Progress in treatment and diagnosis of yaws: hope for eradication?

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Endemic treponematoses are a group of chronic bacterial infections caused by non-cultivable, spiral-shaped bacteria closely related to *Treponema pallidum pallidum*—the syphilis agent.[1] Yaws is the most common of the endemic treponematoses and is prevalent in poor rural communities in remote tropical areas of Africa, Asia, and the Pacific Islands.[1–3] The infection typically affects children and adolescents and is transmitted through skin-to-skin contact with an active lesion. Without treatment, about 10% of people infected with *Treponema pallidum pertenue*—the yaws agent—develop disfiguring and disabling complications. Prevention of yaws is based on interruption of transmission by early diagnosis and treatment of individual cases and mass or targeted treatment of affected communities. Diagnosis of yaws is based mainly on clinical observation and epidemiological findings. However, because yaws can be confused with other diseases that are present in the tropics, diagnosis must be confirmed by laboratory techniques.[3–5]

Yaws was one of the first diseases targeted by WHO for eradication—ie, permanent reduction to zero of yaws prevalence on a worldwide scale. The Global Yaws Control Program ran from 1952 to 1964, treated 50 million individuals, and reduced the prevalence of yaws by more than 95%.[3] Unfortunately, the disease re-emerged in the late 1970s after control efforts waned. In March, 2012, WHO convened a meeting in Morges, Switzerland, to develop a new strategy for eradication of yaws by 2020. The Morges strategy[6] is based on initial mass treatment of endemic communities followed by resurveys every 6 months to detect and treat remaining cases.

Although the task of yaws eradication is daunting, two advances have rekindled hope for success. First, the longstanding WHO-recommended treatment for yaws is one intramuscular injection of benzathine benzylpenicillin (1·2 million units for adults and 0·6 million units for children). Although effective, use of penicillin has many associated issues—eg, the need for refrigeration and for trained personnel to administer the drug, the risk of blood-borne pathogen transmission via needles, and the potential for anaphylaxis. In 2012, Mitjà and colleagues reported that one oral dose of azithromycin (30 mg/kg, to a maximum of 2 g) was as effective as benzathine benzylpenicillin for treatment of yaws-infected children in Papua New Guinea.[7] Azithromycin has several advantages, including safety and ease of administration.[7] If findings of WHO-funded pilot studies confirm the efficacy of azithromycin for yaws, its use as the preferred treatment would greatly simplify the task of community-based mass treatment.

Second, because of the antigenic similarity of the yaws and syphilis agents, serological tests for syphilis are also used for diagnosis of yaws, although these tests cannot differentiate the two diseases.[1,2,5] For serodiagnosis of active yaws infection, detection of antibodies to both non-treponemal (ie, cardiolipin) and treponemal components is needed. During the initial stage of yaws infection, non-treponemal serological tests for syphilis—such as the rapid plasma reagin (RPR) test—become reactive, but after treatment they usually show greatly decreased reactivity or become non-reactive. By contrast, treponemal serological tests for syphilis—such as the *T pallidum* haemagglutination assay (TPHA)—generally remain reactive for life, irrespective of treatment, precluding the ability to distinguish between active and past infections. Although RPR reactivity is a better indicator of active infection and the need for treatment, a serum sample is needed for the RPR test, and the test must be done in a clinical setting, which is rarely available in yaws-endemic areas.

In *The Lancet Global Health*, Telek Ayove and colleagues[8] report a comparison of the Dual Path Platform (DPP) Syphilis Screen and Confirm test (Chembio Diagnostic Systems, Medford, NY, USA) with non-treponemal (RPR) and treponemal (TPHA) serological tests for diagnosis of yaws in two remote communities in Papua New Guinea with a high prevalence of the infection. The DPP point-of-care test detects treponemal (T1) and non-treponemal (T2) antibodies simultaneously.[9] When compared with TPHA, the DPP T1 test had a sensitivity of 88·4% and specificity of 95·2%. By comparison with the RPR test, the DPP T2 test had a sensitivity of 87·9% and specificity of 92·5%. However, sensitivity of the DPP T2 test rose to 94·1%

for specimens with higher quantitative RPR titres—ie, 1:8 or higher. Furthermore, the combined results of the DPP T1 and T2 tests had a sensitivity of 93·9%, compared with the combined results of reactive TPHA and high-titre RPR, which together are judged indicative of true yaws infection. The key value of the DPP test resides in the non-treponemal T2 part, which provides rapid and accurate results for field diagnosis of active untreated yaws infection with only finger-stick blood. Moreover, T2 optical density measurements taken before and after treatment (assessed with an automatic reader) fell progressively after treatment, showing a response comparable with that of quantitative RPR titres and, thus, possibly providing a way to monitor the effectiveness of treatment.

Although advances in the treatment and diagnosis of yaws should substantially help eradication efforts, several uncertainties related to the biology and epidemiology of the disease merit consideration, because they could impede eradication. First, the availability of a vaccine and the absence of a non-human reservoir were key factors for smallpox eradication. However, no vaccine is available for yaws and non-human primates might be a reservoir for the disease.[10] Second, because of the scarcity of adequate surveillance data, the true burden and distribution of yaws is currently unknown.[3] Third, although azithromycin is effective for treatment of yaws, resistance could emerge to this macrolide antibiotic, which has been reported for the syphilis agent.[11,12] Fourth, although the DPP test worked well for diagnosis of yaws in a setting of high prevalence, the positive predictive value of the DPP T2 test will diminish when the prevalence of yaws falls to very low levels, leading to false-positive results and the need for a more specific test to ensure that transmission has been interrupted.[8] Fifth, limited access to mobile populations in remote, sometimes dangerous, areas is a logistical difficulty that must be overcome to prevent reintroduction of yaws to treated communities.[3]

Despite the many hurdles, yaws eradication remains a worthwhile goal that, if successful, would prevent the suffering of thousands of people, particularly children, who are most affected by this neglected tropical disease. The recent elimination of yaws in India,[13] which was the result of an intensive government-backed programme, along with these advances in treatment and diagnosis, rekindle the hope that yaws eradication could be possible, as long as sufficient resources and strong political commitment are available for the very long term.

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I declare that I have no competing interests.

1 Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev* 2014; **27:** 89–115.
2 Mitjà O, Asiedu K, Mabey D. Yaws. *Lancet* 2013; **381**: 763–73.
3 Kazadi WM, Asiedu KB, Agana N, Mitjà O. Epidemiology of yaws: an update. *Clin Epidemiol* 2014; **6:** 119–28.
4 Mitjà O, Lukehart SA, Pokowas G, et al. *Haemophilus ducreyi* as a cause of skin ulcers in children from yaws-endemic area of Papua New Guinea: a prospective cohort study. *Lancet Glob Health* 2014; **2:** e235–41.
5 Mitjà O, Šmajs D, Bassat Q. Advances in the diagnosis of endemic treponematoses: yaws, bejel, and pinta. *PLOS Negl Trop Dis* 2013; **7:** e2283.
6 World Health Organization. Eradication of yaws: the Morges strategy. *Wkly Epidemiol Rec* 2012; **87:** 189–94.
7 Mitjà O, Hays R, Ipai A, et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomized trial. *Lancet* 2012; **379:** 342–47.
8 Ayove T, Houniei W, Wangnapi R, et al. Sensitivity and specificity of a rapid point-of-care test for active yaws: a comparative study. *Lancet Glob Health* 2014; published online May 30. http://dx.doi.org/10.1016/S2214-109X(14)70231-1.
9 Castro AR, Esfandiari J, Kumar S, et al. Novel point-of-care test for simultaneous detection of non-treponemal and treponemal antibodies in patients with syphilis. *J Clin Microbiol* 2010; **48:** 4615–19.
10 Knauf S, Liu H, Harper KN. Treponemal infection in nonhuman primates as possible reservoir for human yaws. *Emerg infect Dis* 2013; **19:** 2058–60.
11 Stamm LV. Global challenge of antibiotic-resistant *Treponema pallidum*. *Antimicrob Agents Chemother* 2010; **54:** 583–89.
12 Mabey D. Oral azithromycin for treatment of yaws. *Lancet* 2012; **379:** 295–97.
13 WHO. Elimination of yaws in India. *Wkly Epidemiol Rec* 2008; **83:** 125–32.