities of vaccination are well known through experiences with the EPI immunization programmes, but another important issue for STI vaccines is acceptability by the target population. Unique barriers to STI vaccine acceptance are likely to be encountered. For example, it could be argued that STI vaccination in adolescents would condone extramarital sex and, despite evidence to the contrary, such arguments are still used in opposition to sex education or condom distribution programmes at schools. Zimet suggests that issues around consent (parental and adolescent) are likely to be key and that substantial research will be required in order to guide programme design. Thirdly, vaccination may influence sexual behaviour by promoting a feeling of invulnerability with a subsequent increase in risky behaviour.

**Individual, community and targeted intervention strategies**

An important consideration in STI control is to decide on strategies that target the individual, the community or special groups of individuals at higher risk of, or more vulnerable to, STIs within communities. Clearly, a number of strategies target the individual such as screening, case management and partner notification, whilst community strategies will include mostly primary prevention such as information, education and communication (IEC) campaigns, or vaccine programmes. In recent years, strategies to control STI through mass treatment programmes have been attempted.

Interventions targeted at individuals may fail to identify or influence behaviours of people at some level of risk but who do not identify themselves with the target group. On the other hand, although general
population or community measures deliver a less intensive dose of intervention to each individual, it is distributed across a large population that includes many individuals at low risk. It has been suggested that both types of intervention are appropriate at different points in the epidemic. At the start of an epidemic when individuals at risk are difficult to distinguish, general population interventions are appropriate. Targeting is indicated when sexual mixing patterns have been identified and later, when the epidemic moves into the general population and core groups have emerged, universal interventions are needed.

STI control programmes need a mix of individual and general population interventions. The challenge is how best to use and combine interventions and how to make sure policy and political support is conducive to help change the social or physical environment in which risk takes place. For example, restrictive policies about prostitution will hamper interventions targeting sex workers; sociocultural environments which promote homophobia or deny sexual health information to adolescents will prevent access of these vulnerable populations to appropriate sexual health services, or may encourage clandestine risk-taking. Economic empowerment of women can also be effective.

**Challenges in STI control**

*Integration of STI prevention and care in reproductive health services*

There is general consensus on the need to integrate STI services into reproductive health services. The rationale is that reproductive health programmes are already high profile and could attract additional funds necessary for STI treatment. In addition, integrated services could reach a wide female population.

It has been suggested that, at a minimum, STI/HIV risk assessment and prevention services should be provided in all MCH/FP clinics, and that integrated services should also include syphilis testing and treatment for all pregnant women attending antenatal services.

In economic terms it is thought that integration will optimise resources, reduce service delivery costs and patient transport costs as well as other opportunity costs relating to multiple health service visits. However, there is little evidence that integration is in fact an effective public health measure. A study of health systems in sub-Saharan Africa suggests that pre-existing vertical management and separate service delivery have hindered efforts to translate concepts into practice. For example, in Kenya the provision of drugs essential for STI treatment has remained separate from existing systems of procurement and in Ghana FP management has remained separate from other ‘integrated’ services. South Africa, on the other hand, has been more
successful in developing an integrated and comprehensive service. This has been facilitated by South Africa’s strong commitment, since 1994, to universal access to comprehensive primary healthcare (PHC). The South African approach has integrated all financial, human resources and logistical systems at provincial level, and the national programmes provide technical support to services through horizontal management systems at all levels. But the South African system is not trouble free. The provision of free comprehensive care has lead to increased demands on the health system and this has stretched the capacity of staff at health facilities as well as finances available for effective drugs. In addition, as elsewhere, an emphasis on clinical care has tended to be at the expense of health promotion services\textsuperscript{65}.

It is important to note that integration of STI services can miss one of the largest target groups – men. This is an important group as men, due to sexual behaviour and increased mobility, are at higher risk, initially, of contracting STI. However, once infected, the clinical management of men is simpler than for women. Investigators in Bangladesh found that there was a substantial unmet need for STI services for men and that, in addition, there was a demand for other reproductive and psychosexual services. It may, therefore, be appropriate to provide comprehensive reproductive health services to men as well as women and this may even prove to be an effective strategy for the control of STI\textsuperscript{66}.

The changing epidemiology of STI

Additional challenges to STI control include the capacity of pathogens to develop resistance to antimicrobials, and the emergence of some pathogens (HSV-2) or conditions (bacterial vaginosis) as novel significant causes of morbidity, including facilitation of HIV transmission.

Global antimicrobial resistance of \textit{N. gonorrhoeae} and \textit{Haemophilus ducreyi}

At present most regions of the world have a high prevalence of \textit{N. gonorrhoeae} and \textit{H. ducreyi} isolates resistant to common antibiotics such as penicillin, tetracyclin or cotrimoxazole\textsuperscript{67}. Resistance is most common in areas of the world where effective treatment is unavailable or expensive and where diagnostic facilities are inadequate (Fig. 4). The high costs of effective agents such as azithromycin and ceftriaxone raise concerns that low or inadequate doses will be used and that this will facilitate the selection of resistance to these drugs also. Conversely, the decreasing costs of agents such as quinolones may precipitate their improper use and self-medication, also leading to increased resistance.

In order to provide effective treatment and prevent the transmission of resistant isolates, regimens need to be tailored to the prevalence of antimicrobial resistance in the locality. This in turn requires information on patterns of anti-microbial susceptibility. Many industrialised countries have
programmes for \( N. \) gonorrhoeae surveillance, but continuous susceptibility data has been lacking in non-industrialised countries. This problem has been approached by the establishment of a global surveillance network – the gonococcal antimicrobial susceptibility programme (GASP). Co-ordinated by WHO, GASP aims to create a network of laboratories which will monitor susceptibility of gonococcal isolates and disseminate information on trends in susceptibility and resistance (Fig. 4). The network is only effectively working in the West Pacific and the Pan-American regions, but efforts are underway to promote the establishment of such networks in Africa.

Surveillance of \( H. \) ducreyi requires a viable culture of the organism. This is a barrier to effective surveillance as isolation of \( H. \) ducreyi is particularly difficult and often has a sensitivity of < 80% \(^67\). In addition, few centres have facilities for culture. Our knowledge of \( H. \) ducreyi resistance is limited to irregular sentinel surveillance data and hence the global prevalence of antibiotic resistant \( H. \) ducreyi is unknown \(^67\).

The emergence of HSV-2 and the changing pattern of genital ulcer aetiologies

World-wide prevalence rates for infection with HSV-2 have been increasing over the last decades. In the US, recent seroprevalence studies indicate that 22–33% of the population is infected with HSV-2, representing a 33% increase over the past 20 years \(^68\). High seroprevalence rates of HSV-2 (40–70%) have been recorded in population-based studies in East and Southern Africa \(^69\).

In countries where syphilis and chancroid are endemic, HSV-2 has traditionally been thought to be relatively less important as an aetiological agent of genital ulcer disease (GUD). This pattern is changing however \(^69\). Recent studies have found that, while GUD attributable to HSV-2 infection is increasing, \( H. \) ducreyi is decreasing in many areas. HSV-2 now typically
represents 40–50% of detectable GUD aetiologies in some settings (Fig. 5). The implications of this increasing problem only begin to be fully appreciated. Given the fact that HSV-2 and HIV may have a synergistic effect, increased levels of HSV-2 in GUD will promote susceptibility to HIV or infectiousness of HIV-infected individuals, whilst HIV will contribute to the further spread of HSV-2 as well as the worsening of the natural course of GUD cases which will lead to many apparent failures of treatment. One consequence is that it may be important to revise the WHO guidelines for syndromic management of GUD and possibly include anti-HSV treatment. Intervention trials evaluating the feasibility and impact of such treatment strategy, with an important outcome in terms of HIV shedding, are urgently required.

The role of vaginal and endogenous infections
Greater more attention has been accorded in recent years to bacterial vaginosis (BV) as a possible significant factor in women’s sexual ill-health world-wide. BV is one of the most common causes of vaginal symptoms among women of reproductive ages and is associated with serious obstetric and gynaecological complication, including premature rupture of membranes, preterm birth and low birth weight infants, as well as pelvic inflammatory disease or endometritis following insertion of intra-uterine devices (IUD) or induced abortion. Recent investigations in Thailand, Uganda, and Malawi have reported associations between BV and HIV, suggesting a possible causal factor in HIV transmission.

Although the role of BV in women’s health in non-industrialised countries has not been fully explored, it is potentially significant as suggested by high prevalence rates (20–50%) and the frequency of BV-associated morbidity in these regions. Moreover, even a moderate relative-risk may translate into a large population-attributable fraction of HIV infection.
It will be important to understand better the determinants of acquisition or maintenance of BV in women, including the role of hormonal factors, menstrual and sexual hygiene. The main obstacles to the control of BV are the difficulty of diagnosing the condition in primary health care clinics lacking microscopy and trained laboratory personnel, and the frequent relapse of the condition despite treatment. The challenges, therefore, will be to devise simpler and more effective methods to diagnose and treat BV and ways to implement and evaluate large-scale BV control programmes in non-industrialised countries.

Mobilising policy, priority setting and capacity building

The failure to control STIs in the past was not solely due to antibiotic resistance nor to any emergent or resurgent organisms, but simply through lack of political will to invest in control measures. In order to mobilise policy, it is vital to identify the barriers that prevent research findings being translated into policy at country level. One such barrier is a lack of appropriate models of service provision which facilitate the design of effective STI control programmes. Another is the lack of operational research into ways of adapting international research findings to the national context.

Many governments are reluctant to confront the STI and HIV epidemics and in many instances countries fail to prioritise activities in the face of severe financial and administrative constraints. Spreading resources across programmes in many sectors risks stretching already scarce resources with negligible or even negative impact. An alternative approach for policy makers would be to implement a smaller, core set of interventions on a national scale and in this way provide a foundation for expansion of activities.

The operational model of STI control discussed above makes it clear that curative services alone contribute a small fraction to STI control efforts and will not solve the problem. It is essential, therefore, to build national capacity in areas that interact synergistically with case management to create an effective and sustainable approach to STI control. Training in all areas is essential and this needs to take place in a policy environment which enables managers to advocate for policy changes which can improve and sustain the national capacity to implement an effective STI control programme.

Future research orientations

In order to control STI better in the future, a number of important research questions will need to be answered, and a number of research strategies will need to be explored:

1. Operational research is required to establish the effectiveness of existing interventions and improve the implementation of these interventions in specific
contexts. For example, operational research to refine and adapt context specific syndromic management algorithms and to assess the cost-effectiveness of various STI case management approaches.

2 Randomised controlled trials (RCTs) are required to examine the comparative efficacy and cost-effectiveness of different partner notification strategies as well as research into cheap strategies for improving patient attendance.

3 There is an urgent need for the development and field-testing of simple rapid diagnostic tests for *N. gonorrhoeae* and *C. trachomatis* so that asymptomatic infections can be detected and treated. Research is required to rationalise available and future diagnostic techniques in order to guide choices as to who should be tested.

4 The development of vaccines and vaginal microbicides is especially urgent for the incurable viral STIs (HPV, HSV-2, HIV). Both the World Bank and UNAIDS have stated that their organisations are making a strong commitment to purchase and distribute effective microbicides when they become available.

5 There is a need for RCTs to assess the effectiveness of primary prevention and behavioural interventions, particularly among vulnerable populations such as adolescents, using STI and HIV incidence as outcome measures. One such trial is currently underway in Mwanza, Tanzania, but more are needed in different cultural and epidemiological settings.

6 Capacity building is an important pre-requisite to enable research in non-industrialised countries and this needs to be developed along with functioning support structures, access to information and positive feed-back – in the form of publications, grants and policy change.

7 In 1999, the World Bank indicated that the international community has the responsibility for ensuring the production of global public goods. However, funding for research and the development of new technology may be a problem when private firms do not have sufficient incentives to develop the technology – the main beneficiaries live in impoverished countries that cannot afford to pay. It is, therefore, a priority to promote public-private partnerships to develop medical products, and to conduct research into how this may best be achieved.

**Conclusions**

STIs have taken on a more important role with the advent of the HIV/AIDS epidemic, and there is good evidence that their control can reduce HIV transmission. Although many cost-effective tools such as condoms, effective drugs and the syndromic approach to case management are already in existence (Table 1), there is an urgent need for research into more interventions such as vaginal microbicides, vaccines and behaviour change.
However, even where existing tools are available, there are barriers to the effective utilisation of these tools (Table 2). These barriers include unavailability or unsuitability of STI services, cultural factors in sexual and health-care seeking behaviour, difficulties in the provision of essential drugs, a lack of political will to develop appropriate policies, and financial support for STI control programmes.

The challenge, therefore, is not just to develop new interventions, but to identify barriers to the effective implementation of existing tools, and to devise ways to overcome these barriers. This ‘scaling-up’ of effective strategies will require an international and a multisectoral approach. It will require the formation of new partnerships between the private and public sectors and between governments and the communities they represent.

Table 1 Public health package for STI control: the key elements

| Promotion of safer sexual behaviour and primary prevention |
| Condom programmes                                      |
| Promotion of appropriate health care seeking behaviour  |
| Integration of STI care into basic healthcare services   |
| Comprehensive and syndromic STI case management         |
| Specific services for populations at high risk           |
| Control of congenital syphilis and neonatal conjunctivitis|
| Development of female-controlled methods (microbicides, female condoms) |

Table 2 Challenges for effective STI control

<table>
<thead>
<tr>
<th>Inappropriate STI services</th>
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<tbody>
<tr>
<td>diagnostic tests, drugs, condoms</td>
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<tr>
<td>training, attitudes, staff numbers</td>
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<tr>
<td>involving public and private providers</td>
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<tr>
<td>Strategies for women, lack of integrated services</td>
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<tr>
<td>Strategies for adolescents, linked with education</td>
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<tr>
<td>Lack of male responsibility, gender inequalities</td>
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<tr>
<td>Societal norms (‘shame’), education, information</td>
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<tr>
<td>Structural issues and capacity</td>
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<tr>
<td>Political/policy will, neglect</td>
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<tr>
<td>Economics, poverty, instability, migration</td>
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