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Vaccine development for syphilis

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Abstract

Introduction—Syphilis, caused by the spirochete *Treponema pallidum* subspecies *pallidum*, continues to be a globally prevalent disease despite remaining susceptible to penicillin treatment. Syphilis vaccine development is a viable preventative approach that will serve to complement public health-oriented syphilis prevention, screening and treatment initiatives to deliver a two-pronged approach to stemming disease spread worldwide.

Areas covered—This article provides an overview of the need for development of a syphilis vaccine, summarizes significant information that has been garnered from prior syphilis vaccine studies, discusses the critical aspects of infection that would have to be targeted by a syphilis vaccine, and presents the current understanding within the field of the correlates of protection needed to be achieved through vaccination.

Expert commentary—Syphilis vaccine development should be considered a priority by industry, regulatory and funding agencies, and should be appropriately promoted and supported.

Keywords

Syphilis; congenital syphilis; HIV co-infection; cross-protection; cellular immunity; humoral immunity; men who have sex with men; vaccine

1. Introduction

Syphilis continues to be a prevalent and significant disease with a worldwide distribution and an estimated global burden of 18 million cases and 5.6 million new cases per year [1]. While over 90% of syphilis cases occur in low- and middle-income countries [2], outbreaks are also occurring in Europe, Britain, the United States, Canada and China [3–9]. In the United States syphilis rates have been sharply rising among men who have sex with men (MSM), from a rate of 15.8 per 100,000 MSM population in 2000 to a rate of 228.8 in 2013 [10]. The incidence of congenital syphilis infections has also been increasing in recent years in both high- and low-income countries. An estimated 1.36 million pregnant women are

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infected worldwide each year, with approximately 520,000 of these pregnancies resulting in adverse outcomes [11]. Congenital syphilis is a leading cause of stillbirth worldwide, with an estimated 7.7% of global stillbirths and 11.2% of stillbirths in Sub-Saharan Africa being attributed to congenital syphilis infections [12–14]. Of note, in the United States congenital syphilis cases increased in 2014 to a rate of 11.6 per 100,000 live births, the highest since 2001 [14], and an even more dramatic rise in congenital syphilis cases has been observed in China, with 69.9 cases per 100,000 live births reported in 2013 [15]. According to the 2010 Global Burden of Disease report, syphilis is estimated to cause 9.5 million years of life lost (YLL), primarily due to the devastating consequences of congenital syphilis [16]. Syphilis also increases both infectivity amongst HIV-positive individuals and susceptibility amongst HIV-negative individuals, resulting in an estimated two- to fivefold increased risk of HIV transmission and acquisition in syphilis patients [17]. Repeat syphilis infections can occur [18], with MSM who are living with HIV being identified as a population at risk for reinfection [19]. In addition to the medical consequences associated with the disease, the economic impact of syphilis infections worldwide is significant. In the United States alone, more than $966 million in public heath dollars are estimated to be spent per year on syphilis-related health care costs, including $185.5 million on infectious syphilis, $28.5 million on congenital syphilis, and $752.2 million on HIV costs attributable to syphilis co-infection [20].

2. Disease progression

Syphilis is a chronic disease caused by the spirochete *Treponema pallidum* subspecies *pallidum* that exhibits alternating symptomatic and asymptomatic stages and varied clinical manifestations. The primary stage of the disease is typified by a painless indurated lesion, termed a chancre, that arises within approximately 3 weeks at the site of initial infection [21]. The chancre resolves within 4 to 6 weeks, and the diverse symptoms associated with the secondary stage of the disease, which most commonly include general malaise, lymphadenopathy and a disseminated rash, arise within 3 months of infection [21,22]. Approximately 3 months after presentation, the symptoms of secondary syphilis resolve and the disease enters an asymptomatic latent stage, which is categorized into early latent syphilis (asymptomatic infection occurring within 1 year of initial infection) and late latent syphilis (asymptomatic infection of longer than 1 year or unknown duration). Approximately 30% of untreated patients with latent syphilis develop symptoms of tertiary syphilis, which can arise up to 40 years after initial infection and involve any organ and tissue, with the most frequent manifestations being the development of gummas, cardiovascular syphilis and late neurological complications including general paresis and tabes dorsalis. Congenital syphilis can cause spontaneous abortion, stillbirth, premature delivery, and neonatal death; surviving infected infants may develop manifestations of congenital syphilis that can include rhinitis (‘snuffles’), skin lesions, interstitial keratitis leading to blindness, and tooth and bone deformities [21].

3. Need for a syphilis vaccine

The current syphilis treatment guidelines from the U.S. Centers for Disease Control and Prevention (CDC) recommend parenterally administered penicillin G to treat all stages of

syphilis, including pregnant women infected with syphilis [23]. Due to the emergence of macrolide-resistant *T. pallidum* strains [24], penicillin remains the antibiotic of choice to treat syphilis infections, with no occurrence of penicillin resistance despite over 70 years of continual use. The fact that syphilis infections are prevalent worldwide, even though *T. pallidum* remains remarkably sensitive to treatment with penicillin, indicates the disease is unlikely to be eliminated using public health screening and treatment programs alone. Indeed, disease incidence remains high despite several intensive public health control initiatives that have been conducted, including the CDC's 1999 and 2006 National Plans to Eliminate Syphilis from the US [20,25]. These initiatives were invaluable in reducing disease incidence amongst key groups, raising awareness of infectious and congenital syphilis amongst both health-care providers and the public, increasing public health- and community-based services to control the disease, and increasing funds and resources dedicated to combating syphilis and other sexually transmitted infections. Further, the World Health Organization's (WHO's) Initiative for the Global Elimination of Congenital Syphilis [26] aided in the elimination of mother-to-child transmission of syphilis in Cuba [27], the first country to attain this goal. Despite these successes the initiatives did not achieve the desired goals of rates of 2.2 or less per 100,000 population (primary and secondary syphilis) [20,25] and 3.9 per 100,000 live births (congenital syphilis) [25] in the U.S., and the global elimination of congenital syphilis [26]. The continuing prevalence of syphilis worldwide highlights the essential need for novel additional measures to stem syphilis transmission that can complement the successful public health initiatives implemented by the CDC and the WHO.

One such measure is syphilis vaccine development. An effective syphilis vaccine would overcome many of the challenges confronting public health-targeted syphilis elimination efforts. These include the difficulties associated with clinical diagnosis of syphilis infections due to the varied clinical presentations of the disease and the frequent lack of familiarity of clinicians with the diverse disease symptoms that may present during the duration of infection. Also, current diagnostic assays have a relatively low sensitivity for detecting early primary stage syphilis infections [28-30], the disease stage that exhibits the highest risk for (1) infectious syphilis and HIV transmission and (2) a negative outcome in a fetus via mother-to-child syphilis transmission. Further, there is complexity associated with accurately diagnosing reinfections due to the propensity for anti-treponemal antibodies to remain detectable despite adequate treatment [31]. Additionally, accurate syphilis diagnosis via conventional testing methods depends upon patient return visit compliance [32], and efficient syphilis treatment relies upon access to adequate supplies of penicillin, which have been documented to be experiencing a long-term shortage [33,34]. These limitations would be alleviated by the development of an effective vaccine that would: (1) prevent *T. pallidum* infection and thus prevent the development of all stages of syphilis and mother-to-child transmission; (2) provide cross-protection among divergent *T. pallidum* strains, which would in turn decrease the incidence of reinfection; and (3) eliminate the reliance on return visits and adequate penicillin supplies for effective syphilis control. Collectively these points make syphilis vaccine development an attractive endeavor that would complement public health campaigns targeting syphilis elimination.

4. Information gained from prior vaccine studies

Compared to fields focused upon vaccine development for other pathogens, limited research has been conducted into the identification and testing of syphilis vaccine candidates. This is at least partially due to the paucity of scientists conducting basic research on *T. pallidum* and the technical limitations associated with research on this pathogen, which includes the fragility associated with its outer membrane and its inability to be cultured and genetically manipulated [21].

Metzger [35] was the first to demonstrate partial protection against *T. pallidum* challenge in rabbits using intravenous and intramuscular inoculations of *T. pallidum* attenuated by short-term storage at 4°C. These studies provided strong evidence for the labile nature of the *T. pallidum* protective antigens, as harsh chemical or heat inactivation abolished the protective capacity of the antigen preparation. Rabbits administered intravenous injections of these aged preparations did not develop lesions or harbor *T. pallidum* at the challenge sites and 6/16 rabbits displayed full immunity based on negative lymph node transfer results [35]. Intramuscular injections of aged *T. pallidum* also afforded partial protection, though not as effectively as intravenous injections. Notably, the dose of inactivated *T. pallidum* had a substantial effect on the resistance of the rabbits to *T. pallidum* challenge, where immunization with 1.2×10^{10} total cells provided improved protection over immunization with $3–6 \times 10^{9}$ total cells [36]. In a hallmark study for the field, Miller [37] demonstrated full protection against *T. pallidum* challenge by immunizing rabbits with *T. pallidum* rendered non-infectious by γ-irradiation. This inactivation method retained the labile surface antigen content and motility of the organism, but rendered the bacteria non-infectious and nonproliferative based on their inability to establish an infection when injected into rabbits. The dose and time-course of this study was based upon previous observations that rabbits injected with fully infectious *T. pallidum* that were treated with penicillin 12 weeks post-infection were resistant to homologous challenge. Because γ-irradiated *T. pallidum* is presumed to be nonproliferative, an increased dose and prolonged injection schedule was predicted to be representative of a similar antigen exposure as that of an untreated 12-week infection with T. pallidum. Rabbits immunized with γ-irradiated *T. pallidum* (3.71×10^{9} total cells) over a 37-week period were fully immune to homologous challenge as demonstrated by the absence of lesions and bacteria at challenge sites and the negative results of lymph node transfers from these rabbits. Remarkably, immunized rabbits retained full protection to challenge for at least one year post-immunization. Of particular relevance, in this study immunized rabbits were not protected against challenge with the Haiti B treponemal strain [37], which was considered at the time to be *T. pallidum* subspecies *pertenue* but is now known to be *T. pallidum* subspecies pallidum [38–41].

From these studies we can draw a number of important conclusions: (1) protective antigens are sensitive and heat labile as development of protective immunity was dependent upon the presence of intact *T. pallidum* with an undisrupted surface; (2) a high dose of inactivated *T. pallidum* over a prolonged immunization schedule demonstrates that protective immunity develops slowly, likely due to the paucity of *T. pallidum* outer membrane proteins and thus repeated exposure to these antigens is required; (3) immunization with *T. pallidum* does not confer cross protection against a heterologous *T. pallidum* strain [37], suggesting that

protective antigens differ between these pathogens; and (4) protection was long-lasting and sterile, demonstrating that in the rabbit model effective immunity can be achieved.

A selection of individual antigens have been used for immunization and tested for protective capacity in animal models including Tp92 (BamA) [40,42], TprK [43–45], TprI [46], TprF [47], Gpd [48], TmpB [49], TpN15 [38], TpN47 [42], Tp0155 [42], Tp0483 [42], Tp0956 [42], 4D [50], and endoflagella [51]. An important distinction between the whole attenuated *T. pallidum* vaccines and recombinant subunit vaccines is the rabbit breed used for immunization. Partial and complete protection using whole-cell attenuated preparations were achieved using Dutch rabbits, whereas New Zealand White rabbits have been used in more recent studies. However, the lack of immunological tools for rabbits renders the significance of this distinction unknown. Rabbits immunized with Tp92 (BamA) [40], 4D [50], Gpd [48], TprF [47], and endoflagella [51] displayed partial protection based upon attenuated lesion development, although none of these studies were able to demonstrate sterilizing immunity to challenge through tissue transfer to a naïve rabbit (rabbit infectivity test; RIT). Immunization with the antigenic and phase variable protein, TprK, elicits promising partial protection in the rabbit model [43–45], with the protective portion of the molecule localizing to the N-terminal region of the protein [44]. However, divergent results have been obtained regarding the protective capacity of several of these proteins, including TprK [52], Gpd [53], and Tp92 (BamA) [42]. These studies suggest that protection against infection will not be conferred by administration of a single *T. pallidum* antigen, and highlights the presence of inter-laboratory variability and the need for standardization of antigen preparation and immunization methodologies between laboratories, including the adoption of good laboratory practices (GLP). Indeed, a recent initiative by the National Institutes of Health (NIH) calls for improvements in the reporting of pre-clinical research to improve reproducibility, encourage transparency through the comprehensive reporting of methodologies, biological materials, and statistical analyses, and improve availability of data and materials for sharing with other research groups upon request [54]. This initiative is supported by major publishers and should be treated as the standard for syphilis preclinical vaccine development.

5. Correlates of protection required for successful vaccination

During syphilis infection, resolution of primary and secondary lesions coincides with cellular infiltrates composed primarily of T-cells and macrophages [55–60]. Primary lesions in humans as well as primary and secondary lesions in rabbits contain predominantly $CD4^+$ T-cells, macrophages, and natural killer (NK) cells, whereas analysis of the cellular infiltrate of human secondary lesions reveals a higher abundance of $CD8^+$ T-cells relative to $CD4^+$ T-cells [60,61]. The induction of a strong delayed-type hypersensitivity (DTH) reaction is critical to the efficient clearance of *T. pallidum* from lesion sites [62]. Such a response requires local production of Th1 cytokines including interferon-γ (IFN-γ), interleukin-2 (IL-2), and interleukin-12 (IL-12) [58,63–67]. Within lesions IFN-γ is secreted by $CD4^+$ T-cells [65,66], NK cells [64], $CD8^+$ T-cells [68], and resident dendritic cells [69], though $CD4^+$ T-cells seem to be the primary source. Subsequent Th1 cytokine-mediated activation of macrophages promotes phagocytosis of opsonized *T. pallidum* (opsonophagocytosis), which is thought to be the major mechanism of clearance [61,64,70–73].

While significant evidence exists to demonstrate the importance of the cell-mediated immune response during syphilis, it is clear that cross-talk with the humoral response is essential. Neither passive immunization with humoral components [74] nor adoptive T-cell transfer [75,76] in animal models confers sterilizing immunity. Furthermore, *T. pallidum* opsonophagocytosis by human or rabbit peritoneal macrophages is dependent upon the presence of immune patient serum [64] or immune rabbit serum [73], respectively, highlighting the importance of humoral components to the cell-mediated response required for efficient clearance of *T. pallidum*. However opsonophagocytosis progresses slowly [77] and ex vivo studies using rabbit peritoneal macrophages [78] or human macrophages [64] reveal that a subpopulation of *T. pallidum* can evade phagocytosis. Persistent subpopulations of *T. pallidum* have been identified in vivo in rabbits within primary lesions and distal host sites [79] and it has been postulated that this evasive subpopulation may have differential susceptibility to targeting by opsonic antibodies relating to differential surface antigen exposure [80] or antigenic variation [81] of surface-exposed proteins. This presents a major challenge to vaccine development, as the elusive nature of the persistent population precludes an effective vaccine regimen to target full immune clearance of *T. pallidum*.

A critical component of *T. pallidum* pathogenesis is vascular dissemination, however, our understanding of systemic immune responses is lacking relative to immune reactions in lesion sites. During secondary syphilis, altered cellular profiles in the peripheral blood include decreased dendritic cells (DCs), IFN-γ-secreting NK cells, and cytotoxic NK cells, which supports the recruitment of these lymphocytes to secondary infection sites [82]. Furthermore, T-cells are activated on a systemic level leading to a T-effector and T-memory/effector dominant immunophenotype [82]. Compared to posttreatment, samples from patients with secondary syphilis exhibit no change in cytokine transcription or secretion from circulating immune cells, indicating that the bacterial burden in the vasculature may be insufficient to induce cytokine production by circulating monocytes [61]. Contrary to this finding, Bernardeschi et al. [83] demonstrated that serum from *T. pallidum* infected patients displayed a predominance of Th1 type cytokines (IFN-γ and IL-10) throughout active stages of infection and low levels of Th2 type cytokines (IL-4 and IL-5) throughout infection relative to untreated patients. Intriguingly, elevated IL-17 and IL-23 levels were observed throughout infection including latent stages, suggesting that *T. pallidum* may provoke some immune stimulation during latency. These contradictory results may stem from differences in methodologies and the focus on serum cytokine levels [83] versus cytokine secretion from specific cell types [61]. Aside from coordinating immune responses to allow for appropriate immune cell recruitment to infection sites, systemic immune responses should promote recognition and clearance of *T. pallidum* within the bloodstream to prevent treponemal extravasation into secondary sites that allow for persistence. This depends upon identification of *T. pallidum* proteins expressed during hematogenous dissemination that play a characterized functional role in this process.

Based on our knowledge of immune clearance of *T. pallidum*, preclinical vaccine investigations should aim to elicit a DTH response to facilitate production of Th1 cytokines that can activate macrophages and promote treponemal opsonophagocytosis. Additionally, effective vaccination needs to also address the persistent *T. pallidum* population that resist

macrophage clearance and target treponemes within the vasculature to inhibit *T. pallidum* seeding into distal infection sites.

6. Rethinking the correlates of protection for HIV-positive individuals

Co-infection with HIV and syphilis results in increased HIV viral loads [84] and increases the risk for HIV transmission [85,86]. Augmentation of a DTH response during *T. pallidum* infection is important for treponemal clearance from lesion sites [62], but relies upon the activity of $CD4^+$ T-cells which presents a significant barrier for HIV-positive individuals due to their low $CD4^+$ T-cell counts. Further to this, the observation that secondary syphilis patients harbor activated $CD4^+$ T-cells in the peripheral blood, and the increased expression of HIV co-receptors CCR5 on $CD4^+$ T-cells and DCs and DC-SIGN on DCs, potentiates a favorable environment for increased HIV infection of $CD4^+$ T-cells [82]. Within primary chancres of HIV-positive individuals, $CD8^+$ T-cells are the predominant lymphocyte, producing IFN-γ and IL-17 to provide a compensatory mechanism for macrophage activation in $CD4^+$ T-cell-depleted chancre sites [68]. High Th1 cytokine levels in primary and secondary lesion sites have been demonstrated in humans regardless of HIV co-infection status [66] and the identification of NK cells as an additional source of IFN-γ [64] may explain this finding. Analysis of serum from HIV-positive individuals revealed lower *T. pallidum*-specific opsonic activity compared to serum from HIV-negative patients [87], which could impede *T. pallidum* clearance from lesions. The role of $CD8^+$ T-cells in chancres found in HIV-negative patients is not fully understood, but it has been hypothesized that these cells could play a role in dealing with rare occurrences of *T. pallidum* in nonphagocytic cells or may become activated by antigen cross-presentation from resident macrophages and dendritic cells [61].

For effective vaccine development, it is critical to consider the altered immune response and compensatory clearance mechanisms in HIV-positive individuals in order to achieve protection for one of the most prominent target populations for vaccination. Recent investigations on cellular immunity in HIV coinfected patients suggest that effective immunization should promote Th1 cytokine production by various immune cell types, including $CD8^+$ and NK cells. However, a better understanding of the altered opsonic response in HIV-positive individuals, as well as the roles of $CD8^+$ T-cells and NK cells in syphilis lesions, needs to be obtained before efficient vaccine development for HIV-positive individuals can be realized.

7. Key considerations for syphilis vaccine design

Four intriguing aspects of *T. pallidum* infection that would need to be targeted in a successful syphilis vaccine are the highly infectious chancre that develops at the site of infection, the extremely invasive nature of the pathogen, and the capacity of the pathogen to cause repeat infections and establish latency despite the development of a robust immune response. The highly invasive nature of *T. pallidum* is exemplified by the fact that the pathogen is able to cross the endothelial, placental and blood–brain barriers early in the process of infection; indeed, central nervous system invasion has been shown to occur in approximately 40% of early syphilis patients [88]. Thus, an effective syphilis vaccine would

need to prevent chancre development, treponemal dissemination, treponemal persistence and reinfection to eliminate disease symptoms within an infected individual and disease transmission at the population level. As previously discussed, studies performed in the rabbit model of syphilis infection demonstrated that chancre development upon virulent *T. pallidum* challenge was attenuated in rabbits immunized with selected members of the *T. pallidum* repeat (Tpr) protein family [45,47]. Subsets of this protein family are predicted to be exposed on the treponemal surface [43–47,89,90], to exhibit extensive sequence variation in predicted surface-exposed loop regions [91], and to undergo both antigenic [92] and phase variation [93], suggesting selected members of this protein family also play a role in treponemal persistence and susceptibility of individuals to reinfection. With respect to the highly invasive nature of *T. pallidum*, the treponemal protein Tp0751 is an adhesin that has been shown to target multiple host components found within the vasculature, implicating this protein in treponemal dissemination via the bloodstream [94–96]. Other adhesins that have been identified in *T. pallidum*, including the adhesins Tp0136 [97,98], Tp0155 [99], Tp0483 [99], Tp0750 [100] and Tp0435 [101], may similarly play a role in treponemal dissemination. Due to the complex pathogenesis at play during *T. pallidum* infection, it is highly likely that a cocktail of syphilis antigens would be needed to attain protection through vaccination, and thus the aforementioned virulence factors may represent likely candidates for inclusion in such a multicomponent vaccine.

Several key issues will need to be assessed during the process of syphilis preclinical vaccine development. These include the number of vaccine administrations required to achieve maximal immunity, the duration of immunity that is induced following vaccine administration, cross-protection against diverse strains, and appropriate multivalent vaccine preparation and adjuvant selection and optimization to achieve the needed immune response for effective protection against *T. pallidum* infection.

8. Notable developments in methodologies pertaining to syphilis pre-clinical vaccine development

A major advancement in syphilis preclinical vaccine studies was the use of real-time quantitative PCR (qPCR) to allow for sensitive detection of *T. pallidum* DNA at distal sites within the infected rabbit [102,103]. However, major limitations of realtime qPCR include the inability to differentiate between live and dead organisms and the difficulty in efficient DNA extraction from complex tissues such as lymph nodes. Fluorescence in situ hybridization (FISH) allows for efficient recognition of *T. pallidum* in intact human and rabbit tissue samples [104] using a species-specific probe that recognizes 16 s rRNA of *T. pallidum*. FISH detection of *T. pallidum* would allow for additional information in experimental syphilis investigations regarding *T. pallidum* localization within tissue samples.

9. Expert commentary

The syphilis field has a paucity of investigators conducting basic research on *T. pallidum*. The field is in need of an influx of new investigators to contribute fresh ideas and interdisciplinary research approaches, particularly in the areas of host-pathogen interactions, basic *T. pallidum* biology, and animal model investigations. Syphilis vaccine development

needs a dedicated source of funding to test current and future vaccine candidates and to attract new investigators to the field. Of equal importance, syphilis vaccine development needs global advocacy. In order to ensure success, syphilis vaccine development needs to be promoted as a priority by governmental and regulatory agencies and supported by funding agencies, not-for-profit and philanthropic organizations, and industry partners. In particular, industry partners need to be secured in order to produce and market a syphilis vaccine. This may require creative approaches such as vaccine purchase commitments funded by international agencies and governments [105] and combination vaccine design whereby a syphilis vaccine is bundled with vaccines against other sexually transmitted infections to enhance industry interest. The latter approach has been successfully used to boost pharmaceutical interest in producing other vaccines, with the most compelling illustration being the success of childhood combination vaccines [106,107]. Also appealing is the concept of ‘piggybacking’ on pre-existing global advocacy initiatives, including the WHO's Strategic Framework for the Elimination of New HIV Infections among Children in Africa by 2015, which encompasses the goal of dual elimination of mother-to-child transmission of HIV and syphilis [108], and existing global vaccine networks, including the Global Alliance for Vaccines and Immunizations (GAVI) [109] and the HIV Vaccine Trials Network (HVTN) [110].

In order to effectively protect against the complexities associated with syphilis infection, including formation of the highly infectious chancre, invasion of *T. pallidum* into multiple tissues and organs, establishment of latent infection, and the propensity for reinfection, a successful vaccine will undoubtedly consist of a cocktail of *T. pallidum* antigens that play essential roles in these critical pathogenic processes.

10. Five-year view

Although limited research has been conducted on syphilis vaccine development to date, with an infusion of funding and regulatory support the field is poised to significantly advance over the next 5 years. The application of modern research tools, including cutting-edge structural and proteomic methodologies, to the study of *T. pallidum* biology will increase our understanding of treponemal pathogenesis and will reveal novel vaccine candidates. Cross-disciplinary studies that consider both sides of the host-pathogen interaction, including the host innate and adaptive immune responses to infection and the corresponding evasion mechanisms employed by *T. pallidum*, will confer an enhanced understanding of the correlates associated with protection from disease, especially in the context of human infection. The existence of an excellent animal model that recapitulates the majority of disease stages and symptoms allows for the conductance of pre-clinical studies that will be informative for ensuing Phase I clinical vaccine trials in humans. Collectively, the application of these research directions and methodologies to *T. pallidum* research will advance the field of syphilis vaccine development and it is anticipated a viable syphilis vaccine candidate will be realized within a 10 year time frame.

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Key issues

- Syphilis is a multistage, chronic infection caused by the spirochete Treponema pallidum subspecies pallidum.
- Syphilis vaccine development is an understudied field that has progressed slowly due to the limited understanding surrounding T. pallidum pathogenesis and the technical complexities associated with research on this bacterium.
- Reliance on public health initiatives alone is ineffective at stemming the spread of syphilis, as evidenced by continued prevalence of the disease worldwide and the increasing rates observed in selected geographical locations and amongst key populations, including men who have sex with men.
- Development of a vaccine for syphilis needs to be prioritized by public health and funding agencies to complement initiatives promoting enhanced syphilis screening and treatment programs.
- Vaccine development studies need to be expanded to include discovery of promising new vaccine candidates, adjuvant optimization, and enhanced understanding of the essential correlates of protection that are necessary to ensure effective protection against disease.
- Industry interest in production and marketing of a syphilis vaccine needs to be secured and may require national and international subsidization commitments.
- A combination vaccine approach that bundles a syphilis vaccine with a vaccine against another sexually transmitted infection will enhance the marketability and profitability of a syphilis vaccine.
- An effective syphilis vaccine is expected to significantly reduce the incidence of both infectious and congenital syphilis and may decrease HIV incidence worldwide.