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Review Article

Vaccines and the looming threat of syphilis

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Abstract

During the past several decades, syphilis has increased in the US and explosively so in China and Russia. While most current cases can be cured by penicillin or second line antibiotics, strains of the syphilis spirochete (*Treponema pallidum*) resistant to the latter have emerged. And the potential of strains to acquire resistance to penicillin via plasmids has recently been recognized. The 36 million-plus undertreated cases of syphilis in the world represent metaphorically a vast global 37°C incubator allowing exchange of antibiotic resistant genes among the human-borne bacteria and theoretically permitting the emergence of penicillin resistant strains. None has yet been identified but they seem inevitable along with the threat of multi-resistant strains.

There is now concern over the lack of new antibiotics to succeed the penicillins. Since such new drugs would likely require a decade or so of research and federal approval, vaccine-based protection is of immediate consideration here. This approach may exploit the new knowledge about the biology of *T. pallidum* strains their many complex antigens, serotypes, and the latter's distribution in populations. Equally important are recent insights into immunology, such as cellular aspects and antigenic competition.

Introduction

While the prevalence of syphilis in the United States has nearly tripled over the past decade or so, this disease may present an even greater threat to public health in the future [1]. During the past two decades in China there has been 30-fold increase in syphilis and in Russia nearly a 70-fold increase. If this 'explosive resurgence' abroad continues and spreads throughout the world, in time it might lead to the emergence of strains of the syphilis spirochete (*Treponema pallidum*) resistant to penicillin, which has been the standard therapy for the infection since the 1940s. Such deadly strains would eventually reach this country. Resistance to antibiotics (including to penicillin) is present in many bacteria and is transferred among them by genetic means discussed later. Conditions for the appearance of resistant strains of syphilis to penicillin and other 'back-up' antibiotics are especially optimal globally with so many millions of untreated persons harboring multi-drug resistant bacteria. Clinicians are worried about the current absence of new antibiotics to treat many newly resistant human pathogens [2].

This essay reviews briefly the global increase of venereal syphilis and discusses the genetic basis of potential penicillin resistance in *T. pallidum* (Sections 2 & 3). During the mid-19th century, vaccines were sought for syphilis unsuccessfully, but a century later they seemed unnecessary with the advent of effective antibiotics. However, today with the theoretical threat of antibiotic-resistant syphilis emerging and in the current absence of new successor antibiotics, there is revived interest in vaccines for syphilis.

Treponema pallidum causes venereal syphilis. Milder, non-venereal, cutaneous infections are produced by other closely related treponemal species/strains, such as yaws, pinta, and bejel (Sec. 4). The genetic relationship among these five pathogens is treated here. New information about treponemal surface antigens is reviewed next (Sec. 5). Genetic typing of *T. pallidum* has revealed that multiple strains are prevalent in a human community at any one time. These may compete with one another during a given luetic infection (Sec. 6 & 8). How to

exploit this newer knowledge in devising a vaccine is the challenge at hand.

The recent resurgence of syphilis (*Lues venerea*)

In the US before the Second World War, syphilis was estimated to have infected 5% to 10% of the US general population and 25% of impoverished groups especially those in southern states. In 1937, US Surgeon General Thomas Parran (1892-1968) had called syphilis the "shadow on the land" [3]. In 1947 the overall prevalence was 66/100,000 but declined dramatically after penicillin became available in the mid-1940s to the level of 2.1/100,000 by 2000 [4]. However, during the so called 'sexual revolution' it rose to 5.5/100,000 by 2013 with 9.3/100,000 in men [1]. A striking example of this increase was the epidemic in San Francisco, where the prevalence was 3.8/100,000 in 1999 and rose to 26/100,000 in 2007 [5] (Table 1).

In China the disease was reported to have been largely eradicated (<2/100,000) in the 1960s by aggressive public health policies of the government. But in recent years there has been an "explosive return of the Great Pox" a 25-fold increase from the early 1990s to 2007 and a further 5-fold increase through 2011 [6-8]. The incidence rose to 8.71/100,000 in 2005 throughout the country and to 32/100,000 in 2011. It was much higher in many cities e.g., 77/100,000 in Shanghai in 2008 [9]. The one-child policy of the Communist government and female-weighted abortions in families led to an excess of unmarried males and accounted for the rise in MSM (male-sex-male) venereal

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Table 1. Global Prevalence of Syphilis per 100,000 Population.

	1947	1956	1988	1995	1996	1999	2000	2005	2007	2008	2011	2013
USA	66	3.9				2.1					5.5	
Men												9.3
San Francisco								3.8		26		
China		<2					8.7			32		
Shanghai									77			
Russia			4		263							
St. Petersburg				318								
Finland				2								

infections [7]. Migration into crowded cities promoted spread of the disease (Table 1).

In Russia, the collapse of its health system during the 1990s has led a similar rise in syphilis and other infectious diseases for syphilis from 4/100,000 in 1988 to 263/100,000 in 1996 [10]. In St. Petersburg the prevalence was 318/100,000 in 1995 [11] (Table 1).

Throughout the world, according to recent estimates, syphilis infects 36 million persons and is newly acquired each year by 11 million more. It causes over 100,000 deaths in spite of penicillin being considered an effective cure for nearly all current luetic infections [12-14] (Table 1).

Penicillin and *T. pallidum*

Since the mid- 1940s, the standard therapy for syphilis has involved various forms of penicillin agents containing a critical β -lactam ring. Syphilitic allergic to penicillin have been treated with second-line antibiotics e.g., macrolides (azithromycin, erythromycin, spiramycin) and tetracyclines (doxycycline, etc.) [15]. However, strains of *T. pallidum* resistant to these second-line antibiotics have appeared an example being azithromycin resistance, which was found in 77.3% of the *T. pallidum* specimens isolated in 2006 in San Francisco [5].

To date, no penicillin-resistant strains of *T. pallidum* have been reported, but they seem inevitable. The 36 million-plus people infected with *T. pallidum* represent a global microbial pool capable of spreading the syphilis among their billion neighbors. Each person (infected or not) is a 37°C incubator harboring in the GI tract and elsewhere a vast array of bacteria which interact with one another notably in transferring genetic information via plasmids. These are small pieces of DNA containing genes, including some coding antibiotic resistance. For example, strains of *Neisseria gonorrhoeae* acquired resistance to penicillin and its derivatives via plasmids encoding β -lactamase activity which came from ampicillin-resistant strains of *Haemophilus influenzae* [16]. The enzyme β -lactamase, inactivates penicillin by disabling its essential β -lactam ring.

Surprising and disturbing to siphilologists was the discovery in 1981 that plasmids exist in *T. pallidum*, thus indicating that it has the potential to acquire resistance to penicillin by genetic mechanisms frequently used by other bacteria [17,18]. One such example is a strain of *Klebsiella pneumoniae* (an enteric organism) containing an enzyme which breaks down carbapenem (a β -lactam antibiotic like penicillin G). The gene for this enzyme is contained in a plasmid, which can move from *K. pneumoniae* to other bacteria (e.g., *T. pallidum*). This condition represents “a risk as serious as terrorism” [19].

The ultimate therapeutic threat would be strains of *T. pallidum* exhibiting resistance to all forms of penicillin and also to backup antibiotics. The medical literature is filled with other examples of multiple drug resistance i.e., in staphylococci, enteric bacilli, *Mycobacterium tuberculosis*, etc. [20]. The World Health Organization and other public health agencies have declared antibiotic resistance to be the greatest threat to global public health [21]. A multiple resistant strain of *T. pallidum* seems likely to appear somewhere and enter the US population, facilitated by the international travel of infected persons.

A growing concern here is that the “developmental pipeline (for new antibiotic agents) is empty” because many drug companies have found this area unprofitable, focusing instead on drugs treating common chronic diseases. Roche “fled the field in 1999.” Eli Lilly “dropped its antibiotic research in 2002,” and other companies joined them in abandoning the area [22]. The continued emergence of drug-resistant bacteria has prompted the US government “to coax companies back to the field,” but the productive momentum they once had may take years to regain.

While new anti-syphilitic drugs would be aggressively sought by the pharmaceutical industry in the event of an epidemic of a resistant strain, there is no great pressure to do so in advance of the therapeutic, commercial demand. Meanwhile, alternate treatments need be considered, such as vaccines. Recent discoveries in the immunology and genetics of the treponemes, extending also to those species/subspecies of this genus causing non-venereal diseases, may help devise an effective vaccine.

Treponemal diseases in the world

Siphilologists have been conflicted over relationships among the various treponemal pathogens accounting for four related diseases seen throughout the world venereal syphilis, yaws, pinta, and bejel (endemic syphilis). All these treponemes are morphologically identical and closely related serologically. All currently are suppressed by penicillin but produce different pathologies, which are summarized below. It’s uncertain whether there is any protective cross-reaction among the four agents, but some reciprocal immunity may exist between yaws and syphilis as judged by the latter’s relative absence in areas with a high prevalence of yaws [23,24].

Venereal syphilis (VS, *lues venerea*) elicits genital lesions (chancres) initially and later affects various organ systems as ‘tertiary sequelae’ in around 30% of untreated cases. In contrast, three non-venereal treponemal infections produce conspicuous lesions on the exposed parts of the body but no significant constitutional/systemic symptoms (i.e., no chills, fever, weight loss, etc.) and no later organ involvement.

Yaws (Y) occurs in warm humid rural areas of Africa, SE Asia, and the Americas and causes multiple granular papillomas on unclothed legs, arms, and the face of children mainly. Pinta (P) is present primarily in South/Central America and causes dry scaly lesions on exposed skin. Bejel (B) is found in the dry, warm Middle East, and in severe cases may produce gummatous ulcerative lesion on the face. Bejel in Europe is also termed endemic syphilis. The latter two (P, B) are characterized also by moist papules in the axilla and skin folds and mucous patches in the mouth.

The characteristic clinical pictures produced by *T. pallidum* and the non-venereal treponemes reflect the particular tissue tropism of the respective infecting species/strains *i.e.*, area of the body primarily affected (tropism, Gr. = 'turning' to some area). The non-venereal treponemes infect mainly the skin and mouth but not the warmer internal organs of the body. For example, unlike venereal syphilis, neither yaws, pinta, nor bejel produces neurological sequelae nor are they transmitted from an infected mother to her foetus [23].

Strain differences may also account for the various clinical pictures seen during late/tertiary stages of venereal syphilis *i.e.*, gummatous bony lesions, cardiovascular pathology, or neurological involvement. One particular strain has been found more often in persons with neurosyphilis than in other syphilitics, again suggesting subspecies tropism [24,25].

Medical historians have speculated on how these subtypes evolved and how *lues venerea* entered into Europe during the mid-1490s. The Columbian theory proposes that this virulent disease arose from a non-venereal treponeme in the Americas and was imported from the Caribbean by infected sailors returning from Columbus' first voyage there. Other theories attribute decaying matter or animals in Africa as the origin of non-venereal treponemes which subsequently infected people and spread via them to the Americas and Europe, ultimately producing *lues venerea*. Endnote #1 summarizes such speculations by three investigators which link the various treponemal strains from an evolutionary standpoint [28-30].

K.N. Harper *et al.* provided scientific support for the Columbian theory of syphilis' entrance into Europe from America based on DNA analyses. This group sequenced select gene regions of twenty-six geographically dispersed strains of pathogenic treponemes and concluded that strains causing venereal syphilis now resemble phylogenetically yaws strains from South America [31]. These studies lead logically to a review of treponemal antigens, strain typing, and distribution of the many *T. pallidum* strains.

Antigens and strain typing of *T. pallidum* subspp. *pallidum*

Subspecies and strain differences reflect in part the complex array of spirochetal surface antigens. Treponemes have a fragile outer membrane and a more stable inner one. The former contains unstable antigenic determinants coded by twelve *T. pallidum* repeat genes (Tpr). Different strains express different combinations of Tpr proteins [32]. The inner membrane contains several lipoprotein antigens (e.g., TpN47, TpN17, etc.), which are accessible for expression only when the outer membrane is disrupted or aged. Adding to this complexity is the fact that within one particular antigen (TprK) are seven discrete variable regions coded by different alleles [33]. The relative importance of these different antigens in producing protective immunity is unclear at present, but progress has begun in distinguishing different strains.

Allen Pillay and colleagues developed a method for typing strains of *T. pallidum* [34]. Intrastrain variability is exhibited by two genes a member of the *T. pallidum* repeat (tpr=Tpr) gene family and the acidic repeat protein (arp) gene. The method involves isolating both genes from a sample, amplifying them by polymerase chain reaction, and analyzing the products of endonuclease digestion. More than 40 strain types have been identified (e.g., 14a, 14d, 15a, etc.) and many subtypes (12df, 14d9, etc.).

Subsequent studies using this new technique have shown that many different strains (up to 16 or so) are present during the same period in a given large urban areas [35]. For example, during 1999-2008, strain type 14d9 represented 53% of the 4 different strains recovered from 69 of persons in San Francisco and 51% of the 8 found in Seattle [5,36]. Strain type 14a comprised 54% of the 4 different strains found in Pretoria and 50% of the 3 in Lisbon [36]. Thus different sexual partners in a community may harbor different strains. To date, so far as I am aware, only one strain has been identified in a given individual, but this may reflect not having examined numerous samples from the same person and perhaps not early enough.

Luetic infections clearance vs. reduction = cure vs. protection

Although lacking confirmation, one current supposition is that a given syphilitic may harbor initially several strains of *T. pallidum* – *i.e.*, genetically different subpopulations, each with a wide repertoire of antigens [37]. This diversity could come about in two ways. 1) contacts with different sexual partners would allow the introduction of several different strains from the different 'spirochetal donors'. 2) New antigenic subtypes might also arise *de novo* by mutations of spirochetes present in an individual.

During the month or so after a person becomes infected from one or more sexual partners and while the immune response is being engaged, many or most of the acquired treponemes are assumed to be cleared, but one or more may persist to produce clinical manifestations [38,39]. Of the several concurrent infecting strains of *T. pallidum*, those with stronger or more accessible antigen may produce a 'robust' immune response and be eliminated by opsonic antibodies/phagocytosis and delayed-type immunity, while the 'weaker' strain/s would evoke a lesser response, might escape immune surveillance, and thus survive in the host to produce disease [32]. Whether immunological tolerance might develop to this 'survivor' strain is a consideration. Cullen and Cremer have made a distinction between protection from the disease (nonsterile immunity due merely to reduced spirochetal numbers) and complete clearance of the organism (sterile immunity) [40].

The following is a plausible 'strain' history for an untreated syphilitic, but this scenario has not yet been validated by typing studies. In a given person, an early reduction in strain varieties from immune surveillance may be offset by new strains acquired during later sexual contacts or possibly by mutations in strains already present. Thus the initial repertoire of treponemal strains in that person may change over time.

Studies on syphilis 'vaccination' past and recent

Philippe Ricord (1800-1889), the famous French venereologist, advocated 'vaccinating' against syphilis in a long series of letters to the Editor of the *Union Médicale of Paris*, 1850-51. (Endnote#2) Syphilologists then distinguished between indurated (hardened) and non-indurated chancres and believed that multiple inoculations

with the “virulent pus” from the latter over many months could be a “prophylaxis against constitutional syphilis” (tertiary sequellae) much as vaccinia from cowpox pustules protects people from smallpox [41]. A contentious issue at that time was how many sequential contacts with chancre fluid/pus were needed to ‘induce immunity’ up to a score or more, some maintained. Proof of immunity for the French investigators then seemed to be merely the later absence of signs of secondary or tertiary syphilis.

Interest in immunizing for syphilis resumed a century later with investigators who sought to obtain non-infectious strains by heating isolates or using other procedures. Their negative results were likely due to labile surface antigens being destroyed in the process. The first limited success was obtained in 1969 by Metzger *et al.* In earlier studies these investigators had established the protein nature of the immunizing antigens and next sought to attenuate/reduce strain virulence by storage at 4°C for 7-10 days. They used a Nichols strain of *T. pallidum* to vaccinate rabbits by IV injections 4-times/week for 7 weeks [42]. Some of the rabbits showed “a high degree of immunity” upon challenge with infectious treponemes *i.e.*, no lesions/chancre appeared at the inoculating sites in the skin. But spirochetes were still latent in the treated rabbits *i.e.*, “sterile immunity” had not been achieved.

In later, more successful immunization studies, James N. Miller sought to preserve labile surface antigens by using a γ -irradiated, now non-infectious Nichols strain. He administered this preparation to rabbits IV daily over a 37-week period and found them “completely resistant to intradermal challenge (with homologous treponemes) administered 10 days after the last immunizing injection” [43]. Protection persisted for one year. There was minimal immunity to challenge with *T. pertenuis*, the agent of yaws thus indicating specificity for venereal syphilis.

The 37-week long injection protocol in rabbits would not be practical in human subjects. In any case, the prospect for successful immunization is complicated by the possibility that several strains of *T. pallidum* may infect a given person at the same time. Whether each impedes or influences the immune responses (and the elimination) of others is an issue examined next.

Antigenic competition

Differences in the immune responses of several concurrently infecting *T. pallidum* strains are likely due to the ‘strength’ of their presenting antigens, but another influence might be that of antigenic competition, as explained next. Immunization with two antigens given together (or within days of each other) elicits separate immune responses for both, but the level of each response is lower with paired stimulation than when either antigen is given alone. In other words, two antigen introduced together limit reciprocally somewhat the response of each other. There is considerable variability here, depending on the type of the antigens, the doses, the timing of each stimulus, etc. The nature of this competition was the subject of scores of research papers and reviews in the 1970s [44,45].

My studies in this area then involved lymph node organ cultures prepared from rabbits primed months earlier with two antigens *e.g.*, bovine serum albumin and diphtheria toxoid. Each culture consisted of a dozen 1 mm³ size lymph node fragments bathed in 1 ml of a chemically defined medium [46]. Incubating the cultures with the antigens on Day 0 for two hours elicited the secondary antibody responses to both, which continued over a month as measured in the medium replaced

every three days. Pooled lymph nodes from a single primed rabbit provides 60-100 culture tubes, thus allowing many variables (each in 4 or more replicate tubes) to be examined in one experiment *e.g.*, detailed dose response effects. The individual responses were measured in the culture medium by hemagglutination titration assays.

The antigenic competition demonstrated in this culture system was not due to some limiting nutritional factor [47]. Related to this phenomenon was the surprising observation that very low levels of certain antibiotics enhanced antibody production in these cultures. For example, adding increasing levels of chloramphenicol or actinomycin D during the inductive phase of the *in vitro* response (Days 0-6), produced the expected dose response inhibition during the subsequent productive phase (Days 6-30+). However, extremely low levels of these same agents included after Day 6 cause a paradoxical increase in the antibody responses [46,48].

This observation led to the isolation and characterization of an ‘antibody inhibitory material’ (AIM) released in the spent medium [48,49]. The highest inhibitory effect was found in medium recovered on Day 6, 9, & 12 of the 18-day culture period. I postulated that the paradoxical increase was due to AIM-containing cells producing less AIM because of their being more sensitive to the low levels of actinomycin D than the antibody secreting cells. Other investigators also identified such inhibitory factors (cytokines) and termed them ‘suppressor’ factor/s *i.e.*, products of so-called ‘suppressor’ cells (Ts). A decade later, ‘T regulatory cells’ (T_{reg}) became the preferred term [50].

More recently, T_{regs} have been hypothesized these to be of two types one is specific for a given antigen, while another is ‘non-specific’ the latter presumably being involved in antigenic competition [50,51]. Examining this phenomenon in terms of antibody production, allergy, and autoimmunity has been the subject of numerous reviews during the past several decades [50-54]. Relevant to the subject of syphilis is whether the multiple antigens of one spirochete strain infecting a person exert antigenic competition with other introduced strains.

A ‘classical’ immunization approach has employed a ‘mild’ live organism related to a major pathogen in order elicit protective immunity against the latter *e.g.*, *M. bovis* for *M. tuberculosis* and cowpox or vaccinia virus for the variola virus. Perhaps a relatively ‘mild’ strain of *T. pallidum* (like one of the non-luetic treponemes) could be isolated and used as a live vaccine for syphilis seeking to protect against the more virulent strains. As noted before, there is a “relative absence of venereal syphilis in areas with a high prevalence of yaws” [23,24].

Vaccines and the two forms of immunity

The focus of a vaccine for syphilis has evolved over the past decade or so. Initially, it has been eliciting a protective humoral response (opsonic antibodies) in order to eliminate *T. pallidum* via phagocytosis. For example, in 2006 Cullen and Cameron discussed various *T. pallidum* vaccines whole cell, subunit, and non-protein carbohydrate antigens, which might mediate ‘opsonophagocytosis’ [40].

A seminal paper in 2011 by Carlson *et al.* viewed the clinical course of syphilis as being determined by the balance between delayed type hypersensitivity (DTH) and humoral immunity to *T. pallidum*. The authors argued that a strong DTH clears organisms initially from the body, while a strong humoral response later leads to “prolonged infection and progression to tertiary disease” [55]. They concluded that a potential vaccine for syphilis should be directed towards the developing the DTH response. This could be enhanced by including BCG in the vaccine.

Finally, in 2014, Cameron and Lukehart emphasized that a successful vaccine should involve both the DTH response and opsonic antibodies/phagocytosis [56]. Thus currently, there seems no consensus for making an effective vaccine.

Summary

The theoretical threat of a multi-resistant strain of *T. pallidum* appearing in the near future is compounded by the current absence of new antibiotics effective against this putative new pathogenic strain. Indeed, this therapeutic void prompted a recent article entitled as a question “A return to the pre-antimicrobial era?” [57]. These two linked concerns provided an excuse to review here new information about syphilis (e.g., treponemal antigens, serotyping, etc.) and old relevant studies (e.g., P. Ricord’s ‘vaccinations’, antigenic competition).

Syphilis therapeutics for over a century has been wedded to the concept of a ‘magic bullet’ (*magische Kugel*) which kills infecting spirochetes. Modification of some past ‘cure’ might include, for example, improvement in heavy metal therapy. Fever therapy was effective in relieving the signs and symptoms in some persons with neurosyphilis. A review of pre-antibiotic anti-syphilitic treatments has been submitted elsewhere. But the other important defense against most infections is the host’s immune response. Developing a vaccine for syphilis will build on the new information about the biology of *T. pallidum* strains and their immunology. Special consideration must be given to the two competing modalities of immunity humoral (opsonization) and cellular (DTH).

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Endnotes

1. Theories on the Origin of Various Treponemal Types

E.H. Hudson (1961) postulated that the treponemal group arose in Africa from spirochetes growing on decaying vegetable matter [26]. In the beginning, a strain appeared which thrived on the exposed skin of natives, producing the clinical picture of yaws (Y). Around 100,000 years ago their infected descendants migrated to other parts of the world (including the Americas), where a new strain, pinta (P), emerged. In the warm areas of the Middle East, bejel (B) evolved and later spread north. In dry, often cold Europe, where clothing was worn, the spirochete could only survive and spread via the moist genital organs, producing a mild infection called endemic syphilis (ES). Hudson did not explain how virulent venereal syphilis (VS) appeared there around 1494.

C.J. Hackett (1963) proposed a comparable evolution of the treponemes with the difference that that the progenitor of the four was pinta, which crossed over from an animal infection to people about 15,000 BC [27]. It originated in Africa, reached the Americas, and many millennia later spawned yaws there. From pinta in Africa arose bejel, which entered Europe in a mild form (endemic syphilis, ES) beginning in the first century BC. It changed abruptly to the virulent venereal syphilis (VS) near the end of the fifteenth century.

The evolutionary scenarios of Hudson and Hackett both favor the Old World origin for the emergence of venereal syphilis in Europe.

R.S. Morton (1968) advanced a variation in this story: namely, in

the later 1490s, *morbus gallicus* involved “two disease existing side-by-side” – the mild endemic syphilis (ES from Africa) long present in Europe and a yaws strain newly introduced from America which evoked an acute illness in the Europeans [28]. For several decades, the severe Columbian (Y) strain dominated as virulent syphilis (VS), but later the milder African strain (ES) became the prevalent one.

2. Philippe Ricord was born in Baltimore of parents who fled there from the French Revolution. During his professional career in Paris, Ricord became the leading physician treating venereal diseases. He is most famous for establishing that syphilis and gonorrhea are distinct diseases thus correcting the confusion in this subject created by John Hunter’s flawed self-inoculation experiments.

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