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Current Status of Syphilis Vaccine Development: Need, Challenges, Prospects

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Abstract

Syphilis is a multistage disease caused by the invasive spirochete *Treponema pallidum* subsp. *pallidum*. Despite inexpensive and effective antibiotic therapy, syphilis remains a prevalent disease in developing countries and has re-emerged as a public health threat in developed nations. In addition to the medical burden imparted by infectious syphilis, congenital syphilis is considered the most significant infectious disease affecting fetuses and newborns worldwide, and individuals afflicted with syphilis have an enhanced risk for HIV transmission and acquisition. The global disease burden of syphilis and failure of decades of public health efforts to stem the incidence of disease highlight the need for an effective syphilis vaccine. Although challenges associated with *T. pallidum* research have impeded understanding of this pathogen, the existence of a relevant animal model has enabled insight into the correlates of disease protection. Complete protection against infection has been achieved in the animal model using an extended immunization regimen of γ -irradiated *T. pallidum*, demonstrating the importance of treponemal surface components in generation of protective immunity and the feasibility of syphilis vaccine development. Syphilis is a prime candidate for development of a successful vaccine due to the (1) research community's accumulated knowledge of immune correlates of protection; (2) existence of a relevant animal model that enables effective pre-clinical analyses; (3) universal penicillin susceptibility of *T. pallidum* which enhances the attractiveness of clinical vaccine trials; and (4) significant public health benefit a vaccine would have on reduction of infectious/congenital syphilis and HIV rates. Critical personnel, research and market gaps need to be addressed before the goal of a syphilis vaccine can be realized, including recruitment of additional researchers to the *T. pallidum* research field with a proportional increase in research funding, attainment of a definitive understanding of correlates of protection in humans, and engagement of industry/funding partnerships for syphilis vaccine production.

Keywords

syphilis; *Treponema pallidum*; vaccine development; animal model; latent infection; HIV susceptibility; congenital infection

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1. Introduction

1.1. Epidemiology

Syphilis is a chronic sexually transmitted infection (STI) caused by the spirochete *Treponema pallidum* subsp. *pallidum*. Infectious syphilis continues to be an important public health burden, with a global prevalence estimate of 36 million cases and over 11 million new infections annually [1]. While the World Health Organization (WHO) estimates greater than 90% of syphilis cases occur in developing nations [2], a recent resurgence of the disease has been observed in numerous developed nations including within Europe [3;4], the UK [5;6], the US [7;8], Canada [9], Australia [10;11], New Zealand [12] and China [13;14]. Congenital syphilis (CS) remains a significant global public health concern and is considered the most common infection associated with fetal loss or stillbirth in low income settings [15;16]. While the predominant burden of congenital infections is observed in sub-Saharan Africa [17], cases of CS are on the rise in China [13] and Canada [18], and CS continues to be found within the US [19]. Symptomatic syphilis infections place individuals at a 2–5-fold enhanced risk for HIV transmission and acquisition [20], and modelling studies demonstrate that effective syphilis control would have a significant positive impact on HIV prevention [21]. The global public health threat posed by syphilis highlights the need for enhanced understanding of syphilis pathogenesis and identification of vaccine targets.

1.2. Need for a syphilis vaccine

1.2.1 Is antibiotic treatment sufficient for global elimination of syphilis?—

Treponema pallidum exhibits complete sensitivity to penicillin treatment, despite 70 years of use of this antibiotic in treating syphilis infections. Standard treatment with parenteral benzathine penicillin G is highly effective for treating all stages of uncomplicated syphilis, and intravenous aqueous crystalline penicillin G or intramuscular procaine penicillin (plus probenecid) are effective for patients with central nervous system (CNS) involvement [22]. The need for parenteral administration of penicillin, however, increases the complexity of treatment, and has led to the use of oral antibiotics such as azithromycin. Over the past decade, macrolide resistance has unfortunately been documented in many countries (reviewed in [23]), and macrolides are not currently recommended for treatment or prophylaxis of syphilis [22].

The continuing high global rates of syphilis, despite the availability of inexpensive and effective treatment, presents the most compelling argument for the need for syphilis vaccine development. In spite of intensive syphilis-targeted public health control initiatives, including the CDC's National Plan to Eliminate Syphilis from the US [24;25] and the WHO's Initiative for the Global Elimination of Congenital Syphilis [26], the goal of syphilis elimination has not been achieved. Although the reasons for failure are undoubtedly multifactorial, partial responsibility can be attributed to the complexity of syphilis diagnosis and treatment, and to lack of access or utilization of prenatal screening programs. First, primary syphilis chancres may go undetected if they present in an area that is difficult to visualize (e.g. cervix, throat or anus/rectum) due to their well-documented painless nature [27]. Additionally, syphilis lesions are prone to clinical misdiagnosis, due to their pleomorphic appearance and lack of physician familiarity with the manifestations of syphilis. Secondary syphilis presents as a very mild to severe generalized rash that may go un-noticed by the patient or may mimic a wide range of conditions [28]. Second, the traditional diagnostic screening algorithm comprises a sequence of diagnostic assays that detect antibodies to lipoidal (e.g. rapid plasma regain [RPR]) and treponemal antigens (e.g. *T. pallidum* particle agglutination [TPPA]). These assays are generally not available in the clinic and thus their diagnostic success depends on high patient compliance to return for test results. New point-of-care tests may increase clinic-based serological screening, but their

reliance on treponemal antigens makes interpretation of reactive results (which could be due to a prior treated syphilis infection rather than a current active infection) difficult to interpret [29]. Third, the need for parenteral administration of penicillin decreases the likelihood that appropriate treatment will be received in resource-poor settings which contain the majority of syphilis infections. Fourth, antenatal care (ANC) is not always available or sought. Estimates from 2008 show that, of 1.36 million pregnant women presenting with syphilis, 20% had not attended ANC and 66% of infected women who did attend ANC still had adverse outcomes due to lack of either syphilis testing or treatment [30]. Lastly, syphilis control solely by diagnosis and treatment will not decrease the risk of HIV transmission/acquisition. Syphilis treatment-seeking is triggered primarily by signs of early syphilis; such patients may have already missed the window of opportunity for reducing HIV risk, as the ulcerative primary stage of syphilis has the highest risk for HIV acquisition and transmission [31]. Elimination of syphilis infections as a risk factor for HIV will only be fully realized through prevention of syphilis by vaccine development. These reasons, combined with the persistent worldwide disease prevalence, make it clear that syphilis control will likely not be achieved solely through targeted “screen and treat” initiatives. Instead, successful elimination will depend upon continued rigorous screening and treatment programs complemented by development and administration of an effective syphilis vaccine.

1.2.2 Vaccine target population—Apart from a few countries, the demographics of syphilis infections show a clear divide between developed and developing countries. In most industrialized countries, syphilis infections are found predominantly among men who have sex with men (MSM), while in developing nations infections occur primarily among the heterosexual population. In the US, both MSM and heterosexual African American populations are at high risk. If an effective syphilis vaccine is developed, it is likely that the vaccine would be targeted according to this demographic profile, at least initially. Successful provision of the vaccine to MSM and other high-risk populations (e.g. sex workers) would be expected both to stem the spread of syphilis infections and decrease HIV transmission. In the US and other countries with multiple high-risk populations, such as China and Eastern Europe, vaccine administration would be expected to be more widespread. In developing nations that have the highest burden of disease, including sub-Saharan Africa and South America, vaccine uptake might be encouraged across the general population, with particular emphasis placed upon women of reproductive age to curtail the incidence of CS.

2. Syphilis pathogenesis

2.1. *T. pallidum* biology

The causative agent of syphilis, *Treponema pallidum* subsp. *pallidum* (*T. pallidum*) is a member of the *Spirochaetaceae* family of spiral-shaped bacteria. It is the only human pathogen in this family to be sexually transmitted, with other well-known family members causing the “endemic treponematoses” bejel (*T. pallidum* subsp. *endemicum*), yaws (*T. pallidum* subsp. *pertenue*), and pinta (*T. carateum*), and the vector-borne diseases Lyme disease (*Borrelia burgdorferi*) and relapsing fever (*Borrelia hermsii*). Members of this bacterial family contain a protoplasmic cylinder surrounded by a cytoplasmic membrane, a thin layer of peptidoglycan and an outer membrane (OM). The characteristic corkscrew motility of these bacteria, which is highly suited for viscous environments [32], is imparted by the periplasmic flagella anchored at each end of the organism. *T. pallidum* is 6 to 15 μm in length and $\sim 0.2 \mu\text{m}$ in diameter. The sequencing of the genome of the Nichols strain in 1998 [33], and subsequent sequencing of additional *T. pallidum* strains from several subspecies, has revealed a very high (>99.8%) sequence homology among the *T. pallidum* subspecies [34]. Further, genome sequencing has illustrated that *T. pallidum* is a prime

example of a pathogen that has undergone genome reduction to increase efficiency, with one of the smallest characterized prokaryotes genomes and complete dependence upon its host for the majority of essential metabolic processes [33;35]. This host dependence provides a significant challenge for research on *T. pallidum* in that the organism must be propagated in animals and is remarkably fragile outside of a mammalian host.

2.2. The natural history of syphilis provides clues regarding critical mechanisms of treponemal pathogenesis

The natural history of untreated syphilis includes distinct primary and secondary stages of disease typified by a chancre at the site of infection and a disseminated rash, respectively. These lesions spontaneously resolve, followed by a period of asymptomatic latency that lasts for the remainder of their lifetimes in most persons. In the pre-antibiotic era, approximately 30% of untreated infected individuals developed tertiary syphilis 10–50 years after initial infection, with the possibility of life-threatening sequelae [36]. The course of untreated infection has provided insight into the critical pathogenic mechanisms utilized by *T. pallidum* to establish and maintain a successful infection. Two key mechanisms that are essential for *T. pallidum* survival are (1) its high invasive capability and (2) its impressive capacity to evade the immune response and persist for extended periods of time.

2.2.1 Invasive capability of *T. pallidum*—The highly invasive nature of *T. pallidum* is most dramatically illustrated by the ability of the pathogen to cross the placental barrier to cause CS and by the fact that at least 40% of patients with early syphilis have CNS invasion [37]. However, dissemination of infection is also exemplified by the widespread secondary rash, the sometimes symptomatic involvement of liver and kidneys, and ocular involvement. Within hours of infection in experimental animals, the highly motile *T. pallidum* disseminates widely via the bloodstream and lymphatics [38;39], and *in vitro* studies have shown *T. pallidum* can penetrate intact membranes and endothelial cell monolayers [40;41]. Invasion of tissues can result only following attachment of *T. pallidum* to cells (e.g. endothelial cells that comprise capillary walls). Several proteins that are active in attachment to host cells, via extracellular matrix bridges, include Tp0136 [42], Tp0155, Tp0483 [43] and Tp0751/pallilysin [44–48]. The invasive capability of *T. pallidum* is crucial to the development of the many clinical manifestations of syphilis, and elimination of this capability should be a central target of a syphilis vaccine to prevent transmission of infectious syphilis, establishment of CS, and progression of disease within an infected individual.

2.2.2 Resolution of early lesions—Primary and secondary syphilis lesions are infiltrated primarily by T lymphocytes, followed by macrophages. The vast majority of treponemes are cleared, with lesion resolution, shortly after macrophage infiltration [49–52]. Detailed examination of the various steps involved in clearance has revealed there is a Th1-type cellular infiltration in which both CD4+ and CD8+ T lymphocytes produce interferon-gamma (IFN- γ). This cytokine attracts and activates macrophages, which are then able to ingest and kill antibody-opsonized treponemes [49;53]. Although vast numbers of treponemes are cleared from lesions, a subpopulation of treponemes persists. *In vitro* studies of these locally persisting organisms show they are resistant to opsonophagocytosis by macrophages [54], and unraveling the possible mechanisms of immune evasion is critical to understanding the lifetime chronicity of syphilis infection.

2.2.3 Contributing factors in treponemal persistence—Following spontaneous resolution of the symptoms of early syphilis, infection becomes asymptomatic and a period of chronic infection, called “latency,” is established. Several hypotheses have been proposed to explain the ability of treponemes to persist, including location in an “immunoprotective

niche” [55] such as the central nervous system, the eye, or inside cells other than professional phagocytes. An additional factor that likely contributes to the remarkable persistence of *T. pallidum* is the reported paucity of proteins presented on the treponemal surface. Freeze-fracture electron microscopy studies initially demonstrated low densities of integral membrane proteins in the OM [56;57], and this was confirmed by recent high-resolution cryo electron tomography [58;59] and scanning probe microscopy [58]. The low density of integral outer membrane proteins (OMPs), and presumably limited antigenic targets, are thought to play an important role in *T. pallidum*’s ability to evade functional immune responses, thus facilitating treponemal persistence [36;60].

A newly recognized factor that is likely to facilitate immune evasion and persistence of *T. pallidum* is the demonstration of antigenic diversity and variation amongst the *T. pallidum* repeat (Tpr) protein family, a subset of which are thought to be located on the treponemal surface [61–63] (Table 1). Two types of antigenic variation have recently been discovered in *T. pallidum*: 1) Phase variation, or ON/OFF expression, of TprE, G, and J occurs by alteration in the lengths of polyG tracts in the promoter region of the genes [64]; 2) Sequence variation of discrete regions of TprK is seen among, and even within, strains [65]. Variation occurs by segmented gene conversion in which segments of new sequence obtained from over 50 chromosomal donor sites can replace portions of 7 variable (V) regions in the *tprK* open reading frame [66]. Sequence variation in V regions results in proteins with altered binding by specific antibodies [67], and immune pressure during infection selects for new variant organisms expressing unique TprK V region sequences [63]. Other members of the Tpr family, TprC and D, have heterogeneity in their sequences among strains and subspecies, but these TprC and D sequences appear to be unchanging during the course of infection. The localization of these diverse regions to predicted surface-exposed loops [68] and the recognition that TprC is a target of opsonic antibodies [62] may help to account in part for the well-recognized observation that persons can be infected with syphilis multiple times, possibly with strains expressing different TprC or D sequences. Vaccine development efforts will need to account for antigenic variation perhaps by focusing on invariant regions on these important protein antigens.

2.3. Technical challenges associated with *T. pallidum* research has limited progress on *T. pallidum* OMP identification

Our overall understanding of *T. pallidum* pathogenesis has been hampered by several characteristics unique to this bacterium. First, continuous *in vitro* cultivation has yet to be achieved, thus limiting the studies that can be performed on *T. pallidum*. Second, to date, *T. pallidum* is genetically intractable and thus there is no genetic mechanism for investigating gene function. Third, the peptidoglycan layer found within *T. pallidum* is located within a cytoplasmic membrane-proximal layer [58;59], making the OM extremely labile and easily disrupted by experimental manipulations such as centrifugation [58]. And fourth, *T. pallidum*’s extremely low OMP content [56–59] makes it refractory to conventional OMP identification methods due to the inadequate sensitivity of these methods.

To circumvent these limitations and to identify candidate OMPs, investigators have relied upon bioinformatic [43;44;69] and structural predictions [62;69;70] and subtractive hybridization methodologies [61], or have used demonstration of functional activities such as host component attachment [42–45;47;48], opsonic antibody reactivity with viable *T. pallidum* [61;71], and antigenic variation [63;65;72]. A list of the surface-exposed OMP candidates identified to date can be found in Table 1.

3. Animal model of syphilis

While several mammals can be infected with *T. pallidum*, only a few develop clinical disease. The fact that rabbits have a naturally occurring venereal disease caused by the closely related *Treponema paraluis-cuniculi* suggests that rabbits may also be susceptible to *T. pallidum*. This is indeed the case, and the only small laboratory animal that recapitulates the multiple stages and chronicity of human syphilis is the rabbit, which is used to propagate the *T. pallidum* subspecies and is the model of choice for studying syphilis pathogenesis and immunity. *T. pallidum* infection of rabbits results in development of primary and secondary lesions, and infection persists asymptomatically for the remainder of the animal's life, as in human infection. Invasion by the organism of the CNS and dissemination across the placenta have been demonstrated in the rabbit model [73;74]. During the past 35 years, work has been conducted in New Zealand white rabbits, although earlier research utilized other rabbit strains. While the rabbit model closely reflects human infection, this model presents challenges particularly for immunological studies due to the unavailability of inbred strains and a relative dearth of immunological reagents for rabbits. In response, we have developed some of our own assays for rabbit cytokines [75], but more assays are required.

4. Critical nature of *T. pallidum* surface antigens for successful vaccine development

4.1. Proof-of-Principle

The most compelling evidence in support of successful syphilis vaccine development is the attainment of complete protection against homologous strain challenge by Dr. James Miller in 1973 [76]. In this study Miller conducted an extended immunization regimen in rabbits, consisting of 60 intravenous injections of a total of 3.71×10^9 γ -irradiated *T. pallidum* over a 37-week period, followed by intradermal challenge of either 10^3 or 10^5 homologous Nichols strain *T. pallidum*. Immunized rabbits displayed complete protection, as demonstrated by the lack of development of chancres at the challenge sites and the absence of infection in naïve recipient animals receiving lymph nodes from the immunized rabbits. Protection persisted for at least one year after the final immunization [76].

This study was groundbreaking in that it established proof-of-principle that complete protection from infection and disease could be achieved in the animal model, albeit through an immunization regimen that is not tenable in humans. Another critical facet of this study was Miller's insightful recognition that the treponemal surface was responsible for conferring the observed protection. Miller reasoned that failure of previous attempts to induce protection using *T. pallidum* inactivated by mechanical or chemical treatments [77–82] (see also detailed reviews in [83;84]) was due to the destruction of labile protective surface antigens. Although most investigators focus on the OMPs of *T. pallidum*, it must be remembered that much of the *T. pallidum* surface is comprised of membrane lipids which induce the anti-lipoidal antibodies used to diagnose syphilis in patients with the VDRL and RPR tests. These lipid antigens were included in the immunogen used by Miller. Separate studies have shown that immunization of rabbits with this lipoidal antigen induces the production of opsonic antibodies and partial protection against infectious challenge [85]. Further, a highly-neutralizing monoclonal antibody derived following immunization of mice with intact *T. pallidum* was shown to have specificity for a phosphorylcholine surface epitope of *T. pallidum*. Passive immunization with this antibody resulted in significant attenuation of infection [86].

4.2. Extended timeline for development of protection

Further, Miller showed that attainment of immunity using γ -irradiated, non-proliferating treponemes required an extended period of 37 weeks, with only partial and no immunity observed over 24- and 12-week immunization periods, respectively [76]. Miller's study also confirmed previous observations that protective immunity against re-infection with homologous *T. pallidum* strains develops, albeit slowly, in the animal model. Complete protection against symptomatic homologous strain challenge develops only after 12 weeks of infection. If rabbits are cured of infection prior to that 12 week milestone, they can be symptomatically re-infected [87–90]. It is now speculated that the slow development of protective immunity to *T. pallidum* correlates with the unusual protein-poor surface of the bacterium. These observations, combined with the protection studies obtained by Miller, reinforce the importance of the surface antigens in generation of protective immunity and target these components for inclusion in an effective syphilis vaccine.

5. Correlates of protection

5.1. Immune correlates in the rabbit model

We know that, during infection, treponemes are cleared from lesions following development of a Th1 response and opsonophagocytic killing of the bacteria. A number of studies have demonstrated that passive administration of very large quantities of antiserum from chancre-immune rabbits are able to delay lesion development in response to infectious challenge, but are not sufficient to prevent it [91], suggesting that antibodies alone cannot eradicate infection. Adoptive transfer of T cells (in inbred hamster [using *T. pallidum* subsp. *endemicum*] and guinea pig studies) yielded only transient and incomplete resistance to infection [92]. Our vaccine studies over the past 15 years have led us to conclude that protection from initial infection in rabbits is dependent upon both induction of a Th1 response in which T cells infiltrate and produce IFN- γ (appearing as a delayed-type hypersensitivity response) and development of opsonic antibodies. We therefore used an adjuvant with components most likely to induce a Th1 response and functional antibody: the Ribi adjuvant containing monophosphoryl lipid A, trehalose dicorynomycolate, and cell wall skeleton. Immunization using this adjuvant with a number of recombinant peptides induced significant protection against infection, as measured by reduction in development of lesions with demonstrable *T. pallidum* and reduction in proportion of lesions that progress to ulceration [61;71;72;93;94]. Unfortunately, the adjuvant used in the above studies is no longer being produced, and attempts to substitute available adjuvants have led to reductions in the level of protection achieved, emphasizing the need for adjuvant research.

5.2 Human immunity to infection with *T. pallidum*

Little is known about the correlates of immunity in humans. It is well recognized that people who acquire syphilis can be re-infected following treatment, and this cycle can be repeated many times. Human challenge studies have shown that persons with late latent syphilis are resistant to symptomatic reinfection with a heterologous strain of *T. pallidum*, but that those with earlier stages show evidence of infection following challenge [95]. This correlates with the lengthy immunization period necessary to induce protection in Miller's successful vaccine. Development of immunity seen in rabbits has components of subspecies- and even strain-specificity [96], most likely related to antigenic differences among strains. Thus, syphilis vaccine development efforts will need to include evaluation of long immunization schedules, and the selection of immunogens will need to recognize antigenic diversity among strains and accommodate the effects of antigenic variation in immune evasion.

6. Essential vaccine considerations

6.1. Critical requirements

At minimum, several key milestones will need to be satisfied in the development and production of an effective syphilis vaccine. First, a vaccine would need to be rigorously shown to induce full protection, rather than inducing partial protection which could lead to unrecognized latent infection. Therefore, such a vaccine would need to a) prevent chancre development associated with primary disease and the lesions associated with secondary disease to abolish transmission of *T. pallidum* and HIV and b) inhibit treponemal dissemination throughout the host to prevent corresponding disease progression and establishment of CS. Second, the vaccine candidate(s) would need to be effective in generating a Th1 response and opsonic antibodies due to the critical role that opsonophagocytosis plays in *T. pallidum* clearance during infection. And third, the vaccine candidate(s) must be selected to ensure the vaccine is broadly protective against many *T. pallidum* strains. These complex requirements are very unlikely to be met using a single treponemal protein, and thus it is probable that an effective syphilis vaccine will constitute a multi-component formulation.

6.2. Gaps that need to be addressed

After almost a century of research, significant insight has been provided into the correlates of protection in the rabbit model. However, successful vaccine development will depend upon extending our understanding of the correlates of protection in humans by fostering exchange of information and samples between the basic research laboratories and the clinics. Development of appropriate and effective adjuvants is essential and is likely to require the participation of industry. Within the realm of research there needs to be the application of large-scale “omics” experimental approaches and data analyses to enhance our understanding of factors such as differential gene and protein expression among *T. pallidum* subspecies and *T. pallidum* subspecies *pallidum* strains. And, most importantly, there needs to be an enhanced effort to conclusively determine the identity of surface-exposed antigens. This includes the OMPs, but also requires that the field pursue non-protein antigens including membrane lipids and post-translational modifications such as glycosylation or methylation of exposed proteins. The field has been focussing on the “easier” protein antigens, perhaps at its peril. The accomplishment of these goals will require attracting a larger number of trained syphilis basic scientists to the field and a commitment of continual and enhanced training and research support that is commensurate with technical barriers and the high cost of performing *T. pallidum* research.

The successful development of vaccines for a developing world market is challenging, as the average timeline for development of a new vaccine is 8–18.5 years at an estimated cost of \$200–\$900 million [97]. However, there is already a significant precedent for the support of pharmaceutical and biotechnology companies in the development of vaccines for diseases that disproportionately affect people in the developing world. The implementation of initiatives such as the Decade of Vaccines in 2010 by the WHO, the United Nations Children’s Fund, the NIH’s National Institute of Allergy and Infectious Diseases, and the Bill and Melinda Gates Foundation has facilitated the creation of a Global Vaccine Action Plan to “achieve key milestones in the discovery, development, and delivery of life-saving vaccines to the most vulnerable populations in the poorest countries over the next decade” [98]. Although such programs undoubtedly draw essential attention and much-needed resources to vaccine development for neglected diseases, the so-called productivity gap, where industry-invested resources do not match the expected product return [99], is a significant impediment to this process. The process of differential pricing, whereby companies charge wealthier countries a higher price for a particular vaccine to offset the

revenue loss associated with provision of that same vaccine to resource-poor nations, has allowed several vaccines to achieve a worldwide distribution [100]. However, the success of such a tiered pricing scheme depends entirely upon the magnitude and demographics of the target population in the developed nations. To facilitate development of a syphilis vaccine, there needs to be an accurate evaluation of the market in the developed world which takes into account the potential of such a vaccine to also decrease HIV incidence, and an assessment of the level of industry interest in vaccine development for this disease.

7. Summary of the benefits of vaccine development for syphilis

Several factors make syphilis an ideal disease for vaccine development. Because *T. pallidum* is an obligate human pathogen with no known animal or environmental reservoir [101], a successful global vaccination program could effectively eliminate this disease. The animal model recapitulates the primary, secondary and latent disease stages observed in humans, permitting appropriate pre-clinical vaccine studies to accurately assess the protective capacity of a syphilis vaccine candidate. The continued complete susceptibility of *T. pallidum* infection to penicillin (and thus, the ability to adequately treat subjects if trial vaccines fail to provide protection) will be extremely attractive for both industry sponsors and volunteer participants in clinical vaccine trials. Further, prior vaccination studies performed using γ -irradiated bacteria in the animal model provides us with proof that protection can be achieved. Although the *T. pallidum* OM, with its constituent lipids and OMPs, presents a challenge for experimentation, the relative simplicity of the treponemal surface may prove to be beneficial for syphilis vaccine development. In fact, if the research and discovery components of syphilis vaccine creation can be completed within the academic realm, then industry costs for vaccine development and delivery would likely be reduced, thus streamlining the production process and increasing industry interest in generation of a vaccine to combat this disease.

8. Conclusions

Vaccination is deemed one of the world's most important and cost-effective public health measures that imparts positive health and economic benefits to society [102]. Considering the continuing global disease burden of syphilis, direct correlation with increased transmission of HIV, and significant morbidity and mortality associated with infectious syphilis and CS, there is an obvious need for conceptual, strategic and financial support for development of a vaccine against this devastating disease.

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Abbreviations

ANC	antenatal care
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CS	congenital syphilis
IM	intramuscular

MSM	men who have sex with men
OM	outer membrane
OMP	outer membrane protein
ORF	open reading frame
STI	sexually transmitted infection
Tpr	<i>T. pallidum</i> repeat
V	variable
WHO	World Health Organization

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Highlights

- Continuing high incidence rates in developing countries, re-emergent disease in developed nations
- Failure of decades of public health efforts to control syphilis highlights the need for an effective, inexpensive vaccine
- Causative agent is *Treponema pallidum*, a highly invasive spirochete that crosses the placental and blood-brain barriers; infection increases HIV transmission and acquisition
- Proof-of-principle shown by complete protection in animal model through immunization with γ -irradiated *T. pallidum*; demonstrated importance of opsonising antibodies and a Th1 immune response
- Urgent needs include recruitment of new investigators to the field, commensurate sustained basic research support and research focussed on definitive identification of surface components, identification of correlates of protection in humans, and selection of effective adjuvants.

Table 1

Surface-exposed *T. pallidum* OMP candidates identified to date

ORF number(s)	Alternative names	Predicted function	Method of identification				References
			Opsonic antibody reactivity	Structural analyses	Host component attachment	Bioinformatics	
Tp0117/131	TprC/D	Strain-specificity (TprC/D), antigenic variation in TprK	X	X		X	[62;68]
Tp0316	TprF		X			X	[103]
Tp0620	TprI					X	[63;65]
Tp0897	TprK		X	X		X	
Tp0326	Tp92, BamA	Outer membrane protein assembly	X	X		X	[70;71]
Tp0136		Host component attachment/degradation			X	X	[42]
Tp0155					X	X	[43]
Tp0483				X	X	X	[43;69]
Tp0751	Pallilysin		X		X	X	[44-48;104]
Tp0966-Tp0969	Potential TolC orthologs	Transport across outer membrane				X	[105]