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Treponema Pallidum Vaccines: Bridging Genomics and Feasible Implementation for the Future of Syphilis Prevention

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Abstract

The global resurgence of syphilis, with rates reaching levels unseen since the pre-antibiotic era, represents a critical failure to integrate scientific advances with behavioral realities. This review examines the development of multi-epitope vaccines against *Treponema pallidum*, exploring genomic insights, biotechnological innovations, and implementation challenges. We analyze how the diminished collective fear of HIV/AIDS, facilitated by effective antiretroviral therapy, has contributed to rising STI rates, particularly among young populations, and evaluate current prevention limitations. Through systematic examination of *T. pallidum* virulence factors organized according to Falkow's molecular Koch's postulates, we present evidence for multi-epitope vaccine strategies leveraging mRNA-LNP platforms. Key findings include proof-of-concept studies demonstrating protective immunity in animal models and identification of conserved antigenic targets suitable for broad-spectrum coverage. Critical implementation challenges encompass translating preclinical successes to human trials, ensuring equitable global access, addressing vaccine hesitancy, and integrating vaccination with behavioral interventions. Ethical considerations, informed by historical injustices such as the Tuskegee Study, emphasize the imperative of transparent, community-engaged development processes. We propose that multi-epitope vaccines represent not merely a scientific opportunity but an ethical obligation, potentially transforming syphilis from a persistent threat to a controlled disease. Success requires coordinated investment in translational research, adaptive regulatory frameworks, and comprehensive equity mechanisms ensuring universal access regardless of socioeconomic status or geographic location.

Keywords: Syphilis, *Treponema Pallidum*; mRNA Vaccines; Multi-Epitope; Genomics; Public Health

Introduction

Historical Background on Syphilis Prior to the Introduction of Antibiotics

Before penicillin's discovery in 1928 and its clinical application in the 1940s, syphilis represented one of humanity's most devastating pandemics. Known as "the great imitator" for its protean clinical manifestations, *Treponema pallidum* infection caused severe complications ranging from disfiguring cutaneous lesions to progressive dementia and death. Historical estimates suggest that approximately 15% of urban European populations were infected during the 19th century [1].

The absence of effective treatments for tertiary syphilis led physicians to employ toxic mercury and arsenic therapies, often causing more harm than benefit. This medical desperation created conditions for some of medicine's most egregious ethical violations, exemplified by the Tuskegee Study (1932–1972). This infamous experiment deliberately denied treatment to 399 African American men with latent syphilis to observe the disease's natural progression. The study continued for 40 years after penicillin's discovery, representing a profound violation of human rights and research ethics that fundamentally shaped modern biomedical ethics and informed consent protocols [2].

Current Paradox on Rising Syphilis Incidence amidst Scientific Progress

Despite penicillin's availability, syphilis is experiencing a global resurgence that challenges contemporary public health frameworks. In the United States, total syphilis rates increased from 39.6 per 100,000 population in 2019 to 62.5 per 100,000 in 2023, with 209,253 reported cases representing the highest annual total since 1950 [3]. These national trends are further detailed by Rankin et al., who documented widening racial, geographic, and behavioral disparities in syphilis incidence across the period 2018–2022 [4]. The World Health Organization reports over 6 million new cases annually, with congenital syphilis remaining a leading preventable cause of neonatal mortality [5].

This resurgence correlates with a significant behavioral phenomenon: the diminished collective fear of HIV/AIDS following the introduction of effective antiretroviral therapy. Do et al. documented rising syphilis incidence among U.S. adults from 2017 to 2024, with particularly steep increases among younger age groups and populations previously considered at lower risk [6]. Multiple studies document declining condom use and increasing high-risk sexual behaviors among adolescents and young adults, particularly in regions with broad HIV treatment access [7]. The European Centre for Disease Prevention and Control reported 35,391 confirmed syphilis cases in 29 EU/EEA Member States in 2022, representing a 34% increase compared to 2021 and a 41% increase compared to 2018 [8]. Concurrently, sexual education programs have been systematically undermined by conservative political pressures, condom use has declined culturally, and the widespread adoption of dating apps has facilitated casual sexual encounters without corresponding increases in preventive awareness [9, 10]. These converging factors drive the contemporary syphilis resurgence.

Limitations of Present Strategies: The Challenge of Sustained Prevention Campaigns

Conventional prophylactic strategies rely primarily on promoting condom use and behavioral interventions, demonstrating significant limitations when confronted with complex human behavioral dynamics. Educational campaigns, while necessary, require continuous investment and renewal and often encounter cultural and religious resistance, as well as limitations in reaching most at-risk populations. WHO surveillance data indicate declining condom use rates among adolescents compared to 2014 baselines, while STI incidence, including syphilis, continues rising [11].

Vaccination offers a fundamentally different approach: providing durable protection independent of behavioral decisions at the moment of exposure and enabling population-level interruption of transmission. Vaccines have historically demonstrated extraordinary success in controlling infectious diseases, from poliomyelitis to human papillomavirus, and represents a more sustainable public health intervention than perpetual educational campaigns. Furthermore, doxycycline post-exposure prophylaxis

(doxyPEP) has emerged as a promising complementary strategy, with systematic review evidence demonstrating a 78% reduction in syphilis incidence among high-risk populations [12], though concerns regarding antimicrobial resistance necessitate careful implementation. Although there are currently no vaccines proven to be effective at controlling *T. pallidum* infection, this narrative review has collated recent evidence on studies developing and testing new vaccine solutions.

The Genomic Revolution and Emerging Vaccine Strategies

T. pallidum genomics has systematically mapped genes corresponding to Stanley Falkow's molecular Koch's postulates of bacterial pathogenesis: adhesion, invasion, multiplication/persistence, immune evasion, and cellular damage [19, 20]. Unlike pathogens deploying potent toxins, *T. pallidum* operates through a coordinated network of surface proteins specialized for different pathogenesis stages.

Table 1: *T. Pallidum* Antigens as Vaccine Candidates Based on Falkow's Molecular Koch's Postulates

Virulence Axis	Gene (*tp*)	Protein	Function	Vaccine Evidence
Adhesion	*tp0751*	Pallilysin	Vascular adhesin/protease, laminin binding	Reduced dissemination in rabbits [13]; subsequent study contested protection and argued it is periplasmic [14]
Adhesion	*tp0954*	Surface adhesin	Placental tropism	An mRNA-LNP vaccine has induced protection in rabbits [15]
Adhesion	*tp0897* (*tprK*)	TprK	Antigenic variation, adhesion	TprD/TprK confirmed as surface-exposed adhesins promoting opsonophagocytosis [16]
Structural/Evasion	*tp0326*	Tp92 (BamA)	β-barrel assembly, immune modulation	Antibodies against BamA ECLs disrupt the outer membrane [17]
Evasion	*tp0574*	Tp47	Inflammatory modulation	Accessory antigen [18]

While several of these antigens have shown promise, a critical review of the literature reveals inconsistent results across independent studies. Most notably, follow-up experiments on TP0751 had entirely contradictory results relative to the exploratory first-evaluation findings. Lithgow et al. (2017) reported that TP0751 immunization reduced bacterial dissemination in the rabbit. However, on re-evaluation, Luthra et al. (2020) found no protective effects, with no signs of opsonophagocytosis and no protection against local or disseminated infection upon challenge with *T. pallidum*. Their data argued that the protein should not have been characterized as surface-exposed, but instead as periplasmic.

Other candidates also require a careful eye. TP0954 showed protection in the rabbit model but is a single unreplicated study, while other candidates like TprK, BamA and Tp47 have only exploratory results pointing to their effectiveness. As they are, these currently explored vaccine candidates are not yet suitable to go to market.

Rationale for Multi-Epitope Vaccine Design

The development of a multi-epitope vaccine against *T. pallidum* could prove necessary due to the pathogen's unique "stealth" outer membrane architecture, which is characterized by low protein density and antigenic variation in families like Tpr, rendering single-antigen vaccines inadequate. Multi-epitope vaccines emerge as rational strategies for vaccine development, as they fundamentally analyse inter-strain conserved epitopes from multiple proteins to reduce escape risk through variation. The necessity for targeting conserved regions is highlighted by genomic studies in South America that revealed lineage-specific tprK diversifi-

cation patterns [21]. Immune response optimization occurs through the strategic combination of B-cell epitopes (neutralizing antibodies) and T-cell epitopes (cellular immunity), which generates robust, durable responses, as evidenced by recent studies demonstrating that epitope-specific T-cell–based vaccines elicit potent cellular immunity and control treponemes in rabbit challenge models [22]. Finally, multi-stage targeting allows for the simultaneous blocking of adhesion (Tp0751/TP0954), immune evasion (conserved TprK), and cellular assembly (Tp92), thereby addressing multiple pathogenesis stages.

Biotechnological Innovations and Mrna-LNP Platforms and Beyond

The COVID-19 pandemic accelerated development of messenger RNA vaccines encapsulated in lipid nanoparticles (mRNA-LNP), generating extensive interest in applying this technology to other infectious diseases [23]. This platform provides specific advantages for *T. pallidum* vaccination: transient expression of complex antigens, robust induction of Th1/Th17 immune responses, and the capacity to incorporate multiple mRNAs into a single formulation [23]. Traditional vaccine platforms face significant limitations for *T. pallidum*. Inactivated vaccines struggle to present surface proteins in correct conformations, potentially reducing effectiveness. The recent development of the first human cell-based cultivation system for *T. pallidum* represents a significant milestone that may facilitate future vaccine antigen characterization [24]. Protein-based subunit vaccines, while safer, have not achieved durable immunity against pathogens with antigenic variation mechanisms. mRNA-LNP approaches, enabling rapid design, multiple antigen inclusion, and enhanced immunogenicity, represent attractive alternatives despite challenges in manufacturing costs and global distribution.

Lu et al. recently demonstrated that an mRNA-LNP vaccine encoding TP0954 provided significant protection in rabbits, reducing bacterial loads and preventing systemic dissemination [15]. This represents the first proof-of--concept that mRNA platforms can effectively prevent syphilis. Furthermore, a separate study by Delgado et al. demonstrated that antibodies against extracellular loops of *T. pallidum* outer membrane proteins, including BamA (Tp92), disrupted outer membrane integrity and neutralized infectivity, validating these proteins as vaccine targets [17]. Future strategies encompass: Multiple mRNA co-formulation (Tp0751, TP0954, conserved TprK, Tp92), Adjuvant optimization for lasting immune responses, Mucosal targeting for local protection and Bivalent/multivalent formulations including other pathogens (HIV, HSV-2).

Critical Implementation Challenges

Translating Preclinical Success to Clinical Trials

The transition from animal models to human trials presents multifaceted challenges. Current rabbit models, while providing proof-of-concept for protective immunity, may not fully recapitulate human immune responses or *T. pallidum* pathogenesis [25]. Key translational challenges include: species-specific immune differences, as human HLA diversity and immune response patterns may differ significantly from animal models; dose optimization, involving the determination of optimal antigen doses and vaccination schedules for humans; safety profile establishment, requiring a comprehensive assessment of mRNA-LNP safety in diverse populations; and endpoint definition, which involves establishing appropriate clinical endpoints for efficacy evaluation in populations with varying baseline risks [13]. Additional practical barriers include: the rabbit model's inability to reproduce congenital or neurosyphilis; the lack of standardized challenge protocols across laboratories; and the absence of validated correlates of protection, making human efficacy prediction entirely speculative [25].

Animal Model Limitations and Human Efficacy Prediction

The transition from animal models to human vaccine efficacy prediction is complicated by inherent limitations that hinder direct translation, though emerging solutions are being developed to bridge these gaps [26]. Primary limitations include anatomical differences, as rabbit and non-human primate models may not fully replicate human mucosal and systemic immune responses, and variations in pathogenesis, where disease progression and bacterial dissemination patterns can differ significantly between species. Furthermore, immune system disparities pose a challenge, as HLA polymorphisms and the overall diversity of im-

mune responses in human populations far exceed the capabilities of standard animal models [26]. Critically, no rabbit model exists for congenital syphilis or neurosyphilis, and almost all studies use the laboratory-adapted Nichols strain, leaving efficacy against diverse clinical isolates unknown. Additionally, rabbit models do not provide adequate assessments of long-term durability of protection, being followed for weeks rather than years. To address these issues, several emerging solutions are being explored, such as the use of humanized mouse models that incorporate human immune system components and advanced organoid systems that provide human tissue environments for studying infection [26]. Additionally, computational modeling is being used to integrate multiple data sources for predicting human responses, alongside correlates of protection studies aimed at identifying specific immune markers that remain predictive of protection across different species [26].

Safety Concerns Specific to Mrna-LNP Syphilis Vaccines

The transition from preclinical research to clinical application for mRNA-LNP syphilis vaccines requires addressing several specific safety considerations despite the proven profile of the platform during the COVID-19 pandemic. Potential concerns include the risk of autoimmune reactions if *T. pallidum* antigens cross-react with human tissues, as well as the potential for excessive inflammatory responses; for instance, research has shown that the lipoprotein Tp0768 can promote H3K18 lactylation and enhance endothelial permeability [18]. Furthermore, ensuring pregnancy safety is critical given the severe impact of syphilis on maternal-fetal health [27], as is establishing safety for immunocompromised populations, such as HIV-positive individuals. To mitigate these risks, researchers are focusing on comprehensive preclinical toxicology across multiple species and selecting antigens that favor proteins with minimal human homology. Additionally, clinical strategies involve graduated dosing studies that start with low doses before escalating carefully, supported by enhanced pharmacovigilance and robust post-market surveillance systems to monitor long-term safety.

Equity, Access, and Ethical Considerations

The development of *T. pallidum* vaccines carries profound ethical weight, particularly given historical injustices exemplified by the Tuskegee Study, which involved the unethical observation of untreated syphilis in 399 African American men [2]. Any future vaccine program must incorporate rigorous principles of equity, transparency, and social justice to prevent the repetition of past ethical failures. Fundamental ethical principles begin with universal access, which requires proactive equity mechanisms like tiered pricing, global procurement agreements, and early technology transfer initiatives to ensure vaccines do not become privileges of specific social classes. Inclusive research design is equally critical, necessitating that clinical trials include populations most affected by syphilis-including racial minorities, sexual minorities, sex workers, and other vulnerable groups-while strictly respecting their autonomy and dignity. Furthermore, transparency and community engagement must be prioritized, ensuring that affected communities are genuine partners in research design, implementation, and evaluation. Finally, reparative justice dictates that vaccine development must actively address past harms through community benefit-sharing, preferential access for historically marginalized populations, and sustained investment in community health infrastructure. These principles translate into contemporary equity imperatives that focus on the Global South and marginalized populations. High-burden regions in sub-Saharan Africa and Latin America, which often have limited purchasing power, must receive priority access through innovative financing and technology transfer [5]. Domestically and globally, groups facing disproportionate syphilis burdens, such as men who have sex with men, transgender individuals, sex workers, and people experiencing homelessness, must be centered in all development and distribution planning [11]. This requires intersectional approaches that recognize how racism, sexism, homophobia, and economic inequality compound syphilis risks, necessitating vaccine programs that address multiple forms of discrimination simultaneously to be truly effective and just [5, 11].

Integration of Behavioral Interventions and Vaccination Strategies

Synergistic Approaches for Optimal Impact

The integration of vaccination and behavioral in-

terventions should be implemented as complementary rather than competing strategies to achieve optimal impact [5]. This involves integrated service delivery through "one-stop" clinics that combine vaccination with STI testing, treatment, and counseling, as well as incorporating syphilis vaccination into HIV prevention programs like PrEP and antenatal care services [5]. Behavioral reinforcement can be achieved by providing risk reduction counseling during vaccination encounters, leveraging vaccine programs for partner notification and contact tracing, and using vaccination campaigns as catalysts for broader community sexual health awareness [5]. Furthermore, technology integration through digital platforms for scheduling and education, data linkage between vaccination records and STI surveillance, and personalized interventions based on risk profiles can further enhance these synergistic approaches. Addressing potential behavioral compensation-where individuals might increase risky behaviors following vaccination-requires proactive management through dedicated monitoring and mitigation strategies. Monitoring involves behavioral surveillance to track changes in vaccinated populations, real-world effectiveness studies across different risk groups, and long-term follow-up to assess sustained protection and behavior patterns. Mitigation approaches include clear communication emphasizing that vaccines provide additional rather than complete protection, the continued promotion of condoms and other behavioral interventions, and careful booster schedule planning to ensure periodic revaccination as needed [5].

Policy and Funding Recommendations

Investment priorities for future syphilis vaccination strategies require a multi-faceted approach to funding and policy, beginning with increased government and international agency investment in translational research and the creation of dedicated funding streams specifically for syphilis vaccine development, alongside incentives for public-private partnerships [5]. Regulatory acceleration is equally vital, necessitating adaptive clinical trial frameworks, fast-track approval processes for high-priority global health interventions, and international regulatory harmonization to ensure efficient global deployment. Furthermore, implementation preparation must involve early investment in manufacturing capacity and supply chain development, the strengthening of healthcare systems in high--burden regions, and proactive community preparation and engagement initiatives. Global coordination mechanisms are essential to sustain these efforts, requiring strong international partnerships under WHO leadership to coordinate global vaccine development, supported by G20 commitments to research and access and integration with existing initiatives like PEPFAR and the Global Fund [5]. Knowledge sharing must also be prioritized through open-access research publication requirements, technology transfer agreements to facilitate global manufacturing, and the systematic sharing of best practices for implementation strategies.

Future Directions and Research Priorities

Scientific and implementation research must advance in several key areas to ensure the success of future syphilis vaccination programs [25]. High-priority scientific advances include the development of improved preclinical models that more accurately predict human responses, the identification of clear correlates of protection to evaluate vaccine effectiveness, and studies focused on the duration of protection to determine optimal vaccination schedules and booster requirements [5, 25]. Additionally, research into population-specific responses is essential to understand how vaccine effectiveness may vary across diverse groups [25]. Parallel to these scientific efforts, implementation research must focus on identifying the most effective delivery strategies for various healthcare systems and populations, alongside economic evaluations to determine cost-effectiveness and guide resource allocation. Understanding the social factors that influence vaccine acceptance and uptake is also critical for designing improvement strategies. Finally, developing best practices for integration approaches will be necessary to seamlessly incorporate new vaccines into existing health programs and clinical workflows.

Conclusion

The resurgence of syphilis in the genomic era represents more than epidemiological failure; it demonstrates our collective inability to integrate scientific advances with behavioral and social realities. We cannot continue combating a 21st-century epidemic with 20th-century conceptual

frameworks. The development of multi-epitope vaccines against *T. pallidum* represents both an unprecedented scientific opportunity and an ethical imperative. Each preventable case of congenital syphilis, every progression to neurosyphilis, and each unnecessary maternal death underscores the urgency for solutions transcending traditional educational interventions. Success requires coordinated action across multiple domains: sustained investment in translational research, adaptive regulatory frameworks that accommodate innovative vaccine platforms, and comprehensive equity mechanisms that ensure universal access regardless of socioeconomic status or geographic location [5]. Policy priorities must include increased investment from government and international agencies, dedicated funding streams, and incentives to foster public-private partnerships. Genomics provides the fundamental framework, immunoinformatics offers sophisticated analytical tools, and mRNA platforms serve as advanced technological vehicles. The remaining challenge is transforming this knowledge into action, ensuring historical injustices are not repeated, and scientific progress benefits all populations equitably. The future of syphilis prevention is being determined by current laboratory research, advances in structural prediction algorithms, and policy decisions regarding research investment. Our generation bears historical responsibility for breaking the cycle of syphilis resurgence, transforming it from a persistent threat into a controlled disease.

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The concept has been developed by V.A. AKJ, CRG and AFMO carefully checked the manuscript content, removed redundancy and checked all the references.

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