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Perspective Piece

Yaws: 110 Years After Castellani's Discovery of *Treponema pallidum* subspecies *pertenue*

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Abstract. Yaws is a neglected infectious disease that affects mostly children and adolescents living in poor, rural communities in humid, tropical areas of Africa, southeast Asia, and the Pacific Islands. The etiological agent of yaws, *Treponema pallidum* subspecies *pertenue* (*T. pertenue*), was discovered by Aldo Castellani in 1905 shortly after Schaudinn and Hoffmann discovered the etiological agent of syphilis, *T. pallidum* subspecies *pallidum*. The discovery of *T. pertenue* enabled the development of animal models and the identification of an effective antibiotic treatment (i.e., penicillin) for yaws. A World Health Organization (WHO) mass treatment campaign from 1952 to 1964 reduced the global burden of yaws by 95%, but failed to eradicate this disease. Today, 110 years after Castellani's discovery of *T. pertenue*, yaws is again targeted for eradication. Recent advances in the treatment and diagnosis of yaws improve the likelihood of success this time. However, several challenges must be overcome to make the goal of yaws eradication attainable.

Yaws is an infectious disease that affects mostly children and adolescents, aged 2–15 years, who live in poor, rural communities in humid, tropical areas of Africa, southeast Asia, and the Pacific Islands.[1] Yaws is currently thought to be endemic in at least 12 countries, but adequate surveillance data are lacking.[2] This disease is transmitted by contact of broken or abraded skin with the exudate of yaws lesions. Clinical manifestations of yaws are divided into stages. Early stage skin lesions are infectious and can persist for weeks or months. Involvement of the bones of the upper and lower limbs and the fingers and toes can cause pain and digital swelling. After the early stage lesions subside due to the host immune response, the patient enters a latent stage that can be lifelong. In about 10% of untreated patients, the infection progresses to the tertiary stage that is characterized by destruction of tissue, bone, and cartilage resulting in disfigurement and disability.[1]

The etiological agent of yaws, *T. pallidum* subspecies *pertenue* (i.e., *T. pertenue*), was discovered in 1905 by Aldo Castellani, a physician and expert in neglected tropical diseases. Castellani had observed spiral-shaped bacteria in lesion material from yaws patients in Sri Lanka (formerly Ceylon), but did not ascribe significance to this observation. However, after learning of the 1905 discovery of the syphilis agent, *T. pallidum* subspecies *pallidum* (i.e., *T. pallidum*), by Schaudinn and Hoffmann[3] and cognizant of the similarities of syphilis and yaws, Castellani examined new scrapings from yaws lesions. Using special staining techniques, he again observed delicate, faintly stained spirochetes that were morphologically indistinguishable from *T. pallidum*. Castellani's preliminary findings were presented to the Ceylon Branch of the British Medical Association in June 1905.[4] After studying lesion material from additional yaws cases, he proposed "*Spirochaeta pertenuis*" (i.e., *T. pertenue*) as the etiological agent of yaws.[5,6] Castellani's findings were soon confirmed by the December 1905 report of Wellman, who had observed spirochetes in the lesions of an African yaws patient.[7]

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The discovery of *T. pertenue* enabled the development of animal models for experimental studies of yaws. Castellani investigated the infectious nature of the noncultivable *T. pertenue* in monkeys.[8] He showed that 1) monkeys could be experimentally infected with an inoculum prepared from the lesions of yaws patients, 2) the inoculum could be rendered noninfectious by removal of *T. pertenue* by filtration, and 3) yaws could be serially transferred in monkeys, and *T. pertenue* was invariably present in "pure culture" in the monkeys' non-ulcerated lesions. Using a modification of Wassermann's complement fixation test for serodiagnosis of syphilis, Castellani detected antibody reactivity in the sera of yaws-infected monkeys, but not naïve monkeys, to antigen in an extract of yaws lesions.[8] In addition, Castellani demonstrated that yaws-infected monkeys were not immune to syphilis and, conversely, that syphilis-infected monkeys were not immune to yaws (i.e., there is no cross-protection conferred by infection).[8] This observation along with the previously published work of Neisser and co-workers,[9] dispelled the belief that syphilis and yaws were the same disease, but with different clinical manifestations because of host genetics and climate. In 1910, Nichols reported that rabbits could be infected intratesticularly with *T. pertenue* and proposed that these animals could provide a more practicable model of yaws for the investigation of immunity and treatments.[10]

Because of the biological similarities of *T. pallidum* and *T. pertenue*, there was optimism that syphilis treatments would be effective for yaws. In 1907, Castellani reported the results of various syphilis treatments on small numbers of yaws patients.[11] He noted a dramatic improvement of yaws lesions following administration of mercury by the oral or intramuscular route. However, as observed with syphilis, mercurials alone were not curative because yaws lesions usually reappeared after treatment cessation. In 1910, salvarsan (compound 606), an arsenical developed by Ehrlich in Germany, showed promising results for syphilis treatment.[12] Castellani noted that salvarsan was more effective than mercury for yaws treatment.[13,14] Strong (1911), Alston (1912), Cockin (1913), and McDonald (1915) reported that one injection of salvarsan, given intravenously or intramuscularly, could cure early and late yaws.[15–18] The few relapses, or possible reinfections, which occurred were successfully retreated with salvarsan. Interestingly, salvarsan appeared to be more

effective for yaws than it was for syphilis. Nichols postulated that the need for prolonged treatment of syphilis with salvarsan was due to the more invasive nature of *T. pallidum*, which enabled it to survive in body sites where the concentration of salvarsan was subtherapeutic.[19] In 1914, Ehrlich developed neosalvarsan (compound 914), which was easier to administer and had less side effects than salvarsan.[12] Harper[20] and Greggio[14] reported that neosalvarsan was effective for yaws treatment. Later, mapharsen, a partially oxidized product of salvarsan, was found to cure syphilis.[12] This arsenical, which was patented in 1937, was less toxic than neosalvarsan and could be given in smaller doses. Longley and co-workers[21] showed that both mapharsen and neosalvarsan were effective for curing rabbits infected with yaws. However, the use of mapharsen for yaws treatment was limited because arsenicals essentially became obsolete when penicillin became available in the 1940s. Following the 1943 report of Mahoney and co-workers[22] on the curative action of penicillin for syphilis, there were multiple reports of small numbers of yaws cases that were cured with penicillin.[23] Dwindelle and co-workers[23] treated 500 Haitian patients in early yaws with penicillin and demonstrated the therapeutic efficacy of this drug, which became the mainstay for the treatment and control of yaws.

Nearly 50 years after Castellani's discovery of *T. pertenue*, a major effort was made to eradicate yaws. From 1952 to 1964, the WHO, in concert with the United Nations Children's Fund (UNICEF), sponsored a mass treatment campaign in 46 countries.[1,2,24] About 300 million people were screened and 50 million or more cases and their contacts were treated with an intramuscular injection of long-acting penicillin. By the end of this campaign, the global burden of yaws was reduced by 95% to 2.5 million cases. Unfortunately, the lack of sustained surveillance and the waning of commitment and resources resulted in the reemergence of yaws in Africa, Asia, and the Pacific in the late 1970s. Although control activities were renewed in several countries and efforts were made to galvanize support from the international community, yaws eradication failed.

Today, 110 years after the discovery of *T. pertenue*, yaws is again targeted for eradication. The WHO's "Morges strategy" for yaws eradication by 2020 is based on mass treatment of individuals in endemic communities followed by clinical and serological surveys at 6-month intervals to detect and treat the remaining cases and their contacts.[24,25] Two recent advances for treatment and diagnosis of yaws should greatly aid eradication efforts. First, Mitja and others showed in two separate studies conducted in Papua New Guinea that a single, oral dose of azithromycin (30 mg/kg body weight; maximum dose of 2 g) is as effective as intramuscular benzathine penicillin (1.2 million units (MU) for adults, 0.6 MU for children) for yaws treatment and is more feasible to administer in the field.[26,27] Azithromycin, which has recently replaced penicillin as the WHO-preferred drug for yaws, will be used for mass treatment in communities where yaws is endemic. Second, Ayove and others[28] showed that a point-of-care serological test for syphilis diagnosis, the Dual Path Platform (DPP) Syphilis Screen and Confirm, is sufficiently sensitive and specific for rapid diagnosis of yaws under field conditions using finger-stick blood. This important development obviates the need for venipuncture to obtain serum samples and for transport of serum samples to a distant laboratory for testing. The DPP test will be used to detect yaws cases that are difficult to diagnose based on clinical symptoms because unrelated bacteria, such as *Haemophilus ducreyi*, can cause phenotypically similar skin lesions.[1] The DPP test may also be used for monitoring the effectiveness of azithromycin treatment.

Undoubtedly, many challenges must be overcome for yaws eradication to succeed. Aside from major financial and commitment issues, several uncertainties related to the biology and epidemiology of yaws could impede this endeavor.[1,2,29] Because there is no vaccine to prevent infection, antibiotic treatment must be effective to interrupt transmission of yaws. The use of oral azithromycin as the first-line drug, while warranted based on logistics, could result in the emergence of azithromycin-resistant *T. pertenue*, as has been observed with *T. pallidum*.[30,31] This possibility requires careful monitoring. Furthermore, although the prevalence of yaws is undoubtedly less than it was at the time of the first WHO eradication campaign, the current burden and distribution of yaws are unknown.[2,24] The inability to find and treat yaws cases, particularly in remote areas of previously endemic countries that have not reported cases to the WHO since 1990, could allow yaws to resurface. Despite these concerns, recent advances in the treatment and diagnosis of yaws and a more favorable climate for control of neglected tropical diseases have renewed hope that yaws eradication can be achieved. What more fitting tribute could there be to Aldo Castellani, the discoverer of *T. pertenue*, than to finally vanquish this "end of the road" disease?

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