Yaws eradication - Challenges and key research questions

Michael Marks[1,2], Oriol Mitjà[3,4], Lasse S Vestergaard[5], Allan Pillay[6], Sascha Knauf[7], Cheng-Yen Chen[6], Quique Bassat[3,8], Diana L. Martin[9], David Fegan[10], Fasihah Taleo[11], Jacob Kool[12], Sheila Lukehart[13], Paul M Emerson[14], Anthony W Solomon[1,2,15], Tun Ye[16], Ronald C Ballard[16], David CW Mabey[1, 2], Kingsley B Asiedu[15]

1 Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT

2 Hospital for Tropical Diseases, University College London Hospitals NHS Trust, London, WC1E 6JB

3 ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain4 Lihir Medical Centre, International SOS, Newcrest Mining, Lihir Island, Papua New Guinea

5 Division for Communicable Diseases, Regional Office for the Western Pacific, World Health Organization, Manila, Philippines

6 Molecular Diagnostics & Typing Laboratory, Laboratory Reference & Research Branch , Division of STD Prevention, Centers for Disease Control & Prevention, Atlanta, USA

7 German Primate Center, Leibniz-Institute for Primate Research, Pathology Unit, Working Group Neglected Tropical Diseases, Göttingen, Germany

8 Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique

9 Division of Parasitic Diseases and Malaria, Centers for Disease Control & Prevention, Atlanta, USA

10 Ministry of Health, Port Vila, Vanuatu;

11 World Health Organization Consultant, Springhill, Brisbane, Australia

12 World Health Organization, Vanuatu Country Office, Port Vila, Vanuatu

13 Departments of Medicine and Global Health, University of Washington, USA

14 International Trachoma Initiative, The Task Force for Global Health, Decatur, USA

15 Department of Control of Neglected Tropical Diseases, world Health Organization, Geneva, Switzerland

16 Center for Global Health, Centers for Disease Control & Prevention, Atlanta, USA

ABSTRACT

Yaws is endemic in West Africa, Southeast Asia and the Pacific. The WHO has launched a campaign based on mass treatment with azithromycin, to eradicate yaws by 2020. Progress has been made towards achieving this ambitious goal, including the validation of point-of-care and molecular diagnostic tests and piloting of the strategy in a number of countries. There is a need to address gaps in knowledge to allow refinement of the eradication strategy. Studies exploring determinants of the spatial distribution of yaws are needed to facilitate completion of baseline mapping. The finding that *Haemophilus ducreyi* causes lesions similar to yaws is particularly important and further work is required to assess the impact of azithromycin on these lesions. The integration of diagnostic tests in to different stages of the eradication campaign requires evaluation. Finally studies to inform the optimum mass treatment strategy for sustainably interrupting transmission must be conducted.

KEY WORDS:

Eradication

Yaws

Neglected Tropical Diseases

Treponema pallidum subsp. *pertenue*

Haemophilus ducreyi

Introduction

Yaws, a disease caused by *Treponema pallidum* subsp. *pertenue*[1], is one of the three endemic non-venereal treponemal diseases[2]. It predominantly affects children living in poor, remote communities and results in lesions of the skin, bone and cartilage. Untreated, the disease can progress to cause destructive lesions of bones and cartilage. Previously, yaws was widespread throughout the tropics[3], but a series of control efforts based on mass-treatment, with intra-muscular penicillin, and case finding led by WHO and UNICEF in the 20th century is estimated to have reduced the burden of cases worldwide by up to 95%[4]. Despite these efforts, regional incidence has rebounded in West and Central Africa, the Pacific and South-East Asia, and yaws remains common in some of the poorest countries of the world.

Momentum for a new campaign against yaws was catalysed by the 2012 publication of a study showing that single-dose azithromycin was clinically highly effective and non-inferior to penicillin[5]. The availability of a single-dose, oral, well-tolerated and proven treatment prompted WHO to develop a new strategy based on total community mass treatment (TCT) with azithromycin and case finding and targeted treatment (TTT) to eradicate the disease worldwide by 2020[6].

In the past 3 years, there have been significant developments in the tools available to support the WHO eradication effort. At the same time, key areas of research have been identified to ensure the international community can overcome some of the challenges related to delivering this goal. We briefly review recent major developments and present the priority research questions in the areas of epidemiology, diagnostics and treatment that must be addressed for the successful completion of the eradication campaign.

Epidemiology and Mapping (Box 1)

A major obstacle to interrupting yaws transmission is the paucity of information about where cases still occur. Prior to mid-20th century eradication programmes, 99 countries were reported to be endemic for yaws[3] (Figure 1). Of these countries, two—India and Ecuador—have reported successful elimination of yaws following large, government-sponsored mass treatment programmes[7,8]. Thirteen countries are currently known to be endemic for yaws, with the major documented foci being in the Pacific, West Africa and South-East Asia. For the remaining 84 previously-endemic countries, there is limited information on the epidemiology of yaws. Improving this situation will require a significant increase in the scale and speed of mapping, but improved epidemiological data are vital to inform decisions about the interventions and resources required to successfully undertake eradication efforts.

Development of a successful mapping strategy requires a number of questions to be answered. A key question is: what are the appropriate evaluation and treatment units for yaws? Experience with other disease programmes has shown that village-level surveys are very labour-intensive. Cases of yaws are known to cluster at at both the household and the village level[9,10]. Climatic factors such as rainfall[11] have been proposed to explain this spatial heterogeneity but there are limited data to explain the clustered nature of the disease, a greater understanding of which would help refine strategies for defining evaluation units. It may be necessary to undertake detailed fine-scale mapping in some areas to allow this question to be explored in more detail. The current WHO eradication strategy defines the treatment unit as the endemic village or community[6]. As the eradication programme scales up, it is likely that delivering treatment at the village level will be impractical and treatment, in the first round, at a larger level may be more appropriate (Box 2).

Initial mapping efforts should be focused on the 13 countries known to be currently endemic, to inform local efforts to interrupt transmission (Table 1). Mapping should also be undertaken in the countries which were formerly classified as endemic, but for which there are no current data. Creation of centralised systems for storing and

displaying data could facilitate more standardised approaches to their collection and analysis, as has happened for other diseases such as trachoma, as well as the rapid implementation of public health interventions in regions or countries where yaws is found.

Clinical diagnosis of yaws alone is unlikely to be reliable enough to inform eradication programmes[12,13] and there is therefore a need to develop a strategy integrating robust diagnostics such as point of care serological tests and new molecular tests[14–18] into national health systems. The case definition used and requirements for mapping may differ between the pre-community mass treatment setting (where a less specific methodology may be acceptable), to a post-mass treatment setting (where both high sensitivity and high specificity will be required to confirm eradication) (Box 2).

Finally, efforts should be undertaken to both learn from and integrate with other large scale mapping projects such as the Global Trachoma Mapping Project[19] and the Atlas of Human African Trypanosomiasis[20]. These efforts have trained large numbers of field staff to internationally recognized standards and developed standard platforms for data capture, analysis and sharing. Development of similar tools for mapping yaws should be a priority. Successful integration of yaws and trachoma mapping has already been accomplished in the Solomon Islands and Vanuatu[9] and similar efforts should be considered elsewhere.

Diagnostics (Box 1)

The renewal of the yaws eradication programme has catalyzed advances in diagnostic tools for treponemal infections. The selection of the most appropriate diagnostic algorithm at each stage of the eradication effort will be critical for success of the program. Historically, clinical and serological diagnostics have been used at all stages of programs. To certify elimination, though it is likely that a more refined

approach will be required in the post-MDA environment to ensure that transmission has been interrupted.

Several recent advances in yaws diagnostics may contribute to mapping and confirmation of elimination. A major focus has been on the validation of a new point-of-care assay – the Dual Path Platform (DPP) Syphilis Screen-and-Confirm assay (Chembio Diagnostic Systems, Inc., NY, USA), which is based on simultaneous detection of antibodies to treponemal and non-treponemal antigens. This point-of-care test has now been shown to be accurate for community screening in yaws-endemic communities and for confirmation of clinically suspected cases[16,17]. Replacing central laboratory RPR testing with the DPP assay may improve the implementation of surveillance in both pre- and post-mass treatment settings. Whilst the DPP has demonstrated high sensitivity in strongly sero-positive individuals, the sensitivity is reduced in individuals with low titre serology[17]. It may therefore be necessary to consider strategies such as repeat or confirmatory testing in some settings.

A large-scale surveillance tool would be useful to identify communities requiring focal mapping. To this end, studies are underway to validate serological testing for yaws on a multiplexed platform that could be integrated with other elimination or national health programs[21]. Ideally this would facilitate differentiation of previous from current infection, the latter of which, applied in appropriate age groups, might be taken to indicate on-going transmission[22].

Subspecies-specific molecular tools to accurately identify the presence or absence of *T. pallidum* subsp. *pertenue* and the mutations associated with azithromycin resistance have also become available[14,15,18,23–26]. Recent data showing that lesion exudate samples collected onto filter paper in the field generate reliable results, will help to overcome a major logistical obstacle previously precluding programmatic application of PCR, allowing these techniques to be used even on samples from the most remote communities in which yaws is found[18]. In addition, the development of other DNA-based amplification techniques, such as a loop-mediated isothermal

amplification test, as a simple and rapid screening tool in the filed or at the point-of-care could be useful in low-resource settings where a sophisticated molecular testing may be impractical. The application of molecular diagnostics, genotyping, and microbiome analysis using whole genome sequencing may also allow a more detailed understanding of the biology of pathogens in cutaneous lesions and the epidemiology of yaws that will permit careful assessment of the efficacy of eradication efforts.

Instruments to differentiate cases of treatment failure from individuals who remain seropositive following successful treatment (serofast status) need to be developed. This is particularly important given the increasing recognition that other organisms may be responsible for causing chronic skin ulcers in yaws endemic communities[12,24]. There is no currently available diagnostic test shown to be of value for this role. Detection of treponemal DNA sequences in blood specimens by PCR has been achieved sporadically in cases of early syphilis[27], but not in cases of yaws[28].

Individuals who had been treated for clinical disease yet remain serofast are likely to require pragmatic retreatment, possibly with an alternative agents such as injectable penicillin. Assuming that treatment of these individuals has been successful then such cases will cease to contribute to transmission and the number of clinical cases should decline. As yaws can relapse for up to 5-10 years surveillance will need to be maintained for a prolonged period to confirm that transmission has truly been interrupted. As the number of clinical cases declines the emphasis of surveillance will switch to serological surveillance of children aged 5 or less to detect the presence or absence of newly acquired infections. Use of this measure should avoid the complexity of dealing with serofast individuals.

Laboratory capacity building is required for distribution and deployment of new diagnostic instruments worldwide. Technology transfer efforts and the identification of appropriate regional and national reference laboratories will be extremely important to support national yaws control programmes. Roll out of new techniques

to local laboratories will require the development and implementation of appropriate quality control and assessment structures.

Non-treponemal causes of yaws-like lesions

The differential diagnosis of ulcerative lesions in tropical countries is broad and includes treponemal infections, pyoderma and polymicrobial tropical ulcers. *Haemophilus ducreyi* in particular has now been shown to be an important cause of ulcerative skin lesions clinically similar to yaws, in Papua New Guinea, the Solomon Islands, Vanuatu and Ghana[12,24]. While some clinical phenotypes—particularly bony disease—are likely to be more yaws-specific, the clinical similarity of non-yaws lesions to common skin manifestations of yaws complicates clinical case reporting by national surveillance programmes[13] and highlights the need for the integration of point of care assays into surveillance strategies to confirm suspected cases of yaws.

An additional complication of yaws-like ulcers that should be considered is that these may affect community perceptions of the efficacy of azithromycin mass treatment. Communities may expect mass treatment to be a solution for all skin diseases as opposed to a specific programme targeting a particular pathogen. How best to educate communities about the intended benefits of yaws eradication programmes should be an area of active research and will require input from social scientists and medical anthropologists. Integrating case management for all skin ulcers, regardless of aetiology, into mass treatment programmes should be considered.

Experimental models suggest that azithromycin will also be effective in treating non-genital lesions caused by *H ducreyi*[29], but further studies will be needed to evaluate this in the field. Data from pilot studies of community mass treatment for yaws eradication showed that the absolute number of lesions caused by *H.ducreyi* was also reduced, although not as markedly as those caused by *T.pallidum* ssp. *pertenue*[30]. Consideration should also be given to a syndromic approach to skin ulcer management, integrating basic skin care interventions such as provision of soap and

ulcer dressings alongside azithromycin mass treatment, a strategy likely to have collateral benefits for both community engagement and general skin health.

Treatment (Box 1)

Until 2012, long-acting injectable penicillin had been the mainstay of treatment for yaws[11]. A landmark study conducted in Papua New Guinea showed that single-dose oral azithromycin at a recommended dose of 30mg/kg (max 2g) was equivalent to treatment with penicillin in both primary and secondary yaws[5] with a clinical and serological cure rate of 95% at six months. Treatment with azithromycin is now central to the WHO eradication strategy and should be more readily accepted by children and their guardians than parenteral penicillin[6].

The current WHO eradication strategy is initial total community treatment with single dose oral azithromycin, followed by subsequent resurveys with targeted treatment of residual cases and contacts. As discussed, selection of the appropriate treatment unit will be important to make this strategy both effective and efficient. In earlier campaigns, failure to treat contacts and latent cases was thought to contribute to rapid return of the disease[31]. This risk should theoretically be reduced by the new mass treatment recommendation.

Pilot studies have recently shown that implementation of the Morges strategy results in a reduction of clinical and latent cases of yaws and may potentially interrupt transmission[30]. For syphilis, mass treatment with azithromycin was shown to be temporarily effective in reducing the prevalence of disease in high risk groups[32] however in these studies, syphilis subsequently rebounded, emphasising the importance of follow-up treatment to clear infection from missed cases and interrupt transmission. The number of rounds of mass treatment and the coverage required to interrupt transmission for yaws is unknown. In the successful elimination campaign in India, community surveillance and targeted treatment were performed every 6 months for a period of 7 years[33]. It is unlikely that it will be possible to conduct randomised trials to answer the questions concerning coverage rates and

numbers of rounds of treatment needed to eradicate yaws. Instead, observational data from pilot MDA programmes and mathematical models should be reviewed to frame optimal community treatment strategies.

The recommended dose of azithromycin for patients with yaws is 30mg/kg (max 2g). A major disadvantage of this regimen is the relatively high incidence of associated gastrointestinal adverse effects of around 15%. Azithromycin is also used for a number of other indications, notably trachoma, at a lower recommended dose of 20mg/kg body weight (max 1g). Lower dose azithromycin is likely to be slightly better tolerated than higher dose treatment. Use of a lower dose could confer significant cost savings for programmes, which is particularly important given the absence of a current drug donation programme for yaws eradication, as well as offering synergies for countries in the Pacific region where which yaws and trachoma are co-endemic. As three of the four most heavily endemic countries are in the Pacific, this could be particularly beneficial. However, these potential benefits will need to be carefully balanced against the possibility of the development of drug resistance. A WHO-sponsored trial is planned for 2015, in Papua New Guinea and Ghana, to determine whether a 20mg/kg dose is effective against yaws.

Emergence of macrolide resistance in *T. pallidum* subsp *pertenue*, which has already occurred with *T. pallidum* subsp. *pallidum*, is a major concern[25,34,35]. Macrolide resistance in treponemes is mediated by point mutations in the 23S rRNA gene[23,25,26,36] and is associated with prior exposure to other macrolides[37]. Surveillance for known macrolide resistance mutations in a very limited number of azithromycin-naïve settings has not detected any azithromycin resistant yaws strains; however, close monitoring after mass treatment will be vital to ensure the success of the eradication strategy.

Other Considerations

Currently, human yaws is not known to have an animal reservoir. However, there are a considerable number of pathogenic *T. pallidum* infections in our closest relatives,

non-human primates in Africa[38–42]. Both asymptomatic infection and clinical disease occur in non-human primates. All the currently sequenced simian samples are closely related to human yaws-causing strains[38,43]. Experimental infection of humans with the Fribourg-Blanc simian strain,[44] and reports on laboratory infections of nonhuman primates with human *T. pallidum* isolates[40] suggest that there is a theoretical potential for zoonotic transmission [44]. At this time the relevance of these findings to the yaws eradication campaign remains limited, but further study is warranted.

Whilst the focus of this article has been on yaws, it is also worth remembering the two other endemic treponemal diseases: bejel and pinta[11]. Available data on these two diseases are even more limited than for yaws, but the clinical and microbiological similarities among the diseases suggest that strategies developed for the control of yaws may be applicable more broadly. Such considerations should be borne in mind, in particular when mapping strategies are formulated, so that opportunities to improve our understanding and control of these diseases are also grasped where feasible.

Alongside the research questions discussed in this article there are a large number of areas where input is required to ensure a sustained and effective worldwide eradication campaign. While yaws eradication is likely to be a cost-effective intervention[45], there is a need to secure financial and political support at the national, regional and international levels. Pilot projects have demonstrated the feasibility of the WHO strategy and should encourage donations of both funds and azithromycin. As well as financial support there is a need to engage with advocacy groups and endemic communities to raise the profile of yaws and highlight the possibility of successfully eradicating the disease. Links to other NTD control programmes should be actively sought in order to build synergies at all stages of the eradication campaign. A major burden of yaws is found in West and Central Africa, which has recently been severely affected by the Ebola epidemic. Although this did not predominantly affect countries where yaws is a major problem, the regional disruption on health care services and personnel caused by the epidemic may impact

on yaws eradication efforts. Finally, the eradication campaign must develop strategies to link into the wider public health systems of the affected countries.

Conclusions

Considerable progress has been made in the last three years in developing strategies and tools for yaws eradication. A simple, cheap and well tolerated oral treatment has been demonstrated to be effective, point-of-care diagnostic tests have been validated and new molecular tests have become available. Studies on the epidemiology of yaws and pilot mass treatment programmes have been rolled out in a small number of endemic countries. In addition, there has been increased interest and support within the academic and global health communities for yaws eradication efforts, as reflected in the increase in research output related to yaws. The WHO Morges strategy represents the cornerstone of efforts to eradicate yaws and international efforts should be focused on continuing to roll-out this strategy in the known endemic countries, whilst simultaneously undertaking work to answer the research questions identified. Advocacy will be critical in the upcoming years to transmit to the wider public health community the importance of addressing this neglected disease and to trigger concrete plans for action towards its eradication. The current yaws programme can benefit from the knowledge and experience both of past yaws campaigns and of other international NTD control initiatives. There are considerable opportunities for synergy among disease control efforts to help lead to a sustained improvement in the quality of life for some of the world's most neglected people.

Table 1: Current epidemiology of yaws

	Number of cases of yaws reported					
COUNTRY	2008	2009	2010	2011	2012	2013
Benin	No data	No data	45	No data	11	No data
Côte d'Ivoire	No data	No data	3740	3343	3092	2256
Cameroon	No data	No data	802	133	59	97
Central African Republic	243	No data	No data	No data	230	No data
Congo	No data	646	No data	No data	197	No data
Democratic Republic of the Congo	383	No data	No data	No data	No data	No data
Ghana	20525	35248	18157	9674	8980	18702
Indonesia	6083	7751	6178	6631	4360	2043
Papua New Guinea	28989	25822	29061	28989	17560	19710
Solomon Islands	No data	No data	20635	No data	12372	14909
Timor-Leste*	No data	No data	No data	No data	No data	No data
Togo	No data	No data	15	No data	No data	No data
Vanuatu	1972	2432	1593	2331	2514	1198

Data taken from the WHO Global Observatory Data Repository[46]

* There are no recent routine reporting data from Timor-Leste, but reports from both the Ministry of Health and WHO Country office indicate that the disease is still known to be endemic in the country.

Box-1

Key Research Questions

Epidemiology

E1. What is the appropriate evaluation unit for a pre-mass treatment survey?

E2. What is the population at risk and distribution of cases in the 13 known endemic cases?

E3. What is the current status of the 84 formerly endemic countries?

E4. Which factors affect the spatial heterogeneity of yaws?

Diagnostics

D1. Can the DPP point of care assay replace traditional serology for all phases of the yaws eradication programme?

D2. Can we develop a tool to allow diagnosis of active yaws from a dried blood spot – facilitating integration of mapping activities with other programmes?

D3. What is the appropriate role of PCR in both the implementation and post-zero cases phases of the yaws eradication programme?

Treatment

T1. How many rounds of mass treatment should be undertaken to interrupt transmission?

T2. Is a recommended dose of azithromycin of 20mg/kg non-inferior to a recommended dose of 30mg/kg?

T3. Does resistance to azithromycin emerge in *Treponema pallidum* subsp *pertenue* following mass treatment ?

T4. What is the impact of community mass treatment with azithromycin on other ulcers, including those caused by *Haemophuls ducreyi*?

T5. What are the best approaches to mobilizing and sustaining communities' support for yaws eradication?

Box 2

Key Definitions

Endemic Status

Endemic Village
A village containing at least 1 indigenous confirmed case

Endemic Country
A country with at least 1 indigenous confirmed case

Formerly Endemic Country
A country which formerly reported yaws but which has either eliminated the disease or for which there is no current data

Implementation Unit

Initial Total Community Treatment
The implementation unit will be flexible covering a population of 100,000-250,000 living in a region where there are known endemic villages

Subsequent Treatment Rounds
The implementation unit be at the level of the individual endemic village

Case Definitions

Implementation Phase

Suspected case
Individual with clinical signs consistent with yaws

Confirmed Case
A suspected case with dual positive serology
(either DPP dually-positive or TPHA + RPR positive)

PCR may be used during the implementation phase to monitor for resistance but is not an essential part of the case definition

Post-zero Phase

Confirmed case
Suspected case with both dual positive serology and positive PCR of lesion material for *T.pallidum* subsp. *pertenue*

Search strategy and selection criteria:

We searched pubmed using the terms yaws, pian, treponema pallidum. Reference lists of identified manuscripts were reviewed to identify additional relevant material. We reviewed literature and statistics held at the World Health Organization, and data presented at WHO consultative meetings on Yaws eradication.

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Conflict of Interest

The authors confirm that they have no relevant conflict of interest to declare.

Author Contributions

MM, LSV, OM and KA conceived of the project. MM wrote the first draft of the manuscript and made revisions. LSV, OM, SK, AP, CYC, DLM, TY, QB, JK, FT, DF, SL, PML, AWS, DCWM, RCB and KA reviewed drafts of the manuscript, provided comments, critical review and helped revise the manuscript.

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