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Review Article

The pathogenesis of syphilis: the Great Mimicker, revisited

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Abstract

Syphilis is a chronic sexually transmitted infection caused by *Treponema pallidum* subspecies *pallidum*. Its protean clinical presentations earned it the name of the 'Great Mimicker'. Understanding of disease pathogenesis and how host–pathogen interactions influence the course of disease have been compromised by the facts that the organism cannot be grown *in vitro* and, as an exclusively human pathogen, inferences made from animal models are of limited applicability. Many questions remain about how *T. pallidum* biology contributes to distinctive features of syphilis, such as its ability to persist in the presence of a brisk host response or its propensity for neuro-invasion and congenital transmission. In 1998, the genome of *T. pallidum* was sequenced. The organism has a relatively small genome, suggesting that it utilizes host biosynthesis to fulfil some of its metabolic needs. While biological functions are suggested for only about 55% of *T. pallidum*'s 1041 open reading frames, even these relatively early studies offer important insights into syphilis pathogenesis. A family of repeat genes, the *Tp* genes, encode proteins homologous to the major sheath proteins of *T. denticola.* Antibodies to the *TprK* variable regions are protective in a rabbit model. With successive passage, increasing diversity is observed in the *TprK* V region genes. Antigenic variation through gene conversion has been hypothesized to be one mechanism of escaping immune surveillance, allowing for prolonged infection and persistence in the presence of a robust host response. Human and animal studies suggest that a Th1 response is elicited in primary syphilis. Progression to the secondary stage is accompanied by a shift to a Th2 response, allowing for incomplete clearance of the pathogen. In pregnancy, intense inflammatory responses and prostaglandins induced by fetal infection may be responsible for fetal death or pre-term delivery and severe growth retardation or other manifestations of congenital syphilis. Understanding of the molecular targets of these immune responses may facilitate the development of vaccines for syphilis.
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Keywords: syphilis; *Treponema pallidum*; pathogenesis

Introduction

Syphilis is a disease of antiquity and despite the availability of relatively sensitive tests and affordable treatment, remains a global health problem. Theoretically, syphilis should be an eradicable disease as it has no animal reservoir, it can be diagnosed and cured with simple inexpensive tests and antibiotics, and it has a long incubation period which allows case finding and epidemiological treatment to prevent further transmission. In fact, however, multiple concerted efforts to eliminate syphilis have failed. Social impediments and resource limitations have contributed to the persistence of syphilis as a public health problem throughout the 20th and into the 21st century. Another important contributor to continuing syphilis morbidity is its prolonged clinical course and the disease's protean manifestations, which has earned it the name of the 'Great Mimicker' (Table 1).

Causative agent

Syphilis is a chronic infectious disease caused by the spirochaete *Treponema pallidum* subspecies *pallidum.* The genus *Treponema* belongs to the order Spirochaetales, consisting of spiral-shaped pathogenic bacteria. Other members of this order are the genera *Borrelia* and *Leptospira*. Apart from *T. pallidum* subspecies *pallidum*, the causative agent of venereal syphilis, other pathogenic treponemes that cause disease in humans include *T. pallidum* subspecies *pertenue*, the causative agent of yaws; *T. pallidum* subspecies *endemicum*, the causative agent of endemic

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Table 1. Clinical manifestations of syphilis

Stage of syphilis	Clinical manifestations
Primary	Chancre, regional lymphadenopathy
Secondary	Maculopapular rash on flank, shoulder, arm, chest, back, hands and soles of feet; malaise, headache, generalized lymphadenopathy; less common: fever, anorexia, weight loss, mucous patches; condyloma lata; alopecia, meningitis; myalgia; ocular complaints; hepatic, pulmonary, and neurological involvement
Latent	Asymptomatic
Tertiary	
Cardiovascular syphilis	Aortic aneurysm, aortic valvular insufficiency, coronary artery ostial stenosis
Neurosyphilis	
Acute syphilitic meningitis	Headache, meningeal irritation, ocular involvement, cranial nerve palsies
Meningovascular	Focal neurological deficits, cranial nerve palsies
General paresis	Prodrome: headache, vertigo, personality disturbances, followed by acute vascular event with focal findings
Tabes dorsalis	Insidious onset of dementia associated with delusional state, fatigue, intention tremors, loss of facial-muscle tone Lightning pains (lower extremities and abdomen most commonly), ataxia, Argyll Robertson pupil, areflexia, loss of proprioception
Gumma	Monocytic infiltrates with tissue destruction of any organ
Congenital syphilis	
Early	Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anaemia, hepatosplenomegaly, neurosyphilis
Late	Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, condylomata, anaemia, Hutchinsonian teeth, eight-nerve deafness, recurrent arthropathy, neurosyphilis
HIV co-infection	Multiple persistent chancres; ocular involvement and neurosyphilis more common; rapid progression to gummatous disease characterized by lesions of skin, bone, and viscera

syphilis; and *T. carateum*, the causative agent of pinta. These so-called 'endemic' treponemes are morphologically identical to each other and to *T. pallidum* subspecies *pallidum*, share a high degree of DNA homology, and are closely related antigenically, but differ in geographical distribution, host tissue specificity, infectivity in animals, and their pathogenesis [1–3]. Unlike for venereal syphilis, people with endemic treponematoses are not at risk of neurological disease or of fetal and congenital transmission to children born to untreated infected women. Non-venereal treponemal infections are often acquired in childhood and are transmitted by non-sexual contact in communities living under poor hygienic conditions. Utilizing penicillin mass treatment programmes in endemic foci, the endemic treponematoses were the focus of global control efforts in the 1950s and 1960s and represent one of the most successful health programmes ever implemented by the World Health Organization. However, more recently they have reappeared in some rural populations in Africa and South East Asia, sometimes in a clinically attenuated form [2]. In addition, some cultivable treponemes such as *T. denticola*, an oral treponeme, have been increasingly implicated in periodontal disease and gingivitis.

Epidemiology

The name syphilis comes from a Latin poem describing an Italian shepherd boy, who contracted the 'French disease' sweeping through Europe in the early 16th century [4]. Although other evidence suggests that syphilis or related diseases were present in Africa, China, and biblical descriptions centuries earlier, a European epidemic coincided with the return of Columbus from the new world in 1493. It was speculated that Columbus's crew might have contracted the 'serpentine disease of Hispaniola' from the island where Haiti and the Dominican Republic are situated today [5,6]. The rapid spread of syphilis in Europe was probably facilitated by the era's wars and movement of troops. Since then, syphilis and its management have been continuing challenges for medical care providers and public health practitioners.

Venereal syphilis is a worldwide disease of only humans [7]; there is no animal reservoir. Syphilis is usually transmitted by sexual contact or from mother to infant. *T. pallidum* may also occasionally be transmitted as a blood-borne infection. Untreated, the infection follows a prolonged course, with nearly all direct mortality arising in a relatively small proportion of cases years after infection due to neurological or cardiovascular complications [8–11]. Syphilis morbidity, however, includes not only the direct impact of the disease itself, but is also amplified by the consequences of transmission to others (including congenital infections) and its role as a synergistic contributor to risk for HIV acquisition. The mortality and morbidity associated with congenital infection are proportionally far greater than for adults and include stillbirth, spontaneous abortion, and, for infants surviving to birth, mental retardation and abnormal growth and development [12].

In common with other bacterial sexually transmitted infections (STIs), both within nations and from a global perspective, syphilis is most common among population subgroups with limited resources or who live on the margins of society. It is more common among the poor, those who lack access to health care, and in those with many sexual partners. The WHO has estimated that 12 million new cases of venereal syphilis occurred in 1999, most of them in developing countries [13] (Figure 1). Congenital syphilis remains a leading cause of perinatal and

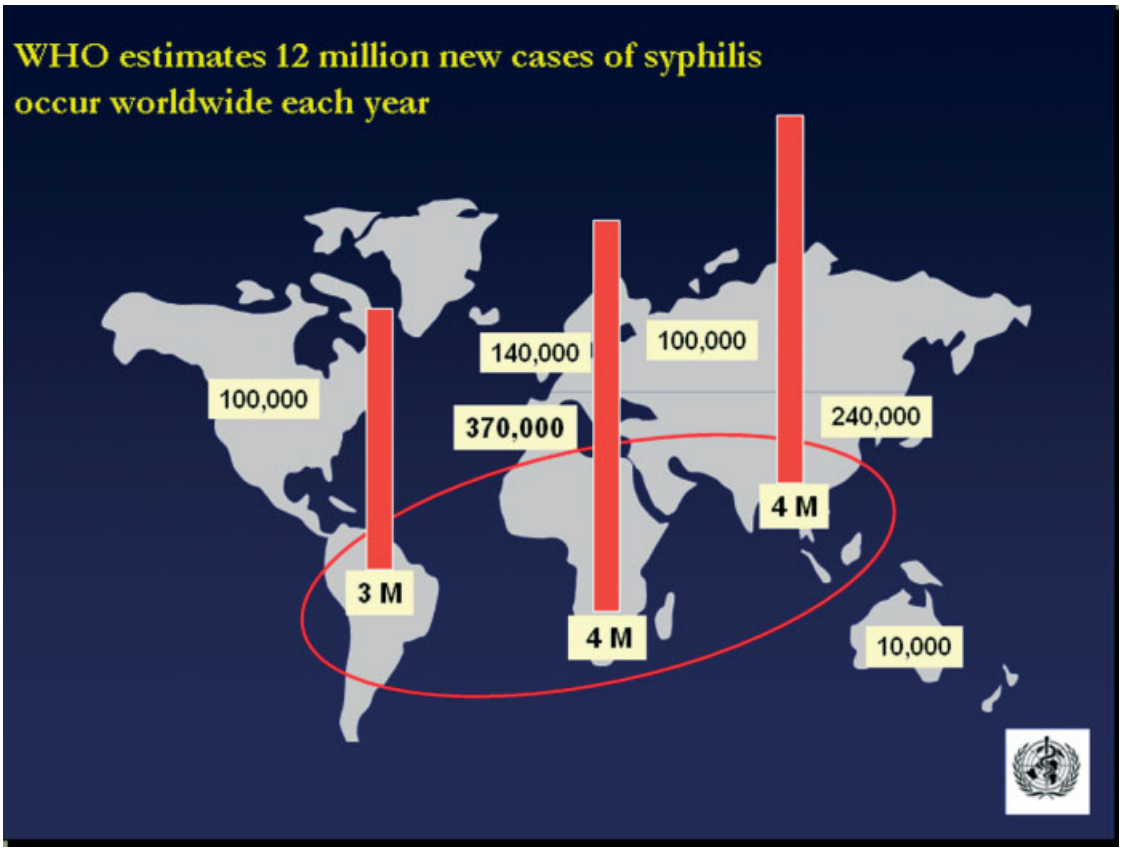

Figure 1. The global distribution of syphilis cases [13]. Regions most affected are circled

neonatal deaths in many developing countries. In countries undergoing social upheaval such as Russia and much of Eastern Europe, the re-emergence of syphilis is a contributor to burgeoning HIV epidemics [14]. In North America and Western Europe, where the disease is less common, syphilis epidemiology has shifted to become disproportionately common among minority populations, among men who have sex with men, or among persons using cocaine and other drugs [15,16]. In the USA, a national elimination programme initiated in the 1990s reduced the rates of new infection to the lowest level recorded; however, over the past 3 years, syphilis epidemiology has shifted to impact a new population (men who have sex with men) and the number of reported cases has again begun to increase [17].

Natural history and clinical manifestations

Syphilis is a chronic illness which, without treatment, may follow a course traditionally divided into primary, secondary, and tertiary stages over a period of many years [8,10,11]. The earliest or primary stage is typically marked by the appearance of a single painless lesion (the chancre) at the site of inoculation on average about 21 days post-infection. In a minority of cases, there may be multiple primary lesions. Primary lesions most often occur on the genitalia and may be accompanied by regional lymphadenopathy. Even without treatment, primary lesions typically resolve spontaneously. While the lesions of primary syphilis are localized to sites of initial inoculation, the pathogen is thought to invade intercellular junctions of the endothelium, resulting in haematogenous dissemination of the organism during the primary stage, seeding the central nervous system and remainder of the body [18]. Resolution of primary lesions is followed on average 6–8 weeks later by the secondary stage, at which time manifestations of dissemination may occur at virtually any location or organ but most commonly at other cutaneous and mucosal locations. Sexual transmission of syphilis occurs following lesion contact and thus is effectively limited to persons with primary and secondary manifestations of infection. Again, even without treatment, both primary and secondary lesions resolve and the infection enters a 'latent' stage in which clinical manifestations are absent. Despite the absence of clinical manifestations, during the latent stage of untreated disease, infection can still be passed to children born of untreated infected mothers. Many years later, a minority of persons with latent syphilis may progress, to late (tertiary) manifestations including neurosyphilis, cardiovascular disease, and lesions of the skin, bones or viscera (gummata). Studies in the pre-antibiotic era showed that 15–40% of untreated infected individuals develop recognizable late complications [11,19].

Much of what we know about the natural history of syphilis has been synthesized from two large prospective studies and one retrospective study. Initiated in

1891 to explore the thesis that the therapy of the day (which in many cases included the administration of repeated doses of mercury-containing anti-microbials and other heavy metals) caused more illness than the untreated infection, the Oslo Study observed 1978 patients with early syphilis for 20 or more years. In this study, diagnosis was primarily made clinically and treatment was not given in most cases. Despite design flaws, it is possible to conclude that about one-third of the patients developed tertiary (neurological, cardiac, and the more benign late gummatous manifestations) complications of infection [20]. Mortality from untreated syphilis was 8–14%. In 1932, the US Public Health Service initiated the infamous Tuskegee study in which 412 African-American men with latent syphilis were monitored without treatment for 40 years, with 204 matched uninfected control subjects. In this study, after 15 years, three-quarters of the men showed evidence of tertiary syphilis, 50% of which were cardiovascular complications [21]. A retrospective study conducted at Yale University School of Medicine analysed the autopsy records of 77 patients with untreated syphilis. Of these, 83% had cardiovascular complications, 9% had gummatous involvement, and 8% had neurosyphilis [22].

Since the advent of penicillin, this drug has been the mainstay of syphilis therapy. Penicillin therapy hastens resolution of clinical manifestations early in the course of infection; prevents or, if present, halts progression of late (tertiary) stages; and prevents transmission to others. Since *T. pallidum* has a relatively long generation time of 30–33 h, long-acting penicillin preparations such as benzathine penicillin G have been the preferred therapy for most patients with syphilis. Unlike many other pathogenic bacteria, at present there is no evidence that the organism has developed penicillin resistance.

Pathogenesis

The pathological findings of syphilis have been described in many excellent reviews [8,10,11] and will not be repeated here. This review will focus on newer knowledge related to the molecular pathogenesis of syphilis from both human and animal models of infection.

T. pallidum is a helically shaped micro-aerophilic bacterium, 6–20 μm in length and 0.10–0.18 μm in diameter. It consists of a central protoplasmic cylinder bounded by a cytoplasmic membrane, an overlying layer of peptidoglycan, and an outer membrane. Motility is conferred by two to three flagella, which originate at each end of the organism. The outer membrane of *T. pallidum* does not contain lipopolysaccharide and has relatively few surface-exposed transmembrane proteins. The lack of outer membrane immune targets has led to *T. pallidum* being labelled as a stealth pathogen [23–25]. Although not much is known about the rare membrane proteins of *T. pallidum*, they have the potential to be virulence determinants and at least one of them has been shown to be a porin [26]. Recent studies have identified a family of *T. pallidum* repeat genes, the *tpr* genes, which encode proteins homologous to the major surface proteins of *T. denticola* that mediate attachment to host tissue, and function as porins [27]. The Tpr proteins are immunogenic in rabbits and one of them, Tpr K, has been shown to be a target for opsonic antibody. Activated macrophages can phagocytize opsonized treponemes and clear them from circulation. Tpr K differs in seven discrete variable regions and in a rabbit model, antibodies to these variable regions offer only homologous protection and not against heterologous strains [28,29]. With successive passage, diversity is observed in the *TprK* V region genes [30]. Antigenic variation through gene conversion in infection has been hypothesized to be another mechanism by which the organism avoids host immune response, allowing for prolonged infection and persistence in the presence of a robust host response. Similar mechanisms have been described for spirochetes of the genus *Borrelia*, which cause relapsing fever [31].

Putative treponemal ligands that bind host fibronectin have been characterized by peptide mapping. An antibody raised against one of the protein fragments inhibited *T. pallidum* host cytadherence [32]. A recent study identified a monoclonal antibody that binds a phosphorylcholine epitope of *T. pallidum.* It can mediate killing *in vitro* and offer partial protection in a rabbit model [33]. Understanding of the structure function relationships of these proteins of *T. pallidum* may provide insights into the unique biology of this pathogen [34].

The study of *T. pallidum* and syphilis pathogenesis has been hindered by the fact that it cannot be cultivated for sustained periods using artificial media. While it can be passaged for a limited number of generations with a generation time of 30–33 h using rabbit epithelial cell monolayers under micro-aerobic conditions at 33–35 °C, these methods currently provide neither the quantity of organisms nor the flexibility in their manipulation to make them useful tools for the study of *T. pallidum*–host interactions. *In vivo* propagation by inoculation of rabbit testis yields substantial numbers of organisms and is the most commonly used method for generating organisms for study. Similarly, while several animal models for syphilis have been described, rabbit models most closely resemble the primary infection and pathogenesis of disseminated infection. Late-stage manifestations have not been documented in any animal model [9].

The complete genome sequence of *T. pallidum* was published in 1998 [35] and provides exciting new opportunities for the study of syphilis pathogenesis. The *T. pallidum* genome is a circular chromosome of 1 138 006 base pairs and contains 1041 open reading frames (ORFs), making it a relatively small bacterial genome. This relatively small genome strengthens the assumption that *T. pallidum* relies on host biosynthetic

pathways for many of its metabolic needs. Biological functions have been predicted for about 55% of *T. pallidum* ORFs and a further 17% show homology with hypothetical proteins from other species; a high proportion of *T. pallidum* ORFs are uncharacterized and presumably contribute to its distinctive and complex parasitic strategy, including immune evasion, latency, and features unique to *T. pallidum* subspecies *pallidum*, that of neuro-invasion, and propensity for congenital infection. The genome sequence does contain ORFs encoding for putative virulence factors similar to known bacterial haemolysins and cytotoxins, but does not appear to have the mechanism for secreting them into the host. Unlike many bacterial pathogens, *T. pallidum* does not appear to have mechanisms for iron acquisition from the host [36,37,38]. Recently identified genetic polymorphisms at two loci have also enabled Pillay *et al* to develop a strain typing system for clinical isolates of *T. pallidum*, providing new tools for the investigation of syphilis transmission and epidemiology [39].

This wealth of new genetic information regarding the predicted physiological and biochemical function and processes of *T. pallidum* may facilitate research that generates novel diagnostic and vaccine targets, and yield further insight into the pathogenesis of syphilis and other treponematoses [40].

Immune response

Infection provokes a strong humoral and cell-mediated immune response early in the course of infection. Serological tests demonstrate antibodies to *T. pallidum* early in the primary stage of infection which remain readily detectable throughout the course of infection and which are utilized to monitor the response to therapy following treatment. The resolution of both the primary and the secondary manifestations of infection correlates with the development of cellular immune responses, both in animal models and in humans. Despite the presence of these brisk immune responses, without treatment, *T. pallidum* is able to survive in the human host for several decades and may continue to be transmitted or cause end-organ damage despite this host response.

Protective immunity

Although patients who have been previously treated for syphilis can be re-infected, untreated patients appear to have at least a degree of immunity to repeated infection. In the 19th century in Dublin, Colles observed that wet nurses who breast-fed infants with congenital syphilis often developed chancres of the nipple, whereas the mothers of such infants did not, implying that they were somehow protected from repeated infection. This has become known as Colles' law. Subsequent studies in which prisoner volunteers in the United States were inoculated with *T. pallidum* likewise demonstrated that men with untreated syphilis did not develop chancres at the site of cutaneous inoculation, while those who had been treated for syphilis in the past, as well as those who had not had the infection, did develop infection [41]. A similar phenomenon, referred to as 'chancre immunity' has been described in the rabbit model. Repeated immunization of rabbits with irradiated *T. pallidum* has been shown to induce complete protective immunity in rabbits [42]. However, antigens eliciting this protective response, as well as the relative contribution of humoral and cell-mediated responses to protective immunity, are not clear. The Tpr K protein of the Tpr family of polymorphic multi-copy repeat proteins, identified through subtraction hybridization and differential immunological screening of a *T. pallidum* genome library, has been shown to be a target for opsonic antibody [27]. Immunization of rabbits with purified Tpr K offered significant, albeit incomplete, protection against infection.

Cell-mediated responses

At all stages of the disease, syphilitic lesions are characterized by vasculopathic changes and local cellular infiltrates consisting of lymphocytes, macrophages, and plasma cells. The importance of cellular immune responses in containing the infection, as well as in pathogenesis, is shown by the presence of granulomata, which, in the case of gummatous disease, assume a necrotizing character. In primary chancres, $CD4^+$ T cells and macrophages predominate, whereas in the lesions of secondary syphilis there is a majority of $CD8^+$ cells. This is surprising, since *T. pallidum* is believed to be an extracellular pathogen. In lesions of both primary and secondary syphilis, increased expression of the Th1 cytokines IL-2 and IFN-gamma is seen in humans, as has been observed in the rabbit model [25,43,44]. Circulating T lymphocytes responsive to treponemal antigens can be detected in late primary syphilis, and cell-mediated immune responses peak in the secondary stage. Increased apoptosis of peripheral blood lymphocytes and $CD4^+$ T cells by a Fas-mediated death pathway in patients with secondary early syphilis could account for the incomplete clearance of *T. pallidum* from the lesions, leading to the establishment of chronic infection [45].

Humoral responses

Circulating antibodies to *T. pallidum* can be found soon after the onset of primary syphilis and reach high titres as the infection disseminates in the secondary stage [46,47]. Human sera containing antibodies can immobilize *T. pallidum* in the presence of complement — the basis of the old *T. pallidum* immobilization test for diagnosing syphilis — and can block attachment of the organism to eukaryotic cells. The antigens to which these immobilizing antibodies are directed are not clear. Antibody can also confer passive immunity in the rabbit model and enhance phagocytosis of *T. pallidum in vitro.*

Innate immunity

T. pallidum does not contain lipopolysaccharide, but the lipoproteins present under the outer membrane are strongly immunogenic and have been shown to activate the innate inflammatory response via the toll-like receptor TLR4 [25,48,49]. These proteins are not surface-exposed, and live *T. pallidum* elicits a much less marked inflammatory response than *T. pallidum* lysates. *In vivo*, lipoproteins of *T. pallidum* are thought to gain access to TLRs on the surface of macrophages following degradation of organisms in phagolysosomal vacuoles [25,31].

Maternal and congenital syphilis

Unlike other treponemes, the causative agent of syphilis is able to cross the placenta and cause infection in the fetus. Syphilis transmission to children born of untreated mothers may occur at any stage of infection. In pregnant women, syphilis may lead to stillbirth or congenital infection of the neonate, resulting in neonatal death or life-long sequelae [12,50–54]. Congenital syphilis is a catastrophic, yet readily preventable, manifestation of failures in syphilis control efforts. Congenital syphilis continues to be a major public health problem in many developing countries where prenatal screening and treatment programmes for syphilis are not effectively carried out [55–57].

In the infected pregnant women, the parasite encounters a host environment that is altered to favour the ontogenic development of the fetus. The key to understanding the pathogenesis of *T. pallidum* in pregnancy lies in understanding the complex relationships between the unique ability of this particular treponeme to cross the placental barrier and its ability to cause the demise of the fetus or the many early and late manifestations of congenital syphilis in a liveborn infant. These relationships are superimposed on the genetic background of the host, which governs the immune responses to infection in different stages of pregnancy [58]. Primary and secondary syphilis in pregnancy will lead to fetal infection in virtually all cases, with approximately 30–50% of pregnancies resulting in fetal death *in utero*, stillbirth or death shortly after delivery [59]. The pathophysiology of fetal syphilis, including haematological, immunological, and sonographic findings, is similar to that of neonatal syphilis [60]. Of 24 women with syphilis, 66% of fetuses had either congenital syphilis or *T. pallidum* detected in the amniotic fluid. The rate of fetal infection was 50%, 67%, and 83% for primary, secondary, and early latent infection, respectively. The longer the mother has been infected before pregnancy, the higher the chance of fetal survival, with infection rates decreasing progressively to 10% in late latency [59,61].

Studies of animal models and human infections of intracellular pathogens such as *Leishmania, Toxoplasma, Plasmodium*, HIV, and herpes viruses have shown that a strong Th1 response to infection during pregnancy may compromise pregnancy outcome. In pregnancy, a gradual dampening of the intensity of the innate and cell-mediated immune responses to favour the maintenance and growth of the fetus may result in incomplete clearance of *T. pallidum* from lesions, hence allowing the development of a chronic infection. Animal models have been useful in providing some clues to the pathogenesis of treponemal infection in pregnancy [58]. There is evidence from human infection and animal studies to suggest that a Th1 response is elicited in primary syphilis and there is a gradual shift to a Th2 response as the disease progresses to the secondary stage. The increased production of inflammatory cytokines IL-2, IFN-gamma, TNF-alpha, and prostaglandins induced by fetal infection together with the intense inflammatory responses associated with activation of macrophages by treponemal lipoproteins may be responsible for fetal death or pre-term delivery in primary or early secondary syphilis and severe growth retardation or some of the manifestations of congenital syphilis. In animal studies, and as in humans, successive pregnancies in the immune host are associated with a less intense immune response that may result in a higher percentage of normal pregnancy outcomes (Kassowitz's law) [12].

A recent study showed that single-dose benzathine penicillin treatment is effective in preventing adverse pregnancy outcomes of maternal syphilis [62]. Stillbirth, low birth weight, pre-term birth, and intrauterine growth retardation were significantly associated with the mother having a high antibody titre, ie active syphilis. A study of 43 women treated for syphilis showed that treatment failures associated with the delivery of a congenitally infected neonate are correlated with high antibody titre at treatment and delivery, earlier maternal stage of syphilis, and less than 30 days between treatment and delivery [63].

HIV and syphilis

Despite the recognition that syphilis and HIV are a dangerous combination, limited conclusive data exist to describe the interaction between the two infections [64,65]. Potential interactions between the two diseases include acceleration of the natural history of either infection, alterations in the clinical or laboratory manifestations of syphilis, increased risk for syphilitic complications, and diminished response to syphilis therapy [10,16,66]. Studies in a small cohort of 52 HIV-infected men with primary and secondary syphilis have shown that increased HIV viral load and decreased CD4 counts are increased with syphilis infection [67]. This, in turn, increases the likelihood of HIV transmission to their sexual partners and could theoretically accelerate progression of HIV infection. Elevations of circulating HIV concentrations and reductions in CD4 lymphocyte counts observed in patients with untreated syphilis–HIV co-infections

revert towards their pre-infection (with syphilis) levels following syphilis treatment. In contrast, several large studies have demonstrated that there is not a significant difference in response to recommended penicillin therapy when syphilis patients with and without concomitant HIV infection are studied [68,69]. Many experts also believe that persistent cerebrospinal fluid abnormalities and clinical neurosyphilis are more common in syphilis patients with HIV co-infection than in those who are not, but no large studies have conclusively demonstrated this to be the case. Similarly, while case reports suggest that the clinical manifestations of syphilis may be modified or the course of disease accelerated in persons with HIV–syphilis co-infections, large studies demonstrating this to be the case are absent. Available data suggest that if the natural history of syphilis is modified by HIV, the difference shows considerable overlap with the course of disease in persons without HIV. Infection with syphilis does increase risk for HIV acquisition, presumably through the presence of ulcers, which serve as a portal for infection to occur.

New tools and interventions

For most of the 20th century, syphilis diagnosis has depended on the visualization of organisms using darkfield or fluorescence microscopy of smears from lesion material, or on results of serological testing. Facilities for specialized microscopy, however, are not widely available and tend to be found only in some dedicated clinics for STD management. Serological diagnosis is far more widely available but its utility is somewhat compromised by false-positive tests, the requirement that most testing be performed in laboratories, and difficulty in differentiating treated from untreated infections. Nonetheless, serological testing has proven to be useful for screening at-risk persons, for serial evaluation of response to therapy following treatment, and for the detection of untreated latent infections. The traditional approach to syphilis serodiagnosis utilizes a two-step approach: first screening with a non-treponemal test such as the rapid plasma reagin (RPR) test and then performing confirmatory testing on those specimens reactive in the screening test using a treponemal test such as the *T. pallidum* particle agglutination assay (TPPA). While effective, this testing approach has sometimes made it difficult to provide timely testing for at-risk persons, groups who are most commonly seen in settings with limited laboratory support. The RPR test is sensitive, inexpensive, and relatively simple to perform, but is often not available at primary health care settings. Similarly, confirmatory assays are usually not available outside of reference laboratories. More recent development of reagents with less stringent storage requirements and mechanisms for performing tests in resource-limited settings (ie solar-powered rotators, less temperature-sensitive reagents, etc) promise to make testing more available. In addition, simple, rapid point-of-care treponemal tests that do not require electricity or equipment are now commercially available, and appear to have sensitivities and specificities comparable to the TPPA (www.who.int/std_diagnostics). These rapid treponemal tests will facilitate decentralized screening in other resource-limited settings. The inclusion of syphilis screening in widespread implementation of prenatal screening programmes to prevent mother-to-child transmission of HIV could be an opportunity to scale up antenatal syphilis screening.

With genome libraries and sequence now available, it should be feasible to explore new diagnostic targets and develop rapid tests and enzyme immunoassays using highly purified, expressed *T. pallidum* gene products [70,71]. The ideal test is one that can inexpensively improve on the traditional testing combination of non-treponemal and treponemal tests and allow quantitative testing to monitor serological response to therapy.

Conclusion and future outlook

Syphilis, the name of this widespread and ancient disease, is familiar to health care providers worldwide. Name recognition, however, belies the complexity of the disease as well as the diagnostic and therapeutic challenges that continue to impact global syphilis control efforts. Syphilis elimination is considered a biologically and epidemiologically feasible goal, as the disease has no animal reservoir and it can be diagnosed and cured with simple inexpensive tests and antibiotics. There has been no evidence of penicillin resistance and the long incubation period favours case finding and empirical or epidemiological treatment to prevent further transmission. Insights into syphilis pathogenesis, enabled through investigation of the *T. pallidum* genome and its products, promise to provide new tools which will give rise to new strategies for syphilis control, vaccine development, and a greater understanding of the biology of the Great Mimicker, *T. pallidum*.

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