



The Role of Immunity in The Epidemiology of Adolescent Syphilis

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ABSTRACT

Introduction. Syphilis is a sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum* and remains a global health problem with a significant increase in prevalence. Adolescents are vulnerable to syphilis because they lack sufficient sexual health information and services. This study aims to explore the role of cellular immune response in the pathogenesis of syphilis in adolescents and the factors that influence it. **Methods.** This research study adopted a systematic literature review methodology, sourcing data from PubMed, Scopus, Web of Science, and Google Scholar databases. **Results.** The results demonstrate a crucial involvement of macrophages, dendritic cells, and T lymphocytes in the cellular immune response against *Treponema pallidum* causes Syphilis. The immune response is principally influenced by variables such as age, nutritional status, and the presence of HIV infection. High infection rates are also attributable to factors such as risky sexual behaviour and socioeconomic conditions. Enhanced interventions, including comprehensive sexual health education and improved access to healthcare services, are crucial for mitigating the adverse effects of syphilis in adolescents. **Conclusion.** In conclusion, this research underscores the necessity of a deeper understanding of the immunopathogenic mechanisms of syphilis in adolescents to facilitate the development of more effective preventive, diagnostic, and therapeutic strategies.

1. Introduction

The World Health Organization (WHO) issued a report stating that in 2022, the approximate incidence of new syphilis cases within the adult population aged 15 to 49 worldwide was eight million.¹ A worldwide public health concern, sexually transmitted infections (STIs) can be contracted through a variety of sexual behaviors. The causative agents of these infections range from bacterial to parasitic organisms and affect individuals irrespective of age or gender. Among the more perilous STIs is syphilis, an infection resulting from the bacterium *Treponema pallidum* and characterized by its considerable multisystemic effects on human physiology.² Syphilis is recognized as a 'master mimic' owing to its varied clinical presentations, frequently resulting in protracted diagnostic processes and delayed initiation of appropriate treatment. The disease exhibits a progression through distinct clinical phases, specifically primary, secondary, latent, and tertiary stages, with the potential for severe sequelae including organ damage and vertical transmission

from mother to fetus.³ The increasing global prevalence of syphilis highlights the necessity for further research into its pathogenesis and spread. Sexual health, a key aspect of human well-being, includes reproductive, emotional, social, and psychological dimensions. The WHO defines sexual health as the holistic state encompassing physical, mental, and social well-being related to sexuality, not merely the absence of disease, dysfunction, or infirmity. Despite being treatable, syphilis remains a global health challenge due to its significant impact on the quality of life of infected individuals, particularly concerning social stigma and psychological effects.⁴ Risky sexual behavior, low socioeconomic status, and HIV-positive status are key risk factors in syphilis transmission, collectively increasing individual susceptibility. Studies suggest that enhanced screening for syphilis, especially among HIV-positive individuals, and interventions targeting high-risk groups can help control its spread.⁵

The period of adolescence (10-19 years) constitutes a pivotal stage in human development, due to its rapid physical, cognitive, and psychosocial

evolution. It is during this time that individuals are inclined to develop behavioral patterns with potential future health consequences. Despite the general perception of adolescents as a healthy population segment, they remain vulnerable to a range of illnesses, including STIs like syphilis, stemming from a deficit in accurate sexual health information and a heightened sense of curiosity that can encourage high-risk sexual practices. Compounding this vulnerability is their limited sexual and reproductive healthcare access, a factor contributing to the substantial number of syphilis cases observed in this age group.⁶ Syphilis unfortunately represents a persistent and significant health crisis in low- and middle-income countries despite ongoing efforts to reduce cases. The disease spreads through sexual activity or vertically from mother to baby during gestation, leading to congenital syphilis with serious complications like birth defects and perinatal death. This cycle highlights the importance of early detection and treatment, especially before the infection progresses to advanced stages with irreversible complications.⁷ The high incidence of STIs, including syphilis, in various regions, especially densely populated urban areas, indicates a need for more effective interventions. Prevention and control efforts primarily target high-risk groups such as sex workers, MSM, and injecting drug users.⁸ Thus, a comprehensive strategy that integrates educational initiatives, health promotion efforts, and improved access to healthcare services grounded in evidence is required.

The purpose of this review was to collate and synthesize current scientific data regarding the function of cellular immune responses in the development and spread of syphilis in adolescents. This study sought to identify and understand the roles of key immune cells, namely macrophages, dendritic cells, and T lymphocytes, alongside critical cytokines such as interferon- γ (IFN- γ), interleukin-17 (IL-17), and interleukin-10 (IL-10), in the immune response to bacterial *Treponema pallidum* which causes syphilis within the adolescent demographic. Moreover, this review investigated factors that modulate cellular immune responses, including age, nutritional status, HIV infection, and risky sexual behavior. The outcomes of this review are therefore expected to have considerable epidemiological relevance, potentially leading to the development of diagnostic biomarkers, vaccines, and improved treatment modalities for adolescent syphilis. Overall, this study intends to offer a thorough summary of existing understanding, pinpoint gaps in current research, and suggest directions for future studies to support initiatives aimed at preventing and controlling syphilis among adolescents.

2. Methods

This study was to investigate the role of cellular immunity in the epidemiology of adolescent syphilis

through a systematic literature review. A comprehensive search strategy was implemented across various electronic databases, namely PubMed, Scopus, Web of Science, and Google Scholar. Relevant search terms, including 'juvenile syphilis', 'cellular immunity', and '*Treponema pallidum*', were employed, with keyword combinations serving to focus the search results. The inclusion criteria incorporated a five-year publication window and manual screening of the bibliographies of pertinent publications. Researchers have selected 33 journals based on inclusion and exclusion criteria. Inclusion and exclusion criteria were applied to ensure the relevance of the selected articles, focusing on articles that addressed the role of cellular immunity in juvenile syphilis, including original research, literature reviews, and meta-analyses, while articles that were not in English or Indonesian and those that were not relevant were excluded. Article selection was performed by researchers independently to determine eligibility for inclusion, with full-text review for articles that met the criteria, and disagreements resolved through discussion or consultation. Data extraction was performed using a standardized form, covering general information of the article, study design, population, cellular immune parameters measured, results, and conclusions. The extracted data were analyzed qualitatively to identify key themes and emerging patterns, using narrative analysis to synthesize findings from multiple studies, as well as descriptive analysis for quantitative data.

3. Epidemiology of Syphilis in Adolescence

Age plays an important role in the differences in immune responses between adolescents and adults. In addition, nutritional status also has a significant impact, where malnutrition can weaken the immune system and increase susceptibility to infection. Co-infections such as HIV are another factor affecting cellular immunity, where HIV-induced immunosuppression can increase the risk of syphilis infection. Behavioral factors, such as risky sexual behavior, also contribute to high rates of Sexually Transmitted Infections (STIs), including syphilis. The prevalence of syphilis is higher among adolescent girls, especially those not attending school. Certain behaviors may contribute to this high prevalence, including early sexual initiation, having multiple partners, and inconsistent condom use. Low socioeconomic status and lack of knowledge about STIs also exacerbate this condition. Other social factors, such as poverty, gender inequality and lack of education, increase adolescents' vulnerability to infection. Therefore, targeted interventions are urgently needed to address these challenges, including through comprehensive sexuality education, promotion of safer sexual behavior, improved access to reproductive health services, as well as economic empowerment for adolescent girls.⁹ Prevention efforts should focus on high-risk groups,

especially out-of-school adolescents, as well as narrowing the knowledge gap about STIs. The psychological impact of syphilis on patients is generally limited, with only a small proportion experiencing increased anxiety, especially at diagnosis. However, sexological impacts are more common, with almost half of patients reporting problems such as decreased sexual desire and loss of trust in partners. Nonetheless, these problems are often temporary after treatment.⁴ Globally, millions of new STI cases occur each year, with adolescents being the most vulnerable age group. Major factors that trigger this vulnerability include risky sexual behavior, lack of adequate sex education, as well as biological factors that increase the risk of infection. In many developing countries, economically and socially marginalized adolescents are at higher risk due to limited access to health information and services. Adolescent health care systems in many countries are often inadequate. Many adolescents are reluctant to seek medical help due to social stigma, shame and judgmental attitudes from health workers. Moreover, significant barriers also arise from issues of accessibility and confidentiality. The situation is further exacerbated by cultural and religious influences that impede comprehensive sex education. Existing health policies often prioritize the management of STI symptoms, rather than addressing fundamental causes such as a lack of sex education and restricted access to healthcare services tailored for young people.⁶ Therefore, a more coordinated global effort is needed to address adolescent STIs through education, prevention, and inclusive and affordable health services.

Other challenges in STI prevention include insufficient pre-referral counseling by health workers and a lack of STI information among adolescents. Patient commitment, family involvement, and drug availability also influence prevention effectiveness. Extensive and intensive STI education is a much-needed step to reduce transmission risk.⁸ The increase in STI infections among adolescents and young adults is a serious concern, as this group represents only one in four sexually active people. This rise is driven by behavioral, biological, and social factors, including increased risky behaviors like multiple partners, low condom use, and substance use during sex. Complex sexual networks, difficulty accessing health services, lack of knowledge about adolescent rights, and concerns about discrimination and confidentiality have also contributed to this increase. The syphilis epidemic among key populations is associated with modern individual and group factors, including a decline in safe sex practices fueled by HIV prevention fatigue, optimism towards Antiretroviral Treatment (ART), increased use of recreational drugs, and expansion of internet and dating app use. The use of Pre-Exposure Prophylaxis (PrEP) with the potential for risk compensation and the practice of 'serosorting' have also played a role in

the increased spread of STIs. In summary, a combination of behavioral, social, and healthcare access factors contributes to high STI rates, especially among adolescents, young adults, and key populations. Other factors contributing to this high prevalence include risky sexual behaviors such as unprotected sex and having a high number of sexual partners, as well as involvement in commercial sex work, low education level, self-reported history of STIs, unemployment, psychoactive substance use, history of imprisonment, homelessness, non-consensual sex, and stigma and discrimination that impede access to health services.¹⁰ In addition, there is a significant association between low monthly family income and syphilis. Women with income equivalent to the minimum wage have a higher risk of syphilis infection, highlighting the role of socioeconomic factors in the spread of the disease. Illicit drug use is also associated with an increased risk of syphilis. Although other risk factors such as low education level, irregular marital status, and history of STIs are often associated with syphilis in the literature, this study found no significant association with these factors.¹¹ By understanding the various factors that influence cellular immune responses in adolescents, more effective interventions can be designed to reduce the negative impact of STIs and improve the overall sexual health of adolescents.

4. Immunopathogenesis of Syphilis

Transmitted through various pathways sexual contact or from mother to baby during pregnancy, syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum*. The disease develops in several stages, namely primary (chancre appearance), secondary (skin eruption), latent (asymptomatic, divided into early and advanced), and tertiary (serious organ damage). Despite the availability of effective treatments for syphilis based on the stage of infection, individuals are not immune to future reinfection.¹² The pathogenesis of syphilis is significantly shaped by the interaction between *Treponema pallidum* and the human immune system. A key characteristic of this bacterium is its ability to evade immune detection through antigenic variation and the suppression of immune responses, resulting in chronic infection. The host's immunological response impacts the severity of clinical signs and the effectiveness of therapeutic regimens.¹³ The role of cytokines in the syphilitic immune response is critical, where the balance between pro-inflammatory cytokines (interferon-gamma (IFN- γ), interleukin-17 (IL-17)) and regulatory cytokine interleukin-10 (IL-10) determines the degree of inflammation and potential tissue damage. In particular, IL-17 is associated with neurosyphilis and the neurological damage that occurs in advanced infection. Recent studies examined the potential of *Treponema pallidum* repeat protein K (TprK), a

protein from *Treponema pallidum*, as a component of a syphilis vaccine.^{14,15}

Findings from this investigation indicate that immunization with rTprK (recombinant *Treponema pallidum* repeat protein K) markedly decreased lesion development and the tissue load of *T. pallidum*. This protective effect was associated with the induction of a strong Th1 cellular immune response, evidenced by increased IFN- γ production, and a humoral response that augmented macrophage-mediated opsonophagocytosis, a critical mechanism for pathogen elimination. Moreover, rTprK immunization demonstrated efficacy in slowing the advancement and accelerating the healing of lesions, thereby potentially reducing the transmissibility of syphilis. The reduced systemic and local *T. pallidum* burdens suggest that rTprK immunization aids in clearing the pathogen at the primary lesion site and preventing its spread. The study also revealed a significant delayed-type hypersensitivity (DTH) response and an upregulation of Th1 cytokines such as IFN- γ , Tumor Necrosis Factor- α (TNF- α), and interleukin-12 (IL-12)¹⁶. In addition, antibodies against rTprK enhanced opsonophagocytosis of *T. pallidum* by macrophages. Although full protection against infection has not been achieved, this study highlights the importance of TprK as a promising candidate component of a syphilis vaccine and emphasizes the need for further studies to explore Th1 cell responses, identify epitopes that can target T and B cell responses, and understand the effects of TprK variation on immune responses.¹⁵

Syphilis is a systemic infection that can negatively affect a multitude of organ systems, including the Central Nervous System (CNS), ocular system, and brain. In adults, the clinical manifestations of syphilis develop in various stages. Primary syphilis usually appears about three weeks after exposure, with an incubation period of between 10 to 90 days.¹⁷ Primary syphilis is characterized by one or more ulcerative lesions called chancre. These lesions are often painless so they can go unnoticed if they occur in the mouth, vagina or rectum. The chancre may persist for two to six weeks before healing spontaneously. About a quarter of patients develop condyloma lata on the genitals or rectum or develop mucosal lesions in the mouth. Secondary syphilis is usually characterized by a mucocutaneous rash on the trunk, palms and soles, which appears between two to 24 weeks after healing of most primary lesions.¹⁸ Symptoms of primary and secondary syphilis may appear together, especially in individuals with HIV infection. When no symptoms are seen, the phase between primary, secondary, and tertiary syphilis is referred to as latent syphilis. Syphilis symptoms may not appear for years or even decades before they finally reappear. Up to two-thirds of patients have latent syphilis that does not progress

to tertiary syphilis. There are three categories of latent syphilis: early latent (occurring within the past year), late latent (more than one year), and latent of unknown duration.¹⁹ Rare manifestations of tertiary syphilis include cardiovascular syphilis with aneurysms or stenosis due to the presence of treponema spirochetes in the thoracic aorta or coronary arteries, as well as syphilitic gumma, which can cause tissue damage in various organ systems, including bones and cartilages.²⁰ Adolescents are a group that is highly vulnerable to syphilis because they are influenced by various social, psychological and behavioral factors that develop during adolescence. One of the main factors is risky sexual behavior, which increases the likelihood of exposure to sexually transmitted infections.²¹ Lack of understanding about sexual health and sexually transmitted infections is also a serious problem, especially as adequate sexual education is often not available in schools or family settings.²²

The innate immune system's role in immunity is especially significant at the beginning of an infection. Natural killer (NK) cells are found in large numbers at syphilis lesion sites, suggesting a strong innate immune response.²³ Trained immunity, a process in which the innate immune system undergoes epigenetic changes that allow for 'memory' of previous exposures, can speed up the response to recurrent infections. However, this immunity can also lead to chronic inflammation that contributes to cardiovascular and autoimmune diseases.¹⁴ Correlation between immunity and epidemiology of syphilis in adolescents is a pertinent area of inquiry (Figure 1).

Epidemiological determinants¹⁷, including age-related physiological variances²¹, co-infections such as HIV^{14,24,25}, and behavioral proclivities associated with heightened sexual risk-taking^{4,26,27}, exert a significant influence on the prevalence and dissemination of syphilis within this vulnerable demographic²⁸. Adolescents exhibiting compromised immune competence²⁹, whether due to concurrent HIV infection⁹, demonstrate an increased propensity towards acquiring the infection, thereby contributing to elevated incidence rates. Concurrently, behaviors that elevate the probability of exposure to *Treponema pallidum*³⁰, the etiological agent of syphilis, such as early sexual debut and multiple sexual partnerships, further exacerbate the epidemiological burden. Conversely, the host's immunological response is instrumental in dictating the clinical trajectory of the infection²³. The bacterium's capacity to evade immune surveillance, thereby fostering chronic infection³¹. Nevertheless, the equilibrium between pro-inflammatory and regulatory cytokine profiles modulates the severity of symptomatic manifestations and the progression of the disease^{32,33}.

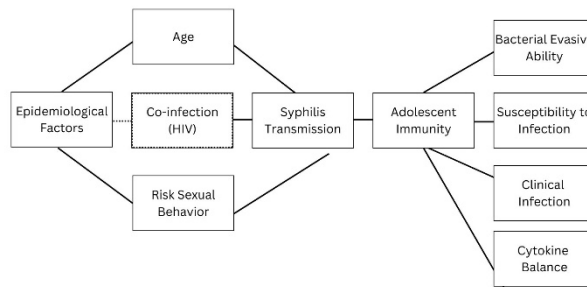


Figure 1. Correlation between immunity and epidemiology of syphilis in adolescents ^{4,10,21}

A deeper understanding of the immunological mechanisms in syphilis infection may aid the development of more effective therapies, such as immunomodulation to overcome immunosuppression or immune hyperactivation. Therapies that focus on increasing IL-10 in syphilis patients may be able to improve the immune response to *T. pallidum*. Further research is needed to understand how the phases of syphilis interact with each other and how the body's immune response affects disease progression. With early detection and more targeted therapy, morbidity and mortality from syphilis can be reduced, especially in vulnerable populations. Collaborative efforts across sectors are needed to ensure access to adequate information and health services for high-risk groups. Consequently, a comprehensive comprehension of both the epidemiological factors driving syphilis and the nuances of the immunological response is imperative for the formulation of efficacious preventative and therapeutic strategies specifically tailored to adolescents.

5. Conclusion

Syphilis is a globally significant Sexually Transmitted Infection (STI) with increasing prevalence across different age groups, including adolescents. The disease is caused by the bacterium *Treponema pallidum* and can develop in several clinical stages, which if left untreated can lead to serious complications, including organ damage and congenital syphilis. Adolescents are vulnerable to syphilis due to lack of sexual health education, limited access to health services, and social and economic factors that influence their sexual behavior. Factors such as age, nutritional status, co-infections (especially HIV), and risky sexual behavior play an important role in the cellular immune response to syphilis in adolescents. The immune response to *T. pallidum* involves various immune cells, including macrophages, dendritic cells, and T lymphocytes, as well as cytokines such as IFN- γ , IL-17, and IL-10. Prevention and control of syphilis in adolescents requires a comprehensive approach, including improved sexual health education, promotion of safe sexual behavior, and increased access to youth-friendly health services. With a deeper understanding of the pathogenesis and immune response of syphilis,

it is hoped that more effective diagnostic and therapeutic strategies can be developed to reduce the incidence of syphilis, especially among adolescents.

6. Author Contribution

Conceptualization, C.P.K. and N.F., Research, C.P.K., N.F., A.G., formal evaluation, Writing (original draft), C.P.K. and R.I., Writing (review and editing), C.P.K., N.F., and A.G. Resource, C.P.K., R.I., A.G., N.F., After reading the paper, each author approved on its content.

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