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Syphilis Vaccine Development: Requirements, Challenges and Opportunities

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Abstract

Syphilis, caused by the spirochete *Treponema pallidum* subspecies *pallidum*, continues to be a prevalent disease in low- and middle-income countries, and has re-emerged in key populations, including men who have sex with men, in high-income nations. The rising number of cases shows syphilis elimination will require augmentation of public health screening and treatment campaigns with syphilis vaccine development and implementation initiatives. Optimal vaccine candidates, deciphered from careful consideration of the pathogenic mechanisms employed by *T. pallidum*, will need to be paired with appropriate human-track adjuvants designed to elicit the correlates of protection needed to prevent infection/disease. This article provides an overview of the development pipeline customized for a syphilis vaccine, including the preferred product characteristics, the investment case, and a proposed vaccinogen selection strategy outlining the essential qualities that need to be targeted by a syphilis vaccine.

Keywords

Syphilis; vaccine; HIV; public health; congenital syphilis

Global resurgence of syphilis

Syphilis is a chronic, multistage disease caused by *Treponema pallidum* subsp. *pallidum*, with a global burden of 36 million cases and 11 million new infections per year.[1] While ~90% of syphilis cases occur in developing nations, outbreaks are occurring in Europe, Britain, the United States, Canada, and China.[1–6] In the United States, primary and secondary syphilis rates have doubled over the period of 2005 to 2013, with over 90% of new infections occurring in men and the highest proportion of cases found among men who have sex with men.[7] Congenital syphilis is the most common infection associated with fetal loss or stillbirth in low income settings, with ~1.4 million pregnant women infected with active syphilis per year,[8] resulting in 305,000 cases of fetal loss/stillbirth and 215,000 infants with prematurity and clinical syphilis.[9] While the predominant congenital syphilis burden is in sub-Saharan Africa and South America, rate increases are being observed in other geographical regions. This is exemplified by the dramatic increase experienced recently in

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China, where congenital syphilis cases rose to a rate of 20 per 100,000 live births.[10] Additionally, symptomatic syphilis infections are estimated to increase HIV transmission and acquisition 2 to 5-fold.[11] The global public health threat posed by syphilis highlights the need for effective syphilis control.

The complementary approach of public health screening/treatment initiatives and vaccine development for syphilis elimination

Targeted public health control initiatives, pioneered by the Centers for Disease Control (CDC - National Plan to Eliminate Syphilis from the US[12,13]) and the World Health Organization (WHO - Initiative for the Global Elimination of Congenital Syphilis[14]), have successfully raised awareness of syphilis prevalence and have undoubtedly averted an even greater spike in disease incidence, but have not achieved the goal of syphilis elimination. The continued high incidence of syphilis worldwide, despite the existence of inexpensive and effective penicillin treatment for over 70 years, emphasizes the need to seek an alternative approach for syphilis control. Further, elimination of syphilis as a risk factor for HIV can be achieved only through prevention of new syphilis cases, as the highest risk for HIV acquisition and transmission coincides with early symptomatic syphilis and frequently precedes diagnosis. Similarly, early maternal syphilis poses the highest risk for *T. pallidum* transmission to a developing fetus,[15] and therefore syphilis prevention through vaccination represents the optimal strategy for congenital syphilis elimination. Thus although continued support of public health syphilis prevention and control programs is imperative, it is apparent that disease elimination will only be realized through implementation of a parallel path of syphilis vaccine development.

Vaccine target population and cost analysis

Apart from a few countries, the demographics of syphilis show a clear divide between high-income and middle- and low-income countries. In industrialized countries, syphilis is found predominantly among men who have sex with men, while in low- and middle-income nations infections occur widely in the heterosexual population. A syphilis vaccine initiative could be targeted to match this demographic profile, at least initially. Immunization of men who have sex with men and other high-risk populations (e.g. sex workers) would be expected to stem the spread of syphilis and to decrease HIV transmission. In nations with a high disease burden, including sub-Saharan Africa and South America, vaccine uptake would be encouraged for the general population, with emphasis on reproductive-aged women to curtail the incidence of congenital syphilis. Recent mathematical modeling studies predict development of a vaccine with an 80% efficacy would eliminate or markedly reduce congenital/infectious syphilis cases, a prediction that remained consistent regardless of whether a mass vaccination or targeted high-risk vaccination strategy was employed.[16]

Preferred product characteristics, tailored for a syphilis vaccine: considerations and challenges

Due to the complexity, extended timeframe and high cost associated with vaccine development pipelines, it is essential that the preferred product characteristics of a syphilis vaccine be thoroughly considered, defined and customized early in the process. Further, the global nature of the public health problem posed by syphilis suggests the vaccine be manufactured for use in low-, middle- and high-income target populations. Standard required qualities from a production standpoint will include a vaccinogen that (1) requires only standard operating procedures and equipment for generation of a high quality vaccine product; (2) can be easily produced and manufactured on large scale to meet supply demand; and (3) exhibits no or minimal batch-to-batch variability and optimal stability regardless of storage conditions. From a public heath perspective, standard required qualities will include a vaccine that (1) uses a routine route of administration; (2) can be inexpensively produced to appeal to industry partners and public health officials and ensure the vaccine reaches target groups; (3) achieves sufficient protection with a reasonable number of immunizations and a convenient immunization schedule to help achieve vaccinee return visit compliance; (4) can be administered safely with no adverse health consequences post-vaccination; and (5) provides long-lasting protection against infection irrespective of age, gender, or route of sexual activity. Pre-clinical studies conducted in the animal model will decipher the immune correlates required for protection from infection/disease, after which a human-track adjuvant can be customized to achieve the necessary correlates of protection using a vaccine formulation safe for clinical trials.

Additional requirements unique to syphilis vaccine development include the following: first, there is a need for the vaccine to be safe for use in pregnant women at any stage of gestation, to combat the deadly consequences of congenital infections. Second, the vaccine needs to be efficacious at preventing all stages of infection to avoid the potential for disease transmission in primary syphilis, the establishment of latency in an infected individual, as well as the debilitating symptoms of secondary and tertiary syphilis. Third, the vaccine must be efficient at inducing cross-strain protection, which is required to protect against reinfection due to the numerous *T. pallidum* strains circulating globally, the well-documented lack of cross-protection induced by syphilis infection[17], and the propensity for individuals to be infected multiple times. And fourth, the vaccine must be effective when administered to HIV-positive individuals, including those taking antiretroviral therapy, due to the high prevalence of HIV/syphilis co-infections[18] and the altered immunity in co-infected individuals. Further, the vaccine would need to be effective in HIV-negative individuals on PrEP, due to the current trend towards expanded use of PrEP amongst higher-risk populations.

The multi-stage disease phenotype and public health significance of syphilis pose unique challenges not encountered with other infectious diseases. The protection afforded by a vaccine must encompass both individual protection (against pathogen dissemination within the body and development of disease symptoms) and public health protection (against disease transmission amongst populations). The period of post-vaccination protection will need to be of a duration that ensures public health protection; if protection is too short in

duration then the public health burden would be great, with a false sense of protection against infectious and congenital syphilis infections and an increased risk for HIV transmission and acquisition. Vaccine implementation initiatives would need to be married with enhanced screening initiatives, to ensure the highest level of global public health is maintained. Complications can be envisioned with previously-infected individuals who remain in a serofast state despite adequate treatment, a situation predicted to affect approximately 12% of syphilis patients.[19] These individuals are likely to maintain their serofast state post-vaccination, despite a presumed lack of active infection, and will thus need to be closely monitored and alternatively assessed for markers of active infection.

Investment case for syphilis vaccine development

An investment in syphilis vaccine development is worthwhile. In the United States, more than $966 million in direct and indirect costs is spent each year as a result of syphilis, including cost of care associated with infectious syphilis ($185.5 million), congenital syphilis ($28.5 million), and HIV attributable to syphilis ($752.2 million).[20] Further, syphilis has the highest disability-adjusted life-years (DALYs) lost of all the curable STIs,[21] and thus, according to this metric, elimination of syphilis would have the highest impact on decreasing disability due to disease morbidity and mortality. The 2015 Global Burden of Disease concluded that syphilis causes 8.71 million years of life lost (YLL), primarily due to the catastrophic and widespread effects of congenital syphilis.[22] Maternal syphilis screening and treatment costs have been estimated at $11–15 per DALY averted.[23] Syphilis vaccination would further reduce this cost/DALY averted, making this one of the most cost-effective public health interventions in the field of sexually transmitted infections.

Proof-of-principle

The most compelling evidence in support of the feasibility of successful syphilis vaccine development is the protection against infection that was achieved by Dr. James Miller in 1973.[24] In fact, syphilis is the only bacterial STI for which a proof of concept vaccine has been developed. In his study, Miller used an extended immunization regimen in rabbits, the optimal animal model for syphilis investigations, with 60 intravenous injections of γ-irradiated *T. pallidum* over 37-weeks, followed by intradermal challenge with the homologous *T. pallidum* strain. Immunized rabbits displayed complete protection against infectious challenge that persisted for at least one year, as demonstrated by lack of chancre development at challenge sites and the absence of infectious treponemes in lymph nodes from the challenged immunized rabbits (Rabbit Infectivity Test, RIT).[24] Miller perceived that the failure of previous attempts to induce protection using *T. pallidum* inactivated by mechanical or chemical treatments was due to destruction of labile surface antigens, which serve as the critical interface between the pathogen surface and the mammalian host. This ground-breaking study demonstrates the feasibility of syphilis vaccine development and highlights the importance of treponemal surface proteins in generating protective immunity. Indeed the unique *T. pallidum* surface, which has few integral outer membrane proteins[25,26] and an unusual lipid content[27], is a major contributing factor to the “stealth” quality of *T. pallidum*[27] and its outer membrane proteins have long been touted as the optimal targets for syphilis vaccine development[17,27–29].

Vaccine development strategy

The most appropriate strategy for developing a successful syphilis vaccine can be predicted by an examination of the natural history of syphilis. Early infection is typified by a primary stage ulcerative lesion, called a chancre, at the site of infection, followed by a disseminated rash and mucosal lesions during the secondary stage of infection.[17] Because syphilis transmission occurs by contact with the infectious primary chancre or secondary lesions, prevention or attenuation of these lesions would be a necessary requirement of a syphilis vaccine, as it would serve to eliminate or reduce person-to-person syphilis transmission. A second critical requirement of a syphilis vaccine is to target dissemination of *T. pallidum* within the infected host. The highly invasive nature of *T. pallidum* is evidenced by the ability of the pathogen to cross the placental barrier to cause congenital syphilis, to invade the central nervous system in ~ 40% of early syphilis patients,[30] to cause the widespread secondary rash, and by the early involvement of liver and kidneys. Animal studies suggest dissemination via the bloodstream and lymphatics begins within hours of infection.[31] The invasive capability of *T. pallidum* is crucial to the development of the serious sequelae of infectious and congenital syphilis, and elimination of treponemal dissemination must thus be a central target of a syphilis vaccine. Such a dual pronged approach, combined with the selection of vaccine antigens that are conserved in sequence to ensure broad protection against circulating *T. pallidum* strains and reinfection, will provide a comprehensive vaccine strategy to protect against syphilis infection at both a public health and an individual level.

Concluding remarks

It is clear that augmentation of public health measures for controlling syphilis with initiatives to foster vaccine development is warranted, and indeed appears to be the only viable path to decrease the burden of infectious and congenital syphilis worldwide. Due to the high prevalence of syphilis/HIV co-infections, particularly amongst men who have sex with men, and the fact that syphilis infection increases the risk of acquisition and transmission of HIV,[11] syphilis control is anticipated to have the added benefit of lessening the global public health burden of HIV. Syphilis vaccine development requires careful consideration of the unique pathogenic strategies and unusual ultrastructure of *T. pallidum*, to enable identification of the optimal vaccine candidates that will target critical steps in the infection process. Future investigations will require determination of the immune correlates associated with protection from disease, and selection of human-track adjuvants to achieve these immune correlates. The syphilis vaccine development pathway will be aided by the pre-existence of an animal model that recapitulates the majority of the disease stages in humans and can be adapted to enable studies of congenital infection, as well as the continued susceptibility of syphilis to penicillin treatment ensuring the safety of downstream clinical trials. A comprehensive syphilis elimination approach that includes vaccine development will allow eradication of a disease that has devastating consequences for sexual and fetal/newborn health, strikes regardless of gender or sexual orientation, and transcends socio-economic status to affect both resource-limited and resource-rich nations.

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Summary

Syphilis vaccine development will complement public health-oriented syphilis prevention initiatives to deliver a two-pronged approach to stemming disease spread worldwide.