SCIENCE & SOCIETY

Conquering sexually transmitted diseases

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Abstract | Sexually transmitted diseases (STDs) are a major public-health problem and also a significant financial burden on the economy. Past and ongoing attempts to create vaccines against sexually transmitted pathogens have met with varying success. This article highlights some of the public-health and social problems that are associated with STDs and the technical and ethical challenges in treating them, and raises several questions that need to be addressed if STDs are to be conquered.

Sexually transmitted diseases (STDs) are caused by pathogens that are transmitted through sexual contact. They make up a major portion of infectious diseases and are a significant public-health and financial burden on society worldwide. There are many types of sexually transmitted pathogens, and each of the diseases that is associated with the different pathogens is unique (TABLE 1). Here we focus on three different sexually transmitted pathogens, namely, HIV, human papillomavirus (HPV) and *Chlamydia trachomatis*, and we illustrate the public-health issues that are associated with infection by these pathogens. HPV and *C. trachomatis* are included as examples of extremely prevalent STDs, and HIV is considered because it is associated with an extremely high rate of mortality.

Impact on society

Public-health burden. If mortality is used as a measure of the impact of an STD on public health, HIV, the causative agent of AIDS, is at the top of the list. HIV infections cost an estimated 2.1 million lives in 2007 alone (FIG. 1), with most cases occurring in developing nations[1]. Significant resources have been allocated to programmes designed to decrease the spread of HIV infection in developing nations, yet these initiatives have not been effective at stopping the AIDS epidemic, and additional control measures to prevent the rapid spread of the virus are urgently needed.

Infections with other STDs are of concern because of the pathologies that are generally associated with the indirect consequences of long-term infection. The major complication associated with HPV infection is cervical cancer, which is caused by transformation of HPV-infected cells long after the initial exposure to the virus. An estimated 273,000 deaths are thought to occur worldwide each year from cervical cancer, and most of these cases result from previous exposure to HPV[2].

Several major diseases are sequelae of *C. trachomatis* infection. Although *C. trachomatis* infections do not typically lead to mortality, untreated infections can stimulate the chronic production of pro-inflammatory cytokines, leading to inflammation and the eventual damage of the infected tissues. This *C. trachomatis*-induced damage increases the risk of pelvic inflammatory disease, ectopic pregnancy, premature delivery and infertility. Although the microorganism can be cleared from infected individuals by antibiotic treatment, diagnosis of the infection often occurs too late, when irreversible tissue damage has already taken place. The epidemic of *C. trachomatis* infection is distributed worldwide, and it has been estimated that there are over 90 million people infected each year (FIG. 2).

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Financial burden. For all STDs, a major problem for society is the amount of money that is spent on the screening, diagnosis and treatment of infections. It requires relatively little money to routinely screen for infection with *C. trachomatis* and to treat infected individuals with antibiotics. However, the cost of treating the sequelae of *C. trachomatis* infection, including treatment for infertility, has been estimated to be billions of dollars per year in the United States alone[3,4].

Similarly, significant public and private funds are used to treat HIV infections (by the administration of anti-retroviral drugs) and HPV infections (usually by the surgical removal of lesions). ‘Curing’ society of some of these STDs would free up a significant amount of capital that could be invested in the treatment of, or in vaccine research for, other diseases that have a large impact on worldwide public health and mortality. These include infectious diseases that are not sexually transmitted, such as tuberculosis, malaria and avian influenza, as well as non-infectious diseases such as cardiovascular diseases and cancer.

Strategies for eliminating STDs

Prevention strategies. Public-health organizations have always promoted prevention of infection as a major strategy to disrupt the spread of STDs. Public-health officials, health-care providers, educators and community-based organizations have advocated preventative approaches, including premarital abstinence, monogamy, and barrier methods of safe sex. Condom use and counselling have been shown to reduce the acquisition and transmission of a number of these pathogens, sometimes with dramatic results. These efforts will continue to be a mainstay of public-heath efforts to combat these diseases, and there is additional appreciation that social networks in a community can have dramatic effects on the spread of STDs[5]. For example, there is a much greater risk of a disease spreading in a community

when individuals in that community have multiple concurrent sexual relationships than when individuals move serially from one monogamous relationship to another. Understanding the dynamics of the spread of STDs in these networks can drive intervention strategies that target individuals who are likely to spread these infections most widely. Control efforts to disrupt spread through social networks can be particularly effective when prevention and treatment information is provided in venues, such as social clubs and internet websites, where people often establish multiple concurrent relationships. In addition, once an infected individual is identified, partner notification efforts can be directed towards treating not only those that have been infected owing to sexual contact with the individual, but also those in the individual's social network that might have been the source of the infection.

Drug-treatment strategies. One strategy for eliminating STDs is to use antibiotics to treat the infections. Depending on the pathogen, drug therapy can either cure the infection or delay disease progression. A number of sexually transmitted bacteria, such as *Treponema pallidum* (the causative agent of syphilis), *Neisseria gonorrhoeae* and *C. trachomatis*, can be eliminated by antibiotic treatment. However, antibiotic resistance has become a problem, especially for *N. gonorrhoeae*[6], and this has spurred an interest in developing more effective antibiotics.

Although potent drug treatments have long been available for many bacterial pathogens, to date no infectious agent has been completely eradicated through the use of antibiotics. One difficulty with this strategy is in maintaining complete drug coverage for a long enough period of time to eliminate the pathogen from the target population. In addition, unless the drug-cured population is quarantined, it is possible for the pathogen to be reintroduced once the antibiotic therapy is stopped. It is also worth noting that most sexually transmitted viruses (such as HIV, HPV and herpes simplex virus) cannot be completely eliminated from individuals by drug treatment, as antiviral drugs only limit viral replication. Unfortunately, drug treatment as a strategy for the eradication of STD pathogens is unlikely to be effective.

Vaccine strategies. In contrast to drug treatment, vaccines against certain infectious diseases have resulted in complete eradication. Smallpox was the first infectious disease to be eradicated by vaccination, and worldwide eradication of polio by vaccination is anticipated in the coming years. Therefore, the development of effective vaccines will be the most efficient way to protect the population against STDs.

Clinically effective vaccines against STDs include the hepatitis B virus (HBV) vaccine and the recently licenced HPV vaccine. Both are subunit vaccines that are composed of viral surface antigens. The plasma-derived HBV surface-antigen vaccine was licensed in the United States in 1981, and was replaced in 1986 by a recombinant vaccine that consists of highly purified HBV surface antigens. The current HPV vaccines contain the recombinant L1 capsid protein from HPV type 16 and HPV type 18, two HPV types that are associated with approximately 70% of cervical cancer cases[7] (BOX 1). The recombinant L1 protein spontaneously self-assembles into virus-like particles that elicit a protective antibody response when they are injected into recipients[8]. Both the HBV and the HPV subunit vaccine have proved effective in preventing infection in vaccinated individuals[9,10], but whether these vaccines will eventually eradicate these STDs remains to be determined. In particular, the elimination of HPV infections through vaccination would require the development of a whole new class of vaccines to cover the virus types that are not targeted by the current vaccines. The challenge in creating a vaccine to protect against all HPV types is the difficult, and perhaps insurmountable, requirement for the vaccine to generate cross-protective antibodies that are effective against the more than 100 HPV types that have been identified.

Challenges for vaccination

Scientific challenges. For both the HBV and the HPV subunit vaccines, eliciting antibody responses against a single surface antigen mediates adequate protection against infection by the virus in most individuals. However, subunit vaccines that target a single antigen might not be sufficient to protect against other sexually transmitted pathogens. Vaccines against HIV have been a challenge to develop owing to the antigenic diversity of HIV isolates, the rapid mutation rate of the virus, and the inability of neutralizing antibodies to access hidden epitopes from the heavily glycosylated gp120 surface protein[11]. Clinical trials have concluded that subunit vaccines that were designed to either elicit gp120-specific antibodies or induce Gag-, Pol- and Nef-specific T cells were ineffective

Table 1 | **Selected common sexually transmitted pathogens**

Pathogen	Diseases and symptoms	Treatment	Immunization
Human papillomavirus	Genital warts, cervical cancer	Surgical removal of pre-cancerous or cancerous lesions	Human papillomavirus vaccine
Chlamydia trachomatis	Urethral infection, pelvic inflammatory disease, ectopic pregnancy, infertility	Antibiotics such as azithromycin	No available vaccine
HIV	AIDS	Suppression of virus with antiviral drug therapy	No available vaccine
Neisseria gonorrhoeae	Gonorrhea; urethral infection, pelvic inflammatory disease, ectopic pregnancy, infertility	Antibiotics such as cephalosporins	No available vaccine
Treponema pallidum	Syphilis; genital ulcers, neurological damage, heart disease	Antibiotics such as penicillin	No available vaccine
Haemophilus ducreyi	Chancroid; genital ulcers	Antibiotics such as azithromycin	No available vaccine
Herpes simplex virus	Genital lesions	Suppression of virus with antiviral drug therapy	No available vaccine
Hepatitis B virus	Hepatitis; liver cancer	Limited therapeutic options	Hepatitis B vaccine
Hepatitis C virus	Hepatitis	Limited therapeutic options	No available vaccine
Trichomonas vaginalis	Vaginal discharge	Antibiotics such as metronidazole	No available vaccine

Figure 1 | **Estimated number of adults and children living with HIV in 2007.** The figure was compiled using data provided by the WHO/UNAID (2007), see Further Information for details.

at reducing the rates of HIV infection[12,13]. An effective vaccine against HIV might have to stimulate multiple immune effector responses, not just antibody or T-cell responses. Although there was a great deal of optimism early in the HIV/AIDS epidemic that a vaccine would be available quickly, there is now a realization that an effective vaccine might take a decade or more to develop.

Similarly, it is likely that multiple arms of the adaptive immune response will have to be induced to generate sterilizing immunity against bacterial STDs such as *C. trachomatis*. Mouse models of *C. trachomatis* infection have suggested that, although antibodies can provide a modest level of protection against infection, alone they do not confer robust immunity[14]. Therefore, other adaptive immune effectors, such as $CD4^+$ and $CD8^+$ T cells, might have to be stimulated to generate a vaccine that is potent enough to protect humans against *C. trachomatis* infections. Indeed, both $CD4^+$ and $CD8^+$ T cells have been demonstrated to contribute to protective immunity in animal models of infection by *C. trachomatis*[14,15]. Because many studies have shown that previous exposure to *C. trachomatis* does not provide significant immunity against re-infection[16], an effective vaccine against *C. trachomatis* would have to elicit an immune response that is superior to that which is provoked by natural infection.

Another challenge in developing an effective *C. trachomatis* vaccine is the danger of recipients developing immune hypersensitivity — an exaggerated immune response to a foreign substance. This was observed in some clinical trials that used whole microorganisms as vaccines. In particular, a clinical trial conducted in the 1960s that used inactivated *C. trachomatis* to protect against ocular infection found that not only was the immunity short-lived, but even more worrisome, some vaccinated individuals developed more severe disease relative to non-vaccinated individuals following subsequent natural exposure to *C. trachomatis*[17]. Therefore, the major challenge in developing a vaccine for *C. trachomatis* is generating one that can elicit sterilizing immunity, presumably by stimulating multiple immune effector responses, while avoiding immunopathology.

Once candidate vaccines have been developed, additional challenges will remain. Testing the efficacy of an STD vaccine in clinical trials is not straightforward. In STD-vaccine clinical trials, health officials are obligated to counsel barrier methods of safe sex as the standard of care, yet these same methods can block transmission of the agent that is under investigation and hence might result in too few infection cases for the effectiveness of the vaccine to be evaluated. This in turn might necessitate the execution of unusually large clinical trials testing many subjects. Another issue to consider when testing a vaccine is whether the effectiveness of the vaccine should be measured by the reduced acquisition of infection or by the reduced incidence of pathology (such as reduced incidences of cancer or infertility).

Social policy and practical issues. Besides the scientific challenges that are inherent in developing vaccines against STDs, there are also a number of social-policy and practical issues to consider. The development of vaccines that are designed to stimulate multiple arms of the adaptive immune response will benefit from increased collaboration among research organizations. Individual academic and industrial laboratories often focus their approach on the development of specific vaccine components that might stimulate only one arm of the immune system. Further complicating these collaborative efforts are the commercial and intellectual-property interests of these laboratories. It might be difficult to encourage companies and other research organizations to develop partnerships because the financial gains that would result from the creation of a successful vaccine by collaborative efforts would be diluted among these organizations. Society would benefit by creating incentives for companies to test combinations of antigens or delivery vehicles used in individual vaccines, as these combinations might have more potency

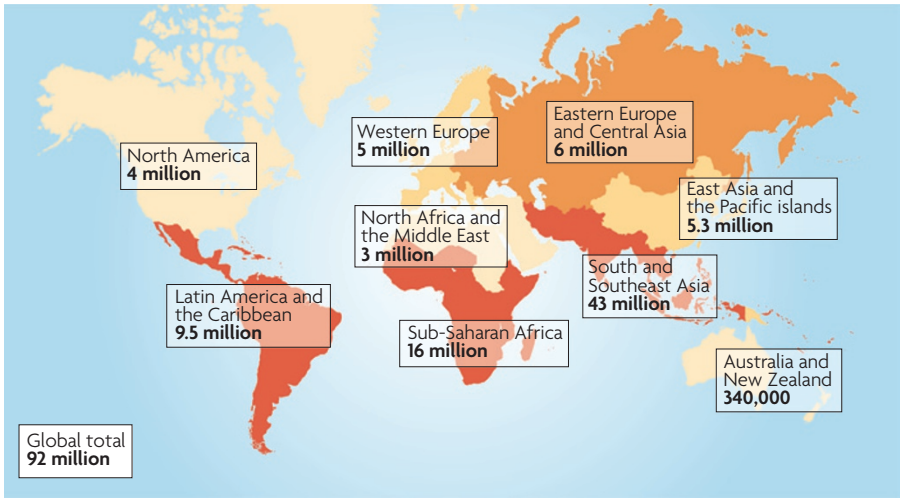

Figure 2 | **Estimated number of new cases of *Chlamydia trachomatis* infections among adults in 1999.** The figure was compiled using data provided by the WHO (2001), see Further Information for details.

Box 1 | **Design and testing of the HPV vaccines**

Two human papilloma virus (HPV) vaccines are currently being marketed in various parts of the world: Gardasil, which is manufactured by Merck & Co., Inc. and Cervarix, which is manufactured by GlaxoSmithKline. Both vaccines contain virus-like particles (VLPs) that are assembled by producing the papillomavirus L1 protein in cultured cells. The vaccines result from work in the early 1990s by several research groups that discovered that the viral L1 protein would assemble into VLPs — structures that, to the immune system, resemble the surface of the actual virus. Both Gardasil and Cervarix contain VLPs derived from HPV type 16 and type 18, the HPV types that are responsible for approximately 70% of cervical cancer cases. Gardasil contains additional VLPs from type 6 and type 11, which together cause approximately 90% of genital warts cases but are not commonly associated with cervical cancer. Both vaccines have been shown in clinical trials to reduce the incidence of infection by HPV type 16 and type 18 (REFS 7,10,19).

When one of these vaccines is administered to a patient, the VLPs stimulate the production of antibodies against HPV type 16 and type 18. If the patient is subsequently exposed to these HPV types by an infected partner, the pre-formed antibodies will help to prevent infection. The vaccines are designed to be prophylactic vaccines (that is, preventative vaccines) rather than therapeutic vaccines; therefore the goal is to administer the vaccine to adolescents before they are sexually active and at risk of exposure to HPV. The current vaccines do not prevent against infection by all of the HPV types that can cause cervical cancer. It might eventually be shown that the current vaccines afford some cross-protection against other cancer-causing HPV types, but the protection against cervical cancer is likely to be incomplete. Additionally, there are still more than one hundred other HPV types that are not targeted by the vaccine, and so immunization with the current vaccines cannot be expected to eradicate HPV.

than STD vaccines formulated by a single research entity.

Another challenge, and the ultimate goal of vaccine development, is to achieve worldwide eradication of the targeted sexually transmitted pathogen. Owing to increasing globalization, STD eradication will not be achieved by vaccinating individuals in the developed world only, as developing nations that don't have access to the vaccines would continue to harbour a reservoir of the pathogen. Therefore, reducing the cost of vaccination and developing cost-effective vaccination programmes for developing countries should be a priority.

However, the need to develop a low-cost, effective vaccine begs the question of who should fund the costs of vaccine manufacture and administration. Is it in the financial interest of the pharmaceutical companies that produce the vaccines to also fund the actual vaccination programmes aimed at STD eradication? Or should the funding rely on private donors and non-governmental organizations? Or should governments fund the costs of these vaccination programmes? And if government funding is expected, do the governments of developed nations have an obligation to fund vaccination programmes for developing countries of which the governments are unable to afford them? Only through dialogue among all of these interested parties will there be progress that leads to the global implementation of vaccination programmes.

Ethical issues. Finally, there are also ethical issues with implementing vaccine campaigns against STDs. Some of these have already been revealed in the controversies that have surrounded the recently licenced HPV vaccine[18]. Currently this vaccine is only offered to females, but full eradication of HPV might require the vaccination of males as well. In males, however, it is unclear whether the HPV vaccine is as effective at preventing infection or blocking transmission, and there is debate as to whether it is even acceptable to vaccinate males when the health benefits are predominantly for females. It is also unclear whether it is financially worthwhile to vaccinate males without having additional data that show that doing so would provide additive benefit in lowering the number of cancer cases in females. The availability of HPV vaccines has also prompted the question of what pressures, if any, should be brought to bear on those who choose not to be vaccinated. Does society have the right to pressure parents or individuals to immunize their children or themselves against a disease for which exposure to can be controlled by the individual? Public health has been advanced in the past when parents have been pushed by physicians, school administrators and child care providers to vaccinate their children. In the developed world, these campaigns have resulted in a dramatic reduction in diseases such as smallpox, polio, whooping cough, diphtheria and measles. Officials have long recognized that the more children that are vaccinated, the greater the protection of all of the children in the community, even the small number of children that have not been vaccinated or for whom the vaccine has not worked. This protective effect, which makes it very unlikely that a pathogen can be introduced and spread, is known as 'herd immunity'. Will herd immunity against HPV be achieved if vaccination remains the choice of individuals? The ultimate goal of the HPV vaccine is eradication of the HPV types that cause cancer. However, unless enough people comply, these HPV types will not be eradicated even though the rates of cervical cancer might decrease. Will the vaccine ultimately be deemed a success if it reduces the mortality and financial burden associated with HPV infections without eliminating the virus from the population?

Future direction

There are many hurdles to overcome in developing vaccines against sexually transmitted pathogens. One serious challenge in protecting against these microorganisms is that many of them cause a life-long persistent infection. As a result, vaccination coverage might have to be maintained for a generation or longer to completely eliminate these microorganisms worldwide. However, a key advantage in targeting these microorganisms for eradication is that they all require person-to-person contact in order to spread. By contrast, it is difficult to envision the same kind of eradication being possible for other classes of pathogens, such as *Salmonella enterica* and *Yersinia pestis* (the causative agent of plague), which have environmental and/or animal reservoirs. Overcoming the technical challenges in vaccine development, in addition to the ethical issues that are associated with vaccine implementation, will be fundamental to decreasing the health and societal problems that are caused by STDs.

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DATABASES

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FURTHER INFORMATION

Michael N. Starnbach's homepage: http://starnbachlab.med.harvard.edu
STD information from the US CDC: http://www.cdc.gov/nchstp/dstd/disease_info.htm
Chlamydia information from the UK Department of Health: http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Chlamydia/index.htm
WHO information on STDs: http://www.who.int/topics/sexually_transmitted_infections/en/
WHO information on HIV/AIDS: http://www.who.int/hiv/pub/en/
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US CDC HPV vaccine recommendations: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm
Who invented the HPV vaccine?: http://jnci.oxfordjournals.org/cgi/content/full/98/7/433
UK NHS information on vaccines and an animation of how herd immunity works: http://www.immunisation.nhs.uk/article.php?id=78

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