VIEWPOINTS

New Treatment Schemes for Yaws: The Path Toward Eradication

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Yaws—an infectious disease caused by *Treponema pallidum* subsp. *pertenue*—is a paradigmatic example of the neglected tropical disease and is reemerging as a public health concern in many countries, causing suffering particularly in children aged <15 years of age in poor rural communities. However, its global eradication, a goal since 1950, may now be closer than ever as a result of the recent expansion and simplification of treatment options to include oral azithromycin. Indeed, the results of a trial published last January [1] allow certain optimism about the treatment and eradication of this ancient disease because a simple single-dose oral treatment targeting whole populations could be sufficient to adequately cure the infection in its early stages and interrupt transmission to others. A new eradication policy around the azithromycin pillar was sketched at a World Health Organization (WHO) consultation meeting held in Morges, Switzerland, in March 2012. It was envisaged that a last global mass campaign in the remaining endemic countries should permit worldwide eradication by 2020 in accordance with the WHO Neglected Tropical Diseases Roadmap [2].

Yaws was one of the first diseases to be targeted for eradication on a global scale. After a WHO-coordinated worldwide control program reduced the number of infections from 50 million in 1952 to 2.5 million in 1964, the disease reemerged in the 1970s when control efforts lagged [3]. According to the most recent estimates reported by the WHO in 1995, >500 000 people, mostly children in poor rural areas, were affected by the disease [4]. Some of the most important endemic foci today are located in Africa (Ghana, Congo, Cameroon) [5], Southeast Asia (Indonesia, Timor-Leste), and the Pacific islands (Papua New Guinea, Solomon Islands, Vanuatu) [6], but figures for the number of people infected are imprecise due to patchy surveying, especially in isolated districts and islands [7].

STANDARD ANTIBIOTIC TREATMENT

The WHO yaws treatment guidelines date to the 1950s, and since then, no alternatives to penicillin for first-line treatment have been introduced. Penicillin was proven to be highly effective against yaws and other treponemal diseases in 1948, and it revolutionized the therapy of these infections. Tests on experimentally infected animals and infected patients showed that benzylpenicillin levels $\geq$0.03 units/mL of serum maintained for at least 7 days were treponemicidal [8]. These levels can be achieved either by giving repeated doses of short-acting benzylpenicillin preparations (ie, aqueous benzylpenicillin) or a single intramuscular injection of slowly absorbed, repository benzylpenicillin preparations such as benzathine benzylpenicillin or penicillin aluminium monostearate [9]. Intramuscular benzathine benzylpenicillin was chosen as the preferred treatment for yaws because of its convenient pharmacokinetics and manufacturing advantages. The WHO guidelines still recommend 1 intramuscular injection of long-acting benzathine benzylpenicillin at a dose of 1.2 MU for adults and 0.6 MU for children [7].

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Although it is generally recognized that treponematoses have remained exquisitely sensitive to penicillin, there are some reports of possible penicillin treatment failures in yaws. In Papua New Guinea, apparent treatment failures were reported in 11 of 39 (28%) cases on Karkar Island [10], and a few penicillin treatment failures have also been observed in Ecuador [11]. It can be difficult to distinguish between reinfection and relapse, and even if penicillin resistance may be a true, albeit rare, event, these clinical failures have had minimal impact on the elimination of the disease in different countries. The development of penicillin resistance often involves the acquisition of new genetic information and a multistep mutational process with a probability of occurrence that is much rarer than those of the single-point mutations that are responsible for macrolide resistance [12].

On the other hand, the large-scale use of benzathine benzylpeniciilin for the eradication of yaws presents several operational obstacles. Experienced medical personnel and the equipment needed to administer intramuscular injections are often lacking in the areas most in need of treatment, and a risk of transmitting bloodborne infections exists if sterile protocols are not followed. Furthermore, benzathine benzylpenicillin requires refrigeration [13], and this is difficult, if not impossible, to achieve in many remote tropical areas [14]. Despite these constraints, efforts to develop new strategies to make eradication easier have been scarce in the last 50 years. In 2007, the International Task Force for Disease Eradication articulated the obvious potential advantages of a single-dose oral drug for yaws and highlighted the need for investigation [15].

REVIEW OF PAST ORAL TREATMENTS

Oral penicillin V for 10 days was used in rural Guyana and successfully cured yaws in individual children and decreased the prevalence in a community [16]; however, such a regimen requiring the administration of multiple oral doses over a number of days has a potential compliance problem and is not suitable as an epidemiological treatment to be employed in eradication campaigns targeting vast areas. There is little information on the use of drugs other than penicillin to treat yaws (see Table 1). Oral tetracycline, doxycycline, or erythromycin for 15 days are also likely to be effective [17–20]. These recommendations, however, are based solely upon known clinical efficacy in small series of patients and not upon the results of any clinical trials. The dosing schedule and duration of tetracyclines and erythromycin again raise the possibility of missed doses and unfinished courses of therapy. Furthermore, the use of tetracyclines in children aged <8 years (in whom many cases of yaws occur) is currently not recommended because of their association with dental staining and interference with bone growth [21].

NEW ORAL TREATMENT

The azalide structure of azithromycin confers a much improved pharmacokinetic profile in comparison with erythromycin. Its unique features—including in vivo activity against *T. pallidum* and high concentrations in tissues relative to serum, resulting in prolonged tissue half-lives—make it an excellent candidate for an oral shortened course therapy for yaws. The oral bioavailability of azithromycin is high (approximately 37%), and tissue concentrations exceed serum concentrations by as much as 100-fold following a single oral dose [22], with high concentrations found in skin and bones, the principal target tissues for yaws. Pharmacokinetic data from clinical studies show that a single 30-mg/kg dose of azithromycin provides drug exposure that is equivalent to at least a 5-day regimen [22]. Both regimens maintain azithromycin

Table 1. Review of Past Oral Treatments and the New Oral Treatment for Yaws

Oral Treatments (Year)	Dosage	Usual Indication of Treatment	Scientific Evidence of Efficacy
Phenoxymethylpenicillin (2003)	7–10 d; 12.5 mg/kg q6h (maximum dose, 300 mg q6h)	Tested for oral delivery in mass campaign	Prevalence of clinical yaws lesions fell from 5.1% to 1.6% 1 year after a treatment campaign in rural Guyana [16]
Tetracyclines (1951)	15 d; tetracycline 500 mg q6h or doxycycline 100 mg q12h	Alternative agents for the treatment of yaws in nonpregnant adults [3]	Efficacy is not well documented. Their use is based upon small series of yaws patients treated with tetracycline derivatives (aureomycin, terramycin, or oxytetracycline) in Africa [17], Haiti [18], and Jamaica [19]
Erythromycin (1963)	15 d; 8–10 mg/kg q6h	Alternative for treating yaws in penicillin-allergic children aged <12 y [3]	Based upon the known clinical efficacy of erythromycin for patients with venereal syphilis [20]
Azithromycin (2012)	Single-dose; 30 mg/kg (maximum dose 2 g)	New first-line oral treatment for yaws	It has been shown to be noninferior to benzathine benzylpenicillin for the treatment of yaws in children in Papua New Guinea [1]

Abbreviations: q6h, every 6 hours; q12h, every 12 hours.

levels in tissue sites of infection above the minimum inhibitory concentration of treponemes for several days after administration has ceased.

In January 2012, an open-label, noninferiority, randomized trial conducted on Lihir Island in Papua New Guinea involving 250 children aged 6 months–15 years with yaws showed that patients treated with oral azithromycin were cured as well as those receiving an intramuscular injection of benzathine benzylpenicillin (96% vs 93%). Oral azithromycin thus met the prespecified criteria for noninferiority. A similar trial is in progress in Ghana, and preliminary observations show results in line with those found in Papua New Guinea (C. Kwakye-Maclean, Ga West Municipal Health Directorate, personal communication). In a review published by Meheus and colleagues in 2010 [23], azithromycin was hinted at as a potential treatment for sporadic cases, but more important, it may represent a suitable tool for deployment in mass treatment campaigns aimed at the global eradication of this disease.

A NEW ERADICATION STRATEGY BASED ON LESSONS LEARNED FROM THE PAST

The biological features of yaws and the diagnostic and treatment tools currently available to combat it make yaws a potentially eradicable disease. First, humans are the sole reservoir, and infection spreads only through close body contact, which would allow some mitigation of the disease incidence simply through public health education. In addition, there are practical diagnostic tools (ie, rapid serological tests) with high sensitivity and specificity to detect levels of infection that can lead to transmission. Finally, the new simple pharmacological intervention based on azithromycin can facilitate mass treatment.

Simply moving from penicillin to azithromycin as a therapeutic tool, however, is unlikely to be sufficient to interrupt transmission of yaws. For each case of yaws detected, there might be 5–10 subclinical cases (seropositive patients without clinical manifestations) [3] that may give rise to infectious relapses for some years. These must also be treated in order to eliminate the reservoir of infection. Problems and systematic failures, which compromised the completion of eradication programs in the 1950s, must be acknowledged and addressed if future campaigns are to be successful [24].

The treatment policies of the 1950s (see Table 2) were based on the prevalence of clinically active yaws in the community, which required purposeful and costly surveys and often focused on the treatment of active cases and contacts. In addition to the logistical problems of administering injectable antibiotics in mass treatment, the imprecise definition of "contacts" [24] and the limitations of the juvenile and selective mass treatment strategies in dealing with latent cases required multiple visits to endemic communities to identify and treat new cases. Most of the active cases found at resurveys were in persons who were in the latent stage originally [25]. This placed a burden upon health services, which were often in areas poorly resourced and under stress in the first place. Understandably, once the prevalence of yaws fell to a low level, active surveillance was discontinued because it was no longer considered cost effective, thus allowing subclinical infections to spread the disease again.

Table 2. Old World Health Organization Treatment Policies for Yaws Based on Benzathine Penicillin (1950s)

Prevalence of Clinically Active Yaws in the Community	Recommended Treatment
High: >10% (hyperendemic)	Benzathine penicillin to the entire population (total mass treatment)
Medium: 5%–10% (mesoendemic)	Treat all active cases, all children aged <15 years and obvious contacts of the infectious cases (juvenile mass treatment)
Low: <5% (hypoendemic)	Treat all active cases and all household and other obvious contacts (selective mass treatment)

The new strategy based on azithromycin, which was outlined at the WHO consultation in Morges in March 2012, aims to be more proactive in order to deal with all potential contacts and latent cases. In view of the ease of administering oral treatment, the new policy employs an initial total community treatment (TCT) in endemic villages or communities, irrespective of the prevalence of yaws (Table 3). Also, to make sure all cases are tracked down and treated, village volunteers (community drug distributors) could play a role in achieving greater coverage (follow-up with missed cases during TCT), and strict follow-up measures, with resurveys/retreatment conducted every 3–6 months, are recommended until 0 case prevalence is reached [26]. By this approach, if the coverage of mass treatment is excellent (>90%) and local health services remain robust and engaged in dealing with cases and contacts in-between services, a few cycles of treatment should interrupt transmission [26].

Once criteria for stopping mass treatment (ie, 0 cases reported) have been met, young children (aged <5 years) should be tested annually for serology. Interruption of transmission in an endemic country would be certified in the absence of any report of the disease for 3 consecutive years and continuous negative serological tests in children aged <5 years, confirming no further exposure to the infection in the community.

Community-based mass administration of azithromycin has been widely used in many locations for the control of trachoma [27], which, like yaws, is a disease common in poor rural communities in developing countries, and has been used in a more limited way to control granuloma inguinale

Table 3. New WHO Yaws Eradication Strategy and Treatment Policies for Yaws Based on Azithromycin (2012)

Component	Recommendations	
Initial assessment	In areas with limited information on yaws: • Review of existing information and/or • Conduct surveys and map clinically and/or serologically endemic villages or communities.	
Treatment policies	First round:	Total community treatment (TCT): Initially treat the entire endemic village or community (recommended treatment coverage of 100%)
	Resurveys and retreatment	3–6 monthly until clinical 0 case prevalence: • Total targeted treatment (TTT); treat all active clinical cases, and their contacts (household, classmates and playmates). • Repeat TCT if coverage in the initial TCT was below 90% or access to the endemic communities is difficult.
Strengthening health and community systems	• Diagnosis and treatment of patients presenting to healthcare (passive case finding) • Also active case finding (eg, by village volunteers) • Tracing and treatment of contacts	
Post-zero case surveillance	• Duration for declaring interruption of transmission: 3 years ▪ Intensive information, education and communication to encourage passive reporting ▪ Immediate investigations of all reported or rumoured cases ▪ Monthly reporting of cases (0 cases should be reported) • Yearly serological surveys in children aged <5 years	

(donovanosis) [28] and outbreaks of venereal syphilis [29]. The use of azithromycin has generally been found to be safe, and there have even been unexpected health benefits reported in some trachoma control programs, such as reduction of all-cause mortality by 50% in children aged 1–5 years in a study in Ethiopia [30] and a significant reduction in prevalence of impetigo and diarrhea among treated children in Nepal [31]. We could find no studies that looked at the impact of trachoma control programs using azithromycin on the incidence of yaws or positive treponemal serology. This may partly reflect the fact that the 2 diseases are most prevalent in different climatic or geographical regions.

Biological evidence that selective pressure can engender resistant strains, as has occurred with the causative agent of syphilis, *T. p. pallidum*, in a number of sexual networks in developed countries, serves as a note of caution about the use of azithromycin. Background macrolide use for unrelated infections (mainly respiratory) is thought to have contributed significantly to the rise of *T. pallidum* strains with increased resistance. Interestingly, clinical treatment failure with macrolides appeared to be uncommon in trials in Uganda [32] and Tanzania [33], and no laboratory evidence of resistance to azithromycin in specimens from 141 patients with syphilitic lesions was found in Madagascar [34]. There is little likelihood therefore that resistance will emerge in resource-poor communities where azithromycin has not been used in the past and where yaws typically occurs [35]. However, the recognition of this possibility dictates that measures be taken to ensure the sustainability of the strategy, including tracking misuse or diversion of the antibiotic for other purposes. Emergence of resistance in *T. p. pertenue* should ideally be prospectively evaluated in the communities where azithromycin is deployed. This will represent a challenge in itself because molecular typing techniques (ie, 23S ribosomal RNA amplification) needed to identify mutations in patients who fail therapy are not readily available in most developing countries. Finally, treatment failure should be monitored, and in cases of treatment failure, patients should be switched to a different antibiotic.

The potential effect of mass treatment with azithromycin on resistance in *Streptococcus pneumoniae* may impact the management of acute respiratory infections in children. This phenomenon has been extensively evaluated after mass treatment campaigns to control trachoma, and the results have been reassuring. Some surveillance studies have demonstrated short-term and not persistent changes in susceptibility patterns in the nasopharyngeal carriage of children [36–38], and the largest surveillance study done to date in a hyperendemic trachoma region did not show an effect of mass treatment with azithromycin on the prevalence of antibiotic-resistant *S. pneumoniae* [39].

PROOF OF PRINCIPLE OF MASS TREATMENT WITH AZITHROMYCIN

A way to secure that the new eradication strategy is both doable and effective is to have a proof of principle that would

provide accurate information for introducing necessary corrective measures. To this end, the WHO is developing standard operating guidelines for pilot studies to assess the impact of mass treatment of yaws using azithromycin in limited geographical areas.

This later phase 3 clinical development should involve larger numbers of patients—including adults, for whom efficacy has not yet been proven—to show convincing, statistically significant evidence of effectiveness in eradicating yaws. The minimum set of essential indicators required for assessing trends in yaws eradication includes clinical signs of the disease, serological prevalence in children, and mass treatment coverage, which are all recommended to be measured in sentinel sites randomly chosen from high endemic areas. Serological prevalence surveys of young children aged <5 years will exclude ongoing transmission (risking that, if tested in the first years, some may have had a period of exposure to transmission). Alternatively, negative nontreponemal tests in those aged <15 years would detect falling serology in treated cases.

COADMINISTRATION WITH OTHER MASS DRUG ADMINISTRATIONS FOR NEGLECTED TROPICAL DISEASES

As a future possibility, national yaws programs may explore synergistic collaboration with other neglected tropical diseases control programs to enhance efficiency and allow better use of limited resources. Available evidence already exists supporting the safety and efficacy of the combination of the commonly used antihelminthic drugs and azithromycin, with no significant pharmacokinetic interactions [40]. However, at this stage, integration of azithromycin for yaws eradication with other Mass Drug Administrations (MDAs) in areas of geographical overlap is not recommended until enough experience has been gathered.

The suitability of coadministering azithromycin with ivermectin and albendazole was evaluated in a crossover study in 18 healthy volunteers. The authors concluded that the magnitude of interactions were minimal (modest increases in ivermectin parameters) and unlikely to be clinically relevant [41]. A further pharmacokinetic model analysis showed that the maximum ivermectin exposures that might be observed during coadministration with azithromycin were below those previously shown to be safe and well tolerated [42]. These analyses called for further pharmacovigilance studies, which are currently in progress.

Regarding the interaction between diethylcarbamazine and azithromycin or other macrolides, there have been no pharmacokinetic studies published so far; however, available information on the kinetics of each drug suggests that interactions may be minimal and have little clinical relevance. Diethylcarbamazine is only minimally metabolized and is eliminated largely unchanged in the urine [43], whereas azithromycin is eliminated to a major extent through the biliary tract and intestinal lumen [44]. Additionally, azithromycin binds little to plasma proteins (7%–52%), making a possible interaction at this level unlikely.

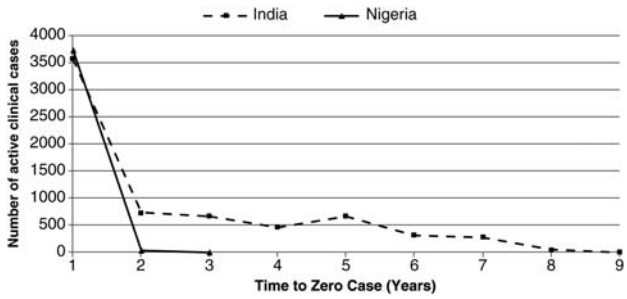

Figure 1. Outcome of yaws elimination programs in India and Nigeria. The India campaign (started 1996) employed the strategy of selective mass treatment with injected penicillin in an at-risk population of 7 million. The campaign in Enugu Ezike, Nigeria (started 1954) employed the strategy of total mass treatment in an at-risk population of 57 000.

Table 4. Assessment of Cost of Treatment for Yaws at a Peripheral Center in Papua New Guinea

	Aged <5 Years		Aged >14 Years	
	Injection Penicillin[a]	Azithromycin	Injection Penicillin[a]	Azithromycin
Drug	0.18 (0.6 MU)[b]	0.27 (500 mg)	0.73 (2.4 MU)	1.10 (2 g)
Water for injection	0.12	…	0.12	…
Syringe and needle	0.30	…	0.30	…
Alcohol swab	0.05	…	0.05	…
TOTAL	0.65	0.27	1.20	1.10

All costs are given in US dollars. Source: Papua New Guinea Medical/Dental Catalogue 2012, Department of Health.

[a] Costs can not be calculated for proper system for disposing needles, time required to prepare and give the injection, pain on the part of the patient, risk of injection abscess, and volume and weight of the drug and all the accompanying materials.

[b] Calculation based on the use of a single drug vial (2.4 MUI) for multiple patients.

THE POSSIBILITY OF GLOBAL ERADICATION

The real prospect of yaws eradication is highlighted by recent experiences in India [45]. Between 1996 and 2003, India undertook a successful campaign employing the conventional strategy of selective treatment with injected penicillin (Figure 1). Since 2004, no infectious cases have been reported. The success in India was clearly due to an excellent and tenacious system for clinical and serological surveillance during and after completion of the program. However, all countries may not have the political commitment and efficient social mobilization of India to deal with only a few yaws cases over a period of 7 years. The high-coverage (95%) treatment of the entire population, as was witnessed in a yaws eradication campaign in Nsukka, Nigeria, in the 1950s, resulted in a fast geometric reduction of prevalence within 6–12 months [26]. An initial TCT, even in low-prevalence-level communities, seems to be the most rapid and economic way to achieve yaws eradication.

Needless to say, issues related to political commitment and costs will be critical. Azithromycin, like benzathine benzylpenicillin, is included in the WHO essential drugs list and is available internationally in generic forms. In Papua New Guinea, for example, there is no drug price regulatory system; therefore price variability across different pharmaceutical suppliers is considerable. However, the costs related to drug acquisition and administration of low-cost generic preparations of azithromycin are highly competitive and may be lower than those of the classic treatment for yaws (see Table 4). On the other hand, given the large number of people to be treated, a donation program would be an essential ingredient of the new eradication effort.

CONCLUSIONS

The strategy for yaws eradication in 1952 called for the screening of patients for clinical disease and their treatment with penicillin. Despite its undisputable success in greatly reducing the number of cases worldwide, the program had 2 glaring deficiencies. First, the strategy had not been validated in pilot studies. Second, for the first 10 years of its history, there was no surveillance, so it was not clear what was actually happening beneath the visible surface [24, 25]. When sample serological surveys were eventually conducted, it was discovered that subclinical infections were far more prevalent than had been recognized. The campaign had largely failed in identifying contacts of those infected and those with latent infections, and surveillance had been discontinued prematurely, allowing subclinical infections to spread the disease again.

Eradication of yaws is now considered biologically feasible, programmatically attainable, and economically affordable. The strategy currently suggested to rid the world of yaws once and forever is total community treatment with oral azithromycin followed by resurveys and repeated total or targeted treatments as required. The new strategy should be validated first in proof-of-principle studies, including appropriate clinical and serological surveys, so we can determine the impact on both clinical and subclinical infections in the treated population, and *T. pertenue* macrolide resistance monitoring should be conducted to ensure sustainability of the strategy. If successful, this strategy will be an effective, logistically feasible, safe, and acceptable protocol for global eradication of this neglected disease.

Notes

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