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The theoretical impact and cost-effectiveness of vaccines that protect against sexually transmitted infections and disease

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ABSTRACT

Sexually transmitted diseases, a source of widespread morbidity and sometimes mortality, are caused by a diverse group of infections with a common route of transmission. Existing vaccines against hepatitis B virus (HBV) and human papilloma virus 16, 18, 6 and 11 are highly efficacious and cost effective. In reviewing the potential role for other vaccines against sexually transmitted infections (STIs) a series of questions needs to be addressed about the burden of disease, the potential characteristics of a new vaccine, and the impact of other interventions. These questions can be viewed in the light of the population dynamics of sexually transmitted infections as a group and how a vaccine can impact these dynamics. Mathematical models show the potential for substantial impact, especially if vaccines are widely used. To better make the case for sexually transmitted infection vaccines we need better data and analyses of the burden of disease, especially severe disease. However, cost effectiveness analyses using a wide range of assumptions show that STI vaccines would be cost effective and their development a worthwhile investment.

1. Introduction

Cost effective vaccination against sexually transmitted infections (STI) is available today in the form of hepatitis B [1] and human papilloma virus vaccination [2,3], but whether future vaccines can also be as cost effective will depend on a range of different factors. These factors include: (1) the cost of the disease; (2) the price of the vaccine; (3) the efficacy or effectiveness of the vaccine; (4) the population requiring immunization; (5) the organization required to provide access to the vaccine; and (6) any alternative interventions against which vaccination has to be measured.

STIs comprise very different organisms grouped according to their route of transmission, with great differences in clinical course and in distribution of infection and disease. These differences include the severity of disease, the duration of infection, the generation of naturally acquired immunity and pattern of spread, all of which play a role in determining how cost effective an STI vaccine could be.

In deciding about the use of resources cost effectiveness analyses allow us to compare the merits of alternative interventions [4]. Models which include the transmission of infection also allow us to explore the potential impact of STI vaccines in different epidemiological contexts and for different vaccine characteristics [5,6].

In this paper, insights from modeling the impact of STI vaccination are discussed as a guide to thinking about the future development and delivery of STI vaccines. The influence of infection and vaccine characteristics on this impact are explored along with the potential design of programs. Finally, illustrative cost-utility analyses are provided for HSV-2 vaccination in the US.

2. The costs of the disease

A summary of the major STIs, the diseases they cause, available treatments and relative prevalence is provided in Table 1 [7]. The burden associated with each disease is a product of its prevalence and its severity. Sexually transmitted diseases (STDs) range in severity from acute hepatitis associated with hepatitis B, cervical and other cancers caused by human papilloma virus infection and AIDS, through to asymptomatic infections caused by the majority of HSV-2, chlamydia and trichomonas infections. Cure is now available for a number of bacterial STIs [8] and treatment to reduce disease severity is available for viral STIs [9]. However, morbidity continues with untreated infections, treatment failure [10], drug resistant infection [11,12] or severe sequelae associated with initially asymptomatic infection [13].

Cost effectiveness analyses for hepatitis B vaccination and for human papilloma virus vaccination are greatly influenced by the severe associated diseases leading to mortality [2,14]. In the case of HPV for lesions that can lead to cervical cancer secondary prevention through screening programs is available and is successful

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Table 1
The major sexually transmitted diseases and a summary of their epidemiology.

	Distribution	Severe disease	Interventions	Vaccine
Virus				
HIV	Generalized/concentrated	AIDS	Treatment;VMMC; PrEP[a]	RV144 (Phase 3)
HBV	Generalized/concentrated	Acute hepatitis Liver cancer Liver cirrhosis	Treatment; transplant	Cheap and available
HR HPV	Widespread	Cervical, vulvar, penile and other Cancers	Screening and ablation	HPV-16/18
HPV 6/11	Widespread	Recurrent respiratory papillomatosisExtensive genital warts		Available
HSV-2	Widespread	Neonatal herpes; HIV risk	Treatment	X
Bacteria/protazoa				
Gonorrhea	Concentrated	Infertility; Ectopic pregnancy; Disseminated; HIV risk	Cure	X
Chlamydia	Generalized	Infertility; Ectopic pregnancy; HIV risk?	Cure	X
Syphilis	Concentrated	Tertiary? Neonatal; Fetal loss; HIV risk	Cure	X
Trichomonas	Locally generalized	Preterm labor; HIV risk?	Cure	X
Chancroid	Highly concentrated	HIV risk	Cure	X

[a] VMMC – voluntary medical male circumcision; PrEP – pre-exposure prophylaxis.

if well-organized [15]. Nonetheless a vaccination program providing primary prevention can still be cost effective because of the failure of the system to screen some women, to catch rapidly progressing lesions and to prevent difficult to detect lesions that lead to adenocarcinomas [16].

Herpes simplex virus type 2 (HSV-2) is highly prevalent in many populations, but often asymptomatic [17]. There are three main reasons why HSV-2 vaccination could be cost effective (1) the virus causes psychosocial problems because of the long term infection, its infectiousness and the risks of infecting partners; (2) the risks of vertical transmission and the severe disease associated with neonatal infection; and (3) its role in enhancing susceptibility and transmissibility of HIV. Syphilis is less prevalent, but in addition to being associated with HIV acquisition is, in pregnant women, a cause of adverse pregnancy outcomes, including fetal loss, still births and congenital syphilis [18]. Gonorrhea and chlamydia can also cause neonatal disease [19] and appear to be associated with HIV risk [20]. In the case of gonorrhea and chlamydia, infertility and ectopic pregnancy are currently the major diseases [21].

A further concern for bacterial STIs, especially gonorrhea, is that resistance to antimicrobials has emerged [12]. Given its rapid evolution and recombination gonorrhea has been able to become resistant to most classes of antibiotics used in its treatment. This undermines current interventions and could allow rapid reinvasion where gonorrhea is currently controlled.

The burden of disease for STIs is extremely difficult to quantify for a number of reasons [22,23]. First, surveillance is inadequate, particularly in many of the resource poor settings where STI incidence is possibly highest; second there are sensitivities over the reporting of stigmatized conditions; third many infections are asymptomatic and many symptoms are not unique to particular infections; fourth the causal association between the STIs and disease is often difficult to quantify, as is the case for infertility caused by chlamydia [24] and preterm labor caused by trichomonas [25] and HIV transmission associated with all the different STDs [20].

Nonetheless informed investment in STI vaccine development requires an estimate of the potential impact of the vaccine. The World Health Organization has estimated that there were half a billion new cases of curable STIs amongst 15–49 year olds in 2008 [26]. The scale of this estimate, based on published prevalence surveys, is driven by chlamydia and trichomoniasis prevalence and has been translated via age specific incidence estimates alongside Disability Adjusted Live Year (DALY) estimates for specific causes into a global burden of disease. It is estimated that the curable STDs contribute 11 million DALYs per year, largely driven by neonatal syphilis [27].

An interesting example of the difficulty in measuring the incidence of STIs and the severity of disease is provided by genital warts. These can be prevented by vaccination against HPV 6 and 11, with these two types included in one of the two currently available HPV vaccines [28]. Is an additional cost justified if we can prevent genital warts? This question can only be answered if we know the incidence of genital warts and suffering they cause. This has led to studies better characterizing the incidence of genital warts and the willingness of people to pay to prevent them [29,30]. This work suggests that they are more serious than was previously believed.

Primary prevention through vaccination can reduce treatment costs in addition to preventing suffering associated with disease. However, the extent to which program costs can be averted depends on whether screening to identify and treat asymptomatic infections or providing specialist clinics to treat sexually transmitted infection continue to be required in spite of reduced incidence associated with vaccination. When infection is eliminated (or eradicated) and minimum vigilance is required to prevent reintroduction these costs will no longer be incurred.

In a review of PubMed with search terms: (Costs OR Cost-effectiveness OR Cost-Benefit) AND (syphilis OR Gonorrhoeae OR Chlamydia OR Herpes Simplex Virus Type 2 OR Trichomonas) a picture was developed of the type of costs data available for STDs from developed and developing countries which is summarized in Table 2. It is notable that costs are available for HIV, HBV and HPV; the latter two potentially because vaccines became available and drove a need for data to assist with decisions. It is also notable that the burden is largely estimated from medical care costs in developed countries, where treatment is available. This leaves the question of whether this is appropriate care [31,32]. The costs estimated for the US by Owusu-Edusei and colleagues for the total lifetime direct medical cost associated with the 19.7 million cases of STIs in 2008 were $15.6 (range, $11.0–$20.6) billion with contributions from: chlamydia $516.7 million; gonorrhea $162.1 million; hepatitis B virus $50.7 million; HIV $12.6 billion; human papilloma virus $1.7 billion; herpes simplex virus type 2 $540.7 million; Syphilis $39.3 million; trichomoniasis $24.0 million. Costs of alternative interventions such as screening programs are not included in these direct medical cost estimates. For Chlamydia in the US, there was an assessment of the societal cost of STDs via productivity losses [33]. In the US the evidence suggests a very large burden of treatment costs for STDs. Elsewhere the burden is poorly measured, but as the infections are widespread and severe disease can follow, it is likely substantial.

3. The price of the vaccine

It is obvious that the more expensive a vaccine is to manufacture and distribute the less cost effective it will be. Requirements, such as multiple doses and a cold chain can increase manufacturing and distribution costs. Even more problematic would be the requirement for repeated immunizations over a long period.