

# Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial

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## Summary

**Background** Yaws—an endemic treponematoses and, as such, a neglected tropical disease—is re-emerging in children in rural, tropical areas. Oral azithromycin is effective for syphilis. We assessed the efficacy of azithromycin compared with intramuscular long-acting penicillin to treat patients with yaws.

**Methods** We did an open-label, non-inferiority, randomised trial at Lihir Medical Centre, Papua New Guinea, between Sept 1, 2010, and Feb 1, 2011. Children aged 6 months to 15 years with a serologically confirmed diagnosis of yaws were randomly allocated, by a computer-generated randomisation sequence, to receive either one 30 mg/kg oral dose of azithromycin or an intramuscular injection of 50 000 units per kg benzathine benzylpenicillin. Investigators were masked to group assignment. The primary endpoint was treatment efficacy, with cure rate defined serologically as a decrease in rapid plasma reagin titre of at least two dilutions by 6 months after treatment, and, in participants with primary ulcers, also by epithelialisation of lesions within 2 weeks. Non-inferiority was shown if the upper limit of the two-sided 95% CI for the difference in rates was lower than 10%. The primary analysis was per protocol. This trial is registered with ClinicalTrials.gov, number NCT01382004.

**Findings** We allocated 124 patients to the azithromycin group and 126 to the benzathine benzylpenicillin group. In the per-protocol analysis, after 6 months of follow-up, 106 (96%) of 110 patients in the azithromycin group were cured, compared with 105 (93%) of 113 in the benzathine benzylpenicillin group (treatment difference  $-3.4\%$ ; 95% CI  $-9.3$  to  $2.4$ ), thus meeting prespecified criteria for non-inferiority. The number of drug-related adverse events (all mild or moderate) was similar in both treatment groups (ten [8%] in the azithromycin group vs eight [7%] in the benzathine benzylpenicillin group).

**Interpretation** A single oral dose of azithromycin is non-inferior to benzathine benzylpenicillin and avoids the need for injection equipment and medically trained personnel. A change to the simpler azithromycin treatment regimen could enable yaws elimination through mass drug administration programmes.

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## Introduction

Yaws—an endemic treponematoses and, as such, a neglected tropical disease—is re-emerging. 40 years after a worldwide control programme almost eradicated the disease, it has re-emerged in children in poor, rural, and marginalised populations in parts of Africa, Asia, and South America. Yaws is caused by *Treponema pallidum* subsp *pertenue*, and affects mainly skin, bones, and cartilage. The disease has a natural history in primary, secondary, and tertiary stages. Unless diagnosed and treated at an early stage, yaws can become a chronic, relapsing disease, and can lead to severe deforming bone lesions in the long term.<sup>1</sup>

Between 1952, and 1964, WHO and UNICEF led a worldwide campaign to control and eventually eradicate yaws and other endemic treponematoses.<sup>2</sup> Yaws became the second disease targeted for eradication, after smallpox. Control programmes were established in 46 countries and, by the end of 1964, the number of cases had reduced by 95%, from 50 million to 2.5 million. However, control efforts were gradually abandoned in

most countries<sup>3</sup> and the disease re-emerged in the late 1970s, prompting the adoption of WHO's assembly resolution 38.58.<sup>4</sup> According to the last estimate by WHO in 1995, more than 500 000 children were still affected in Africa, Asia, and South America.<sup>5</sup>

Penicillin remains the drug of choice to treat endemic treponematoses.<sup>6,7</sup> WHO guidelines recommend one intramuscular injection of long-acting benzathine benzylpenicillin at a dose of 1.2 MU for adults and 0.6 MU for children;<sup>8</sup> however, other guidelines recommend higher doses.<sup>9</sup> This treatment is effective and has several advantages, as described for venereal syphilis.<sup>10</sup> Although this treatment is cheap and well tolerated, it has drawbacks, including the operational and logistical difficulties related to treatment with drug injection, the potential risk of transmission of blood-borne pathogens with unsafe injection practices, the pain related to deep intramuscular injection of a large volume (4 mL), and a high rate of self-reported allergy to penicillin.

Oral phenoxymethylpenicillin for 7–10 days (50 mg/kg daily in four doses; maximum dose 300 mg four times a

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day) was effective in a yaws control programme.<sup>11</sup> Such a regimen overcomes the disadvantages of intramuscular drug administration, but poor adherence to a multiday treatment regimen is a risk. In pilot studies of the potential of oral, single-dose treatment against several infectious disorders, azithromycin—a macrolide antibiotic with a long half-life in tissue—seemed to be a valuable drug against *Chlamydia trachomatis*,<sup>12</sup> *Neisseria gonorrhoeae*,<sup>13</sup> and *Haemophilus ducreyi*<sup>14</sup> infections. Promising results were also reported from a large-scale study<sup>10</sup> done in Tanzania, with two regimens to treat early syphilis: one oral dose (2 g) of azithromycin and one intramuscular dose of benzathine benzylpenicillin 2·4 MU. A multicentre trial<sup>15</sup> in North America and Madagascar had similar findings.

The immediate-release formulation of azithromycin given in one oral dose of 30 mg per kg of bodyweight has been approved and widely used to treat acute otitis media in children since 2001.<sup>16,17</sup> The product is available as an oral tablet or as syrup, which is easier to administer to very young children.

We assessed the efficacy of a single oral dose of azithromycin compared with the standard single intramuscular dose of benzathine benzylpenicillin to treat yaws.

## Methods

### Study setting and patients

We undertook a prospective, open-label, non-inferiority, randomised controlled trial at Lihir Medical Centre in Papua New Guinea between Sept 1, 2010, and Feb 24, 2011. The Lihir islands are geographically remote, and despite being host to a major gold-mining operation since 1995, the living conditions and sanitation remain basic in most areas. Yaws is still a substantial cause of morbidity in Papua New Guinea.<sup>18,19</sup> Monthly reports for monitoring several indicators of infectious diseases and maternal and child health are being collected via forms from hospitals, health centres, and aid posts throughout the country. The national health department estimated the number of yaws cases to be 17 000 nationwide in 2003, and 23 000 in 2008, of which 5000 were in New Ireland province, where Lihir Island is located, and another 5000 in the neighbouring province of West New Britain (unpublished).

All patients examined in the outpatient medical department and suspected to have primary-stage or secondary-stage yaws were assessed for possible inclusion in the study. Eligible patients were children aged 6 months to 15 years with a rapid plasma reagin titre of at least 1 in 16 and a reactive *T pallidum* haemagglutination test. Exclusion criteria were known allergy to penicillin or macrolide antibiotics, use of antibiotics active against *T pallidum* during the preceding month, and known or suspected coexisting diseases for which additional antibiotic treatment with drugs effective against *T pallidum* would be needed (use of quinolones, sulphonamides, trimethoprim, and metronidazole was allowed).

A diagnosis of yaws chancre (primary stage) was established by dermatological examination on the basis of chronic (symptomatic for >2 weeks), painless, atraumatic ulcers with raised margins. Criteria for the diagnosis of secondary yaws included the presence of one or more of: multiple hyperkeratotic papules; polyarthralgia; or bone pain and swelling affecting the fingers or toes, forearm, tibia, or fibula. When an overlap between the stages occurred (ie, primary lesion persisting after the appearance of secondary yaws symptoms) we classified the case as secondary stage. The study was approved by the National Medical Research Advisory Committee of the Papua New Guinea Ministry of Health. All patients, or their parents, provided signed informed consent.

### Randomisation and masking

Eligible participants were randomly assigned, by use of a computer-generated random-numbers list, to receive either 30 mg/kg (maximum 2 g) azithromycin orally or 50 000 units per kg (maximum 2·4 MU) benzathine benzylpenicillin by intramuscular injection. Randomisation was done in permuted blocks of four and in a 1:1 ratio. The allocation was concealed from investigators by use of opaque, sealed, and sequentially numbered envelopes that were opened after the study team had decided to enrol a patient. Laboratory technicians were unaware of participants' treatment allocation, treatment response, and previous rapid plasma reagin results at all times. All participants received directly observed treatment, but masking of patients was not possible for logistical reasons.

### Procedures

The primary endpoint was serological cure, defined as a decrease in the rapid plasma reagin titre by at least two dilutions at the 6-month follow-up examination, compared with the titre at time of treatment. For ulcers, improvement of lesions in 2 weeks after treatment was also needed. Secondary endpoints were the individual components of the primary endpoint, cure rate 3 months after treatment, and cure rates according to stage of yaws, rapid plasma reagin titre at treatment, and history of household exposure.

To guarantee timely follow-up of participants, we implemented a community-based follow-up strategy. A field team, consisting of a physician, a laboratory technician, and a local health worker, located patients twice a week (for follow-up visit) at their residence by tracking detailed locator information. All participants were re-examined 2 weeks after treatment to assess clinical resolution. Photographic documentation of skin lesions was obtained at diagnosis and at the 14-day follow-up visit for comparison over time. Patients with worsening ulcers were retreated with benzathine benzylpenicillin (at the same dose). We assessed all participants at 3 months and 6 months after treatment. A 5 mL blood sample was obtained at each follow-up visit for serological analysis for

*T pallidum*. All rapid plasma reagin tests were done in duplicate by two independent trained technicians at the Lihir Medical Centre microbiology department, and tests were done a third time in cases of discrepant results.

Safety assessments included documentation of immediate adverse events and patient-reported adverse events. So that immediate reactions could be recorded and treated, patients stayed at the health centre for 30 min after treatment. Patient-reported adverse events were assessed at the 2 week examination. Patients (or their parents or guardians) were explicitly asked about pain at site of injection, rash, fever, vomiting, diarrhoea, and stomach pain.

### Statistical analysis

This study was based on the notion that azithromycin would be non-inferior to benzathine benzylpenicillin for the primary efficacy outcome, with use of a pre-specified non-inferiority margin; the upper limit of the 95% CI for the difference in cure rates between groups would not exceed 10%. We calculated that a sample size of 242 patients (121 per group) would give a power of 80% to test the hypothesis of non-inferiority. This sample size accounted for an expected efficacy of benzathine benzylpenicillin of 95%,<sup>11,20</sup> a non-inferiority margin of 10%, and a one-sided type 1 error rate of 0.05, with the assumption that 10% of participants would be lost to follow-up.

We selected the per-protocol population for the primary analysis. This population included all patients who underwent randomisation and who completed the study procedures to month 6. We also did a supporting analysis with the intention-to-treat (missing equals failure) population, which included all eligible patients, and in which patients with missing data were regarded as having treatment failure.

For analysis of the primary endpoint (cure rate at 6 months), we estimated two-sided 95% CIs for the difference in cure proportions between the benzathine benzylpenicillin group and the azithromycin group according to Altman and colleagues' method.<sup>21</sup> We used the same method to analyse secondary binary endpoints. We did additional post-hoc analyses to assess the consistency of treatment effects in subgroups defined according to disease stage, rapid plasma reagin titre, and household exposure, with Fisher's exact test. To compare baseline characteristics and adverse events between the treatment groups, we used two-sided *t* and Fisher's exact tests with a significance level of 0.05. We did all statistical analyses with Stata (version 11.1).

This study is registered with ClinicalTrials.gov, number NCT01382004.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the

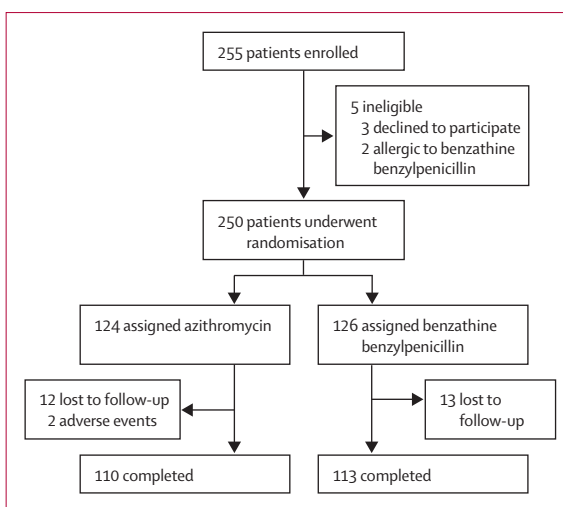


Figure 1: Trial profile

	Azithromycin (n=124)	Benzathine benzylpenicillin (n=126)
Age (years)	9.2 (3.7)	8.4 (3.3)
Male sex	54 (44%)	59 (47%)
Exposure*	26 (21%)	20 (16%)
Clinical presentation		
Primary stage	50 (40%)	56 (44%)
Secondary stage	74 (60%)	70 (56%)
Persisting ulcer	18 (15%)	15 (12%)
Secondary skin lesions	16 (13%)	11 (9%)
Arthralgias	68 (55%)	64 (51%)
Bone swelling or pain	12 (10%)	10 (8%)
RPR titre at treatment		
≤1 in 32	47 (38%)	60 (48%)
≥1 in 64	77 (62%)	66 (52%)

Data are mean (SD) or number (%). RPR=rapid plasma reagin. \*Household exposure to other children with open skin ulcers during the previous 3 months.

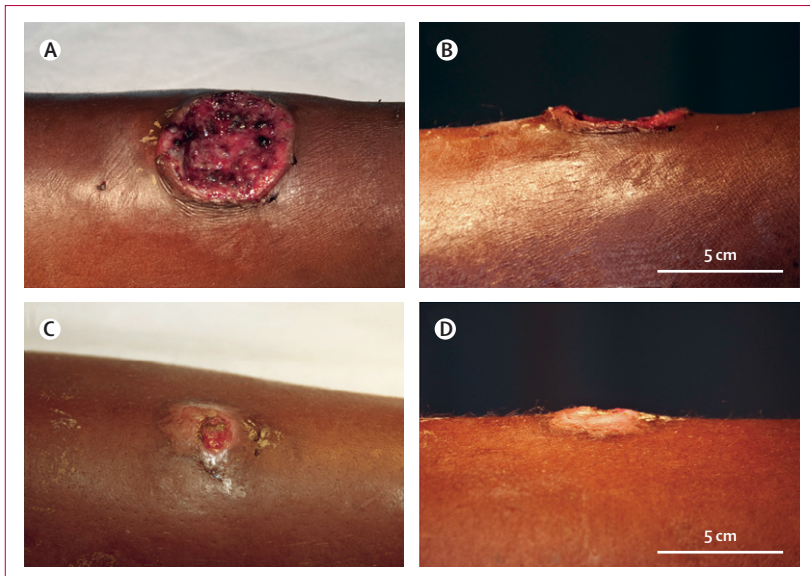
Table 1: Baseline characteristics of the intention-to-treat population

data in the study and had final responsibility for the decision to submit for publication.

### Results

Figure 1 shows the trial profile. 250 patients with serologically confirmed yaws were randomly assigned to receive either azithromycin or benzathine benzylpenicillin. Baseline clinical and serological characteristics of the two treatment groups were similar (table 1). Mean age of the participants was 8.8 years (SD 3.6; range 8 months to 15 years). 42% of patients had primary yaws (table 1). The rapid plasma reagin titre was less than 1 in 32 in 107 (43%) participants and 1 in 64 or more in 143 (57%; table 1).

25 (10%) of the 250 participants could not be traced: ten (4%) of these children could not be located for any



**Figure 2:** Ulcers in patients with primary-stage or secondary-stage yaws who were re-examined 2 weeks after treatment

(A, B) Red, moist, bedded, 5 cm ulcer on the left leg of a 9-year-old patient with primary yaws. (C, D) Partially epithelialised tumour 2 weeks after treatment with azithromycin.

follow-up visit and 15 (6%) were lost after the first follow-up visit. We could not locate seven (3%) participants because they provided an invalid address, and 18 (7%) were originally from the study area but moved elsewhere during follow-up. Two patients did not complete follow up because of adverse events related to drug administration. The remaining 223 patients constituted the per-protocol population.

Adverse events in the first 14 days of treatment were reported by ten (8%) of 119 patients interviewed in the azithromycin group, and by eight (7%) of 121 in the benzathine benzylpenicillin group. Of participants given azithromycin, six (5%) reported nausea, two (2%) stomach pain, and two (2%) vomiting within 30 min of taking the drug. We classed the two patients who vomited as having had treatment failure in the intention-to-treat analyses, and they were retreated with benzathine benzylpenicillin. In patients given benzathine benzylpenicillin administration-related adverse effects were the most common. Six (5%) patients in the benzathine benzylpenicillin group reported persistent injection-site pain, despite use of lidocaine 1% as a diluent, and two (2%) had an injection-related abscess. No serious adverse events were reported during treatment or for the entire follow-up period.

129 participants with ulcers (in primary or secondary stage) were re-examined 2 weeks after treatment; the ulcers had resolved in 51 (40%) and were healing in 70 (54%; figure 2). The rates of healing did not differ significantly between the two treatment groups (data not shown). We classed the remaining eight (6%) patients (four in the azithromycin group and four in the benzathine benzylpenicillin group) as having clinical treatment failure.

In both the per-protocol and intention-to-treat analyses the criteria for non-inferiority were met for the composite primary endpoint of serological cure at 6 months and clinical healing of ulcers. In the per-protocol analysis, 106 of 110 patients assigned azithromycin were cured at 6 months compared with 105 of 113 patients in the benzathine benzylpenicillin group (risk difference  $-3.4\%$ , 95% CI  $-9.3$  to  $2.4$ ; table 2). Incidence of the individual components of the primary endpoint and intermediate cure rates did not differ significantly between groups (table 2). In the intention-to-treat population, 106 of 124 patients assigned azithromycin and 105 of 126 patients assigned benzathine benzylpenicillin met the criteria for the primary endpoint ( $-2.2\%$ ,  $-11.1$  to  $6.8$ ; table 2).

In subgroup analyses, the cure rates at 6 months according to yaws stage, rapid plasma reagin titre at treatment, and household exposure did not differ significantly between treatments in the per-protocol population (table 3). No participant in either treatment group had recurrent clinical signs of yaws or serological evidence of recurrence during the 6-month follow-up period.

	Azithromycin % (95% CI)	Benzathine benzylpenicillin % (95% CI)	Risk difference % (95% CI)
<b>Primary population (PP) analysis (n=223)*</b>			
Primary endpoint: cure at 6 months	96.4% (91.0-98.6)	92.9% (86.7-96.4)	-3.4% (-9.3 to 2.4)
Cure at 3 months	80.0% (71.6-86.4)	80.5% (72.3-86.8)	0.5% (9.9 to 10.9)
Serologically defined cure at 6 months	100% (96.5-100)	96.3% (90.3-98.8)	-3.7% (-7.2 to -0.1)
Clinical cure of ulcers 14 days after treatment	96.4% (91.3-98.6)	96.5% (91.0-98.6)	0.1% (-4.8 to 5.0)
<b>Secondary population (ITT) analysis (n=250)†</b>			
Primary endpoint: cure at 6 months	85.5% (78.2-90.6)	83.3% (75.9-88.8)	-2.2% (-11.1 to 6.8)
Cure at 3 months	71.0% (62.5-78.2)	72.2% (63.4-79.7)	1.3% (-9.9 to 12.4)
Serologically defined cure at 6 months	88.3% (81.4-92.9)	86.1% (78.8-91.1)	-2.3% (-10.7 to 6.1)
Clinical cure of ulcers 14 days after treatment	85.4% (78.2-90.6)	86.5% (79.5-91.4)	1.0% (-7.6 to 9.6)

PP=per protocol. ITT=intention to treat. \*Including only patients with complete follow-up and study endpoint.

†Including all randomised patients; we regarded patients with missing data as having treatment failure.

**Table 2:** Incidence of clinical endpoints

	Azithromycin % (95% CI)	Benzathine benzylpenicillin % (95% CI)	Risk difference % (95% CI)
<b>Cure at 6 months by yaws stage</b>			
Primary	90.9% (78.8-96.4)	89.1% (78.2-94.9)	-1.8% (-13.7 to 10.0)
Secondary	100% (94.5-100)	96.6% (88.3-99.1)	-3.4% (-8.1 to 1.2)
<b>Cure at 6 months by RPR titre at treatment</b>			
≤1 in 32	100% (90.8-100)	92.9% (83.0-97.2)	-7.1% (-13.9 to -0.4)
≥1 in 64	94.4% (86.6-97.8)	93.0% (83.3-97.2)	-1.4% (-9.9 to 7.0)
<b>Cure at 6 months by household exposure</b>			
Positive	100% (85.1-100)	100% (81.6-100)	..
Negative	95.5% (88.9-98.5)	92.0% (85.0-95.9)	-3.5% (-10.3 to 3.4)

Data are for the per-protocol analysis. RPR=rapid plasma reagin.

**Table 3:** Subgroup analysis of the primary endpoint at 6 months

## Discussion

Our findings show that azithromycin was non-inferior to benzathine benzylpenicillin for the primary composite endpoint of serological cure at 6 months and healing of ulcers. Furthermore, the two treatment groups had similar rates of cure at 3 month follow-up and in subgroups defined according to demographic and biological characteristics. These results add to previous evidence of the suitability of use of a single dose of a drug such as azithromycin to treat various infectious diseases (panel). Rates of serologically defined cure at 6 months were substantially higher than expected for both treatments, which validates our non-inferiority hypothesis for the estimated penicillin cure rate. All participants had a lower rapid plasmin reagin titre at 6 months than at 3 months, including 150 (67%) patients who seroconverted. Additionally, we did not identify any clinical or serological relapse after cure at 6 month follow-up. The azithromycin regimen did not resolve active primary lesions in four patients. However, in the three cases of failure that could be investigated, an immunoperoxidase stain from a skin biopsy specimen was negative for spirochaetes; therefore, we could not confirm the biological treatment failure.

Azithromycin was well tolerated and no major adverse effects occurred. Of participants who were treated with azithromycin and interviewed, 8% reported mild to moderate side-effects that were mainly gastrointestinal. Only two children vomited within 30 min of oral azithromycin administration, thus negligible drug absorption would have occurred. These children were then re-treated with benzathine benzylpenicillin. The small number of participants vomiting after administration emphasises the suitability of azithromycin for mass treatment programmes.

Our study had several limitations. First, diagnostic criteria for inclusion in the study of primary lesions did not include a microbiological test (eg, darkfield microscopy); therefore, the non-healing ulcers could have had post-treatment infection by other pathogens. However, darkfield microscopy is rarely used to diagnose treponemal infections because rapid serological tests are available. Second, the imprecise definition of serological cure, which could lead to overestimations in true rates of cure, is a major issue affecting all research on the treatment of treponematoses. Because laboratory technicians in this study were unaware of participants' treatment assignments, this drawback should not have biased the comparison of cure rates between the groups. Third, 6 months of follow-up might not be sufficient to assess the results after antibiotic treatment for yaws. Four participants in the benzathine benzylpenicillin group did not achieve serological cure. This finding could represent a slower than usual decline in non-treponemal test titres after treatment, rather than a true penicillin-resistant infection. Finally, because our trial design required patients to meet certain prespecified criteria, and because

### Panel: Research in context

#### Systematic review

We searched PubMed from Jan 1, 1952, to Aug 1, 2010, with the terms "yaws", "*Treponema pallidum*", "penicillin", and "azithromycin". We searched for trials that assessed the efficacy and safety of single-dose oral azithromycin to treat infectious diseases in adults and children. We identified two randomised controlled trials,<sup>10,12</sup> which showed the efficacy of oral azithromycin for the treatment of treponemal disease (syphilis) in adults. However, we did not identify any study that explored yaws treatment with azithromycin. We searched only publications written in English.

#### Interpretation

Our results provide substantial evidence of the non-inferiority of a single oral-dose of azithromycin compared with the standard recommended therapy—benzathine benzylpenicillin—for treatment of yaws. This finding represents a potentially useful advance in yaws control.

the study was done in one centre, our findings might not be generalisable to all children with yaws.

Two important reasons for caution with use of azithromycin are the sustained success of benzathine benzylpenicillin treatment for yaws, and the emergence of azithromycin-resistant *T pallidum*. Clinical treatment failure with penicillin has been reported for yaws,<sup>20</sup> although, because in-vitro culture for *T pallidum* has not been achieved,<sup>22</sup> penicillin resistance has not been proven by microbiological methods. Moreover, in countries such as Papua New Guinea, cases of reinfection are occurring, which suggests increased tolerance of some *T pallidum* subsp *pertenue* strains to penicillin treatment.<sup>23</sup> Azithromycin resistance in the non-venereal treponemes has not been investigated, but resistance in the syphilis treponeme is geographically clustered—eg, more than 95% resistance in Shanghai versus 0% in Madagascar.<sup>24,25</sup> In areas where mutations have been found (eg, Seattle, USA) the frequency of resistance has increased substantially in the past 10 years.<sup>26</sup> Use of azithromycin in the Lihir Island community to treat other infections has been scarce, which might explain why we did not encounter a substantial problem with resistance in our study since there had been very little selective pressure. Nonetheless, *T pallidum* subsp *pertenue*, seems to have two of the genes encoding 23S ribosomal RNA where the mutation that confers high-level resistance to macrolides is located, as does *T pallidum* subsp *pallidum*.<sup>27</sup> Thus, close monitoring for potential treatment failure should be considered in future studies of azithromycin.

With yaws re-emerging, treatment with an effective drug that can be easily administered on a large scale is the preferred method for treatment, prevention, and, eventually, elimination worldwide. Elimination programmes need to take account of all epidemiological,

biological, and pharmacological factors, and the practical considerations of a mass campaign to deliver and administer drugs in isolated and under-resourced communities. The potential for treatment of yaws with an oral, single-dose drug has been explored in this context. Azithromycin overcomes the major logistical and medical disadvantages of the present regimen: it avoids the need for injection equipment and medically trained personnel, which can be scarce in countries with few health resources; it prevents all the injection-related risks and side-effects; and it can be safely administered to individuals with penicillin allergy (1% in our trial population). Although we did not formally assess the relative costs related to drug acquisition and administration, low-cost generic preparations of azithromycin are widely available and the treatment could therefore be highly cost effective.

Our findings provide clear evidence that one high dose of azithromycin is non-inferior to benzathine benzylpenicillin for treatment of yaws. If further studies confirm our findings (a similar trial is in progress in Ghana, West Africa (Kwakyie-Maclean C, Ga West Municipal Health Directorate, personal communication), the next step is to attempt elimination and possibly eradication of the disease in the remaining endemic countries with mass drug administration programmes under WHO's leadership.

#### Contributors

OM conceived and designed the study. OM, RH, AI, MP, and RP contributed to the recruitment, clinical care, and follow-up of patients. OM, EdL, and QB analysed and managed the data. DF did all laboratory tests. OM, RH, and QB wrote the article.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### Acknowledgments

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#### References

- Meheus A. Non-venereal treponematoses. *Medicine* 2005; **33**: 82–84.
- Guthe T, Willcox RR. Treponematoses: a world problem. *WHO Chron* 1954; **8**: 37–113.
- Antal GM, Causse G. The control of endemic treponematoses. *Rev Infect Dis* 1985; **7** (suppl 2): S220–26.
- WHO. Resolutions and decisions: WHA31.58 control of endemic treponematoses. May 24, 1978. [www.who.int/neglected\\_diseases/mediacentre/WHA\\_31.58\\_Eng.pdf](http://www.who.int/neglected_diseases/mediacentre/WHA_31.58_Eng.pdf) (accessed Nov 21, 2011).
- WHO. Recent news from WHO. *Bull World Health Organ* 2007; **85**: 74.
- WHO Scientific Group. Treponemal infections. Technical Report Series No 674. Geneva: World Health Organization, 1982.
- Antal GM, Lukehart SA, Meheus AZ. The endemic treponematoses. *Microbes Infect* 2002; **4**: 83–94.
- WHO. Yaws: a forgotten disease. January, 2007. <http://www.who.int/mediacentre/factsheets/fs316/en/> (accessed Nov 21, 2011).
- Meheus AZ, Narain JP, Asiedu KB. Endemic treponematoses. In: Cohen J, Powderly SM, Opal WG, eds. *Infectious diseases*, 3rd edn. London: Elsevier (in press).
- Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med* 2005; **353**: 1236–44.
- Scolnik D, Aronson L, Lovinsky R, et al. Efficacy of a targeted, oral penicillin-based yaws control program among children living in rural South America. *Clin Infect Dis* 2003; **36**: 1232–38.
- Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. The Azithromycin for Chlamydial Infections Study Group. *N Engl J Med* 1992; **327**: 921–25.
- Handsfield HH, Dalu ZA, Martin DH, Douglas JM Jr, McCarty JM, Schlossberg D. Multicenter trial of single-dose azithromycin vs ceftriaxone in the treatment of uncomplicated gonorrhoea. *Sex Transm Dis* 1994; **21**: 107–11.
- Martin DH, Sargent SJ, Wendel GD Jr, McCormack WM, Spier NA, Johnson RB. Comparison of azithromycin and ceftriaxone for the treatment of chancroid. *Clin Infect Dis* 1995; **21**: 409–14.
- Hook EW 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis* 2010; **201**: 1729–35.
- US Food and Drug Administration. Briefing document for zithromax accelerated dosing; treatment of acute otitis media. Nov 7, 2001. [www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm209921.pdf](http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm209921.pdf) (accessed Nov 21, 2011).
- Dunne MW, Khurana C, Mohs AA, et al. Efficacy of single-dose azithromycin in treatment of acute otitis media in children after a baseline tympanocentesis. *Antimicrob Agents Chemother* 2003; **47**: 2663–65.
- Talwat E. Papua New Guinea yaws problems assessed. *Southeast Asian J Trop Med Public Health* 1986; **17** (suppl 4): 59–65.
- Manning LA, Ogle GD. Yaws in the periurban settlements of Port Moresby, Papua New Guinea. *P N G Med J* 2002; **45**: 206–12.
- Backhouse JL, Hudson BJ, Hamilton PA, Nesteroff SI. Failure of penicillin treatment of yaws on Karkar Island, Papua New Guinea. *Am J Trop Med Hyg* 1998; **59**: 388–92.
- Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. In: Altman DG, Machin D, Bryant TN, Gardner MJ, eds. *Statistics with confidence: confidence intervals and statistical guidelines*, 2nd edn. London: BMJ Books, 2000: 171–90.
- Stamm LV. Global challenge of antibiotic-resistant *Treponema pallidum*. *Antimicrob Agents Chemother* 2010; **54**: 583–89.
- Mitjà O, Hays R, Ipai A, et al. Outcome predictors in treatment of yaws. *Emerg Infect Dis* 2011; **17**: 1083–85.
- Martin IE, Gu W, Yang Y, Tsang RS. Macrolide resistance and molecular types of *Treponema pallidum* causing primary syphilis in Shanghai, China. *Clin Infect Dis* 2009; **49**: 515–21.
- Van Damme K, Behets F, Ravelomanana N, et al. Evaluation of azithromycin resistance in *Treponema pallidum* specimens from Madagascar. *Sex Transm Dis* 2009; **36**: 775–76.
- Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med* 2004; **351**: 154–58.
- Stamm LV, Bergen HL. A point mutation associated with bacterial macrolide resistance is present in both 23s rRNA genes of an erythromycin-resistant *Treponema pallidum* clinical isolate. *Antimicrob Agents Chemother* 2000; **44**: 806–07.