

## Single-dose azithromycin to treat latent yaws



Yaws, caused by *Treponema pallidum* subsp *pertenue*, was the first disease to be targeted for eradication by WHO.<sup>1</sup> As with other treponemal infections, such as syphilis, some people develop latent infection. These individuals have positive serological test results for yaws but no clinical signs of disease. Importantly, latent yaws can relapse, which most frequently occurs in the first 5 years after infection,<sup>2</sup> and, therefore, these people represent an important source of reinfection in endemic communities.

In 2012, WHO developed a strategy for yaws eradication<sup>3</sup> based on mass treatment of communities with single-dose oral azithromycin. WHO's previous yaws eradication campaign, in the 1950–60s, was based on mass treatment with long-acting injectable penicillin. Although this approach substantially reduced the worldwide prevalence of yaws, it did not result in eradication. Failure to identify and treat latent cases adequately in endemic communities was probably a crucial factor in this outcome.<sup>4</sup>

The initial studies of single-dose azithromycin for the treatment of yaws focused on patients with active primary and secondary yaws,<sup>5,6</sup> and showed high clinical and serological cure rates 6 months after treatment. Subsequent community studies showed similar reduced prevalence of active yaws with mass treatment, plus apparent reductions in the prevalence of latent yaws.<sup>7,8</sup> All these studies, however, were limited by short follow-up, which has probably led to underestimation of the true effects of treatment, because rapid plasma reagin (RPR) titres can take 12–24 months to fall by two dilutions or revert to negative after successful treatment, particularly in people with latent yaws.<sup>9</sup>

In *The Lancet Global Health*, Oriol Mitjà and colleagues<sup>10</sup> provide the most comprehensive data so far on the effects of single-dose azithromycin on latent yaws. They enrolled 311 participants with suspected yaws and RPR titres of 1:8 or higher into a prospective cohort study. Importantly, the researchers used molecular diagnostics to differentiate individuals who were seropositive for yaws and had skin lesions containing DNA of *T pallidum* (active yaws) from those whose skin lesions were caused by other organisms, such as *Haemophilus ducreyi* (latent yaws). A particular strength of the study is the long duration of follow-up; the

primary endpoint was serological cure 24 months after treatment. 273 individuals (108 with active yaws and 165 with latent yaws) completed follow-up. The proportions of patients with serological cure at 24 months were similar in patients with active and latent yaws. At 6 months, serological cure was seen in 88% and 83% of participants, respectively, but at 24 months, the proportions had increased to 94% and 92%, respectively. This marked increase in the latent yaws group underscores the usefulness of the long follow-up in this study.

Several questions remain unanswered by Mitjà and colleagues. First, some individuals who did not achieve serological cure might have been serofast (ie, cured but remained seropositive). The authors excluded people with RPR titres lower than 1:8 at baseline, which should have kept the number of serofast individuals enrolled to a minimum, but could explain why some participants had not achieved serological cure by 24 months. No test is available to distinguish latent infection from serofast status, but such a tool would be useful for yaws eradication programmes. Second, participants without adequate serological responses might have been reinfected during follow-up, but, again, no test can distinguish reinfection from serological failure. The current study was done within a community mass treatment programme, which would have minimised but not eliminated the risk of reinfection. Third, the serological cure rate at 6 months is lower in Ghana than that in Papua New Guinea.<sup>5,6</sup> Studies with extended follow-up, as in that done by Mitjà and colleagues, would be helpful to assess differences in cure rates between countries and their underlying reasons. Resistance to azithromycin has limited its use in the treatment of syphilis and, although resistant strains of *T pertenu*e have not yet been reported, it remains a concern for yaws elimination programmes. Finally, WHO also recommends mass treatment with azithromycin for the control of trachoma, but at a lower dose than that used for yaws.<sup>11</sup> The results of a completed trial should provide data on the effectiveness of lower-dose azithromycin used to treat active and latent yaws to help guide scale up of integrated mass drug administration programmes in countries where yaws and trachoma are coendemic.

Published Online  
October 26, 2017  
[http://dx.doi.org/10.1016/S2214-109X\(17\)30424-2](http://dx.doi.org/10.1016/S2214-109X(17)30424-2)  
See [Articles](#) page e1268

\*Michael Marks, David Mabey

Clinical Research Department, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK  
 michael.marks@lshtm.ac.uk

We declare no competing interests.

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

- 1 Marks M, Solomon AW, Mabey DC. Endemic treponemal diseases. *Trans R Soc Trop Med Hyg* 2014; **108**: 601–07.
- 2 Perine PL, Hopkins DR, Niemel PLA, St John R, Causse G, Antal GM. Handbook of endemic treponematoses: yaws, endemic syphilis and pinta. Geneva: World Health Organization, 1984.
- 3 WHO. Eradication of yaws—the Morges strategy. *Wkly Epidemiol Rec* 2012; **87**: 189–94.
- 4 Hackett CJ, Guthe T. Some important aspects of yaws eradication. *Bull World Health Organ* 1956; **15**: 869–96.
- 5 Kwakye-Maclean C, Agana N, Gyapong J, et al. A single dose oral azithromycin versus intramuscular benzathine penicillin for the treatment of yaws—a randomized non inferiority trial in Ghana. *PLoS Negl Trop Dis* 2017; **11**: e0005154.
- 6 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, randomised trial. *Lancet* 2012; **379**: 342–47.
- 7 Marks M, Vahi V, Sokana O, et al. Impact of community mass treatment with azithromycin for trachoma elimination on the prevalence of yaws. *PLoS Negl Trop Dis* 2015; **9**: e0003988.
- 8 Mitjà O, Houinei W, Moses P, et al. Mass treatment with single-dose azithromycin for yaws. *N Engl J Med* 2015; **372**: 703–10.
- 9 Janier M, Hegyi V, Dupin N, et al. 2014 European guideline on the management of syphilis. *J Eur Acad Dermatol Venereol* 2014; **28**: 1581–93.
- 10 Mitjà O, González-Beiras C, Godames C, et al. Effectiveness of single-dose azithromycin to treat latent yaws: a longitudinal comparative cohort study. *Lancet Glob Health* 2017; published online October 26. [http://dx.doi.org/10.1016/S2214-109X\(17\)30388-1](http://dx.doi.org/10.1016/S2214-109X(17)30388-1).
- 11 Solomon AW, Marks M, Martin DL, et al. Trachoma and yaws: common ground? *PLoS Negl Trop Dis* 2015; **9**: e0004071.