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A BRIEF REVIEW ON YAWS

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Abstract:

Yaws, an infectious disease caused by Treponema pallidum ssp. pertenue, is endemic in parts of West Africa, Southeast Asia and the Pacific. The disease frequently affects children who live in poor socioeconomic conditions. A global eradication campaign using injectable benzathine penicillin was carried out by WHO and the United Nations Children's Fund (UNICEF) between 1952 and 1964. Recent developments using a single dose of oral azithromycin have renewed optimism that eradication can be achieved through a comprehensive large-scale treatment strategy. Based on the clinical features Yaws are classified into primary yaws, secondary yaws and tertiary yaws. Due to the antigenic similarity of the yaws and syphilis agents, serological tests for syphilis were used for diagnosis of yaws. The purpose of this review is to increase the awareness of the condition and discuss the new approach amongst the global health community.

Key words: *Yaws, neglected tropical diseases, eradication, Treponema pallidum*

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INTRODUCTION:

Yaws is a neglected non-venereal endemic treponematosis caused by the bacterium Treponema pallidum subspecies pertenue[1]. The term *yaws* is thought to be of Caribbean origin. In the language of the Carib Indian people, *yaya* is the word for "a sore." Alternatively, the disease term yaws may have come from Africa where the word *yaw* may have meant "a berry." Because the lesions of yaws look like berries, the disease is also called *frambesia* (or *frambesia tropica*) from the French *framboise*, meaning "raspberry." Other older names for yaws include *granuloma tropicum*, *polypapilloma tropicum*, and *thymiosis*.

Treponema pallidum pertenue, Treponema pallidum endemicum, and Treponema pallidum carateum are the causative agents of yaws, bejel (or endemic syphilis), and pinta, respectively. Although not fatal, these infections cause painful and sometimes disfiguring lesions of the skin, cartilage, face, soft tissue of the mouth, and bones. In about 10% of chronic untreated cases, permanent disability and associated stigma may result. The endemic treponematoses and sexually transmitted syphilis cannot be distinguished by serological tests and all respond to treatment with injectable benzathine penicillin [2]. In endemic regions, it is known by many names, including *pian* (French); *framboesia* (German, Dutch); *buba* (Spanish); *bouba* (Portuguese)[3].

Presently, yaws is reported from 14 countries spread across three regions of WHO namely Africa, South-East Asia and Western Pacific regions; 21 to 42 million people live in endemic areas[4]. Until, recently, India also reported yaws from some localized areas; in 1996, it reported 3571 cases from 51 districts in 10 states, with nearly 90 percent cases occurring in three states of Odisha, Chattisgarh and Andhra Pradesh[5,6]. Yaws, the most prevalent of these three diseases, is found primarily in poor rural communities in warm, humid, and tropical forest areas of Africa, Asia, Latin America, and the Pacific. Children aged less than 15 years who live in poor socioeconomic conditions constitute the main reservoir of infection; transmission occurs through direct skin contact with the fluid from an infected lesion. Although yaws-like lesions have been found in primates in jungles in Africa, it is unclear if they can transmit the disease to humans[7]. The aim of this article is to provide a better understanding of the historical efforts to achieve yaws eradication.

HISTORY

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[8].

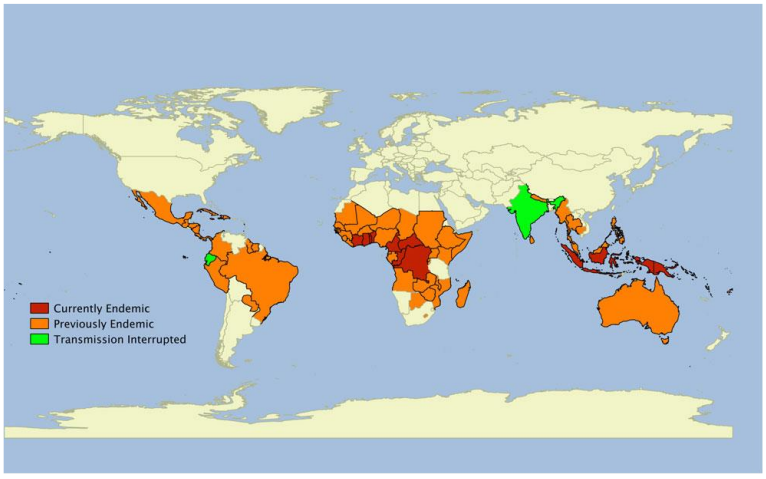

Fig.1: Worldwide distribution of yaws. Data taken from the World Health Organization. Global Health Observatory Data Repository.

WHO organized the first international conference[9] in March 1952, on yaws in Bangkok, Thailand, attended by 70 participants from 23 countries. The objectives of this meeting were to assess the global status of yaws and to share the experiences gained in pilot countries with other endemic countries. In November 1955, WHO convened a second international conference on yaws in Enugu, Nigeria, attended by 53 participants from 30 countries [10]. Africa was chosen as the venue because it was the home to about half of the estimated 50 million yaws cases in the world at that time. The venue in the eastern part of Nigeria was also chosen because of active and successful yaws control activities. The objectives of the conference were to review the progress made and provide guidance to health authorities of the endemic countries. Basic operational principles to guide yaws eradication were established, noting that success would depend on 100% treatment coverage of both active clinical disease and latent infections; anything below 90% was considered inadequate. In

1956, the Pan American Sanitary Bureau, now Pan American Health Organization (PAHO), organized a seminar on the eradication of endemic treponematoses in the Americas at Portau- Prince, Haiti. At this meeting, which was attended by 48 participants, the practicability of yaws eradication was stressed, and a plan for a coordinated implementation in the region was agreed upon [11,12].

EPIDEMIOLOGY

Yaws is found in warm and humid environments [13] and affects mostly children between 2 and 15 years old, who are considered as the reservoir for infections. The disease is spread by direct skin-to-skin, non-sexual, contact often after a cut or abrasion in the lower legs[14]. Presently, yaws is reported from 14 countries spread across three regions of WHO namely Africa, South-East Asia and Western Pacific regions; 21 to 42 million people live in endemic areas. Recently, India also reported yaws from some localized areas; in 1996, it reported 3571 cases from 51 districts in 10 states, with nearly 90 percent cases occurring in three states of Odisha, Chattisgarh and Andhra Pradesh. There are a further 76 countries that previously reported yaws, throughout Africa, the Americas, Asia and the Pacific, for which adequate up-to-date surveillance data are not currently available[15].

ETIOLOY

Yaws is an endemic relapsing treponematosis caused by *Treponema pallidum* subspecies *pertenue* "and is one of 17" neglected tropical diseases affecting primarily young children (<15 years of age) living in tropical regions with an average temperature of 80°F[16-18]. *Treponema pallidum* is a spirochaete that cannot be cultured in vitro. They divide slowly (every 30 h), have a characteristic corkscrew-like motility and can move through gel-like environments such as connective tissue. They are rapidly killed by drying, oxygen exposure or heating, and they cannot survive outside the mammalian host. The four pathogenic treponemes are morphologically and serologically indistinguishable, and share at least 99% DNA sequence homology. Whole-genome sequencing has demonstrated that the genome of *T. p sp.* pertenue differs by only 0.2% from that of T. p ssp. Pallidum, the causative organism of venereal syphilis[19]. The phylogenetic relationship between different subspecies of treponemes is not clear, as very few isolates of the non-venereal subspecies are available[20].

SIGNS AND SYMPTOMS

Based on the clinical features Yaws are classified into-

Primary yaws

The initial lesion of primary yaws is a papule appearing at the site of inoculation after 21 days (range 9–90 days). This 'Mother Yaw' may evolve either into an exudative papilloma, 2–5 cm in size, or degenerate to form a single, crusted, non-tender ulcer (Fig.2). The lower limbs are the commonest site for primary yaws lesions, but other parts of the body may all be affected. Unlike venereal syphilis, genital lesions are extremely uncommon. In untreated individuals, primary lesions may heal spontaneously over a period of 3–6 months, leaving a pigmented scar [21]. Primary lesions may still be present in patients who present with secondary yaws.

Fig. 2 Lesions of primary yaws. A, typical ulcer of primary yaws. B, papilloma of primary yaws .

Secondary yaws

After 1–2 months (sometimes up to 24 months), haematogenous and lymphatic spread of treponemes may result in progression to secondary yaws, which predominantly affects the skin and bones, often with general malaise and lymphadenopathy[22,23]. Alongside the skin, involvement of the bones is one of the cardinal features of secondary yaws. The most common manifestation is osteoperiostitis, involving the fingers (resulting in dactylitis) or long bones (forearm, fibula and tibia) which results in bony swelling and pain (Fig.3).

Tertiary yaws

The destructive lesions of tertiary yaws were previously reported to occur in up to 10% of untreated patients but are now rarely seen. As in other stages of the disease, the skin is most commonly affected. Nodular lesions may occur near joints and ulcerate, causing tissue necrosis. Destructive lesions of the face were one of the most marked manifestations of late-stage yaws.

Fig.3 Bony lesions of secondary yaws.

Diagnosis

Because of the antigenic similarity of the yaws and syphilis agents, serological tests for syphilis are also used for diagnosis of yaws, although these tests cannot diff erentiate the two diseases[24]. For serodiagnosis of active yaws infection, detection of antibodies to both non-treponemal (ie, cardiolipin) and treponemal components is needed. During the initial stage of yaws infection, non-treponemal serological tests for syphilis—such as the rapid plasma region (RPR) test— become reactive, but after treatment they usually show greatly decreased reactivity or become non-reactive. By contrast, treponemal serological tests for syphilis— such as the *T pallidum* haemagglutination assay (TPHA)— generally remain reactive for life, irrespective of treatment, precluding the ability to distinguish between active and past infections. Although RPR reactivity is a better indicator of active infection and the need for treatment, a serum sample is needed for the RPR test, and the test must be done in a clinical setting, which is rarely available in yaws-endemic areas[25].

The DPP point-of-care test detects treponemal (T1) and non-treponemal (T2) antibodies simultaneously, when compared with TPHA, the DPP T1 test had a sensitivity of 88·4% and specificity of 95·2%. By comparison with the RPR test, the DPP T2 test had a sensitivity of 87·9% and specificity of 92·5%. However, sensitivity of the DPP T2 test rose to 94·1% for specimens with higher quantitative RPR titres— ie, 1:8 or higher. Furthermore, the combined results of the DPP T1 and T2 tests had a sensitivity of 93·9%, compared with the combined results of reactive TPHA and high-titre RPR, which together are judged indicative of true yaws infection. The key value of the DPP test resides in the non-treponemal T2 part, which provides rapid and accurate results for field diagnosis of active untreated yaws infection with only finger-stick blood. Moreover, T2 optical density measurements taken before and after treatment (assessed with an automatic reader) fell progressively after treatment, showing a response comparable with that of quantitative RPR titres and, thus, possibly providing a way to monitor the effectiveness of treatment[26,27].

MODE OF TRANSMISSION

Yaws is transmitted by direct (person-to-person) contact with the exudate or serum from infectious yaws lesions. The capability of the treponemae to penetrate through the intact skin is doubtful, and the presence of minor skin lesions, abrasions and even scratches seem to facilitate penetration and infection by the treponemae. Indirect transmission by insects and contaminated utensils (fomites) is generally of limited significance.

TREATMENT

Drug of choice - Inj Benzathine penicillin

Alternate drugs – Tetracycline, Erythromycin

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 >0.03 units/mL of serum maintained for at least 7 days were treponemicidal[28]. 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[29].

Intramuscular benzathine benzylpenicillin was chosen as the preferred treatment for yaws because of its convenient pharmacokinetics and manufacturing advantages. The WHO guidelines still recommend one intramuscular injection of long-acting benzathine benzylpenicillin at a dose of 1.2 MU for adults and 0.6MU for children[30]. 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[31], and a few penicillin treatment failures have also been observed in Ecuador[32].

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[33]. 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[34], and this is difficult, if not impossible, to achieve in many remote tropical areas[35].

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 [36].

Oral treatment method

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 , 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.

Although advances in the treatment and diagnosis of yaws should substantially help eradication efforts, several uncertainties related to the biology and epidemiology of the disease merit consideration, because they could impede eradication[37]. Table 1 shows the drugs used for yaws eradication programme.

Table 1 : Dosages of drugs used in Yaws Eradication Programme

Age	Drug	Dose	Route	Duration
< 10 yrs	Benzathine benzyl penicillin	0.6 million units	IM	Single dose
> 10 yrs	Benzathine benzyl penicillin	1.2 million units	IM	Single dose
< 8 yrs	Erythromycin	30 mg/ Kg body weight in 4 divided doses daily	Oral	15 days
8-15 yrs	Tetracycline or Erythromycin	250 mg four times daily	Oral	15 days
> 15 yrs	Tetracycline or Erythromycin	500 mg four times daily	Oral	15 days
Tetracycline or erythromycin are given to patients allergic to penicillin. Tetracycline is not given to pregnant and lactating mothers and children below 8 years.				

Prognosis

Positive outcomes correlate directly with earlier onset of treatment. Treatment of early lesions with a single dose of penicillin reduces infectivity within 24 hours, with complete healing within two weeks[38]. Skin lesions may require several months to heal. Therefore, a strict follow-up regimen is warranted to detect latent cases and to prevent the late stages and severe soft tissue and bony deficits[39].

ERADICATION EFFORTS

The emergence of azithromycin as an effective, single dose oral agent for the treatment of yaws has led to renewed interest in the disease. In 2012, the WHO outlined a new strategy (the Morges strategy) for yaws eradication. This strategy is based on community mass treatment with single-dose oral azithromycin, with subsequent clinical case detection to direct further rounds of mass or targeted treatment with azithromycin. The WHO is aiming to eradicate the disease by 2020[40]. Both India and Ecuador have reported eliminating yaws since 2000, and their experiences are informative for the current global eradication campaign. Ecuador experienced a large drop in yaws incidence and prevalence following the initial WHO campaigns of the 1950s, but further control efforts were complicated by the anecdotal nature of case reporting. Ecuador instituted a more sustained surveillance programme in the late 1980s, combining continuous village-level monitoring for skin lesions with formal surveys conducted every 5 years that included clinical and serological screening. Individuals identified as having yaws (active or latent) were treated with injectable benzathine penicillin. In surveys conducted between 1988 and 1993, the prevalence of yaws

dropped by over 90%, and in a follow-up survey conducted in 1998, no new cases were been detected. In India, initial eradication efforts were launched in the 1950s, but the disease rebounded in the 1970 and 1980's. In 1996, the government launched a yaws eradication programme[41].

The eradication of yaws will require considerable support from partners across the health and development sectors, and a number of challenges need to be overcome for this effort to be successful. Accurate epidemiological data are lacking from both currently and formerly endemic countries, and a significant investment to improve this situation is urgently needed. The development and validation of near patient and laboratory tests specific for treponemal subspecies are urgently required, in view of the increasing recognition that other bacteria can cause phenotypically indistinguishable skin lesions. Integration of these tools, and monitoring for the emergence of macrolide resistance, will be of critical importance as the programme moves forward.

CONCLUSION:

For more than sixty years, the WHO has sought to exterminate one of the more treatable, neglected tropical diseases. We reviewed published data, surveillance data and data presented at yaws eradication meetings. Azithromycin is now the preferred agent for treating yaws. Point-of-care tests have demonstrated their value in yaws. There is limited data from 76 countries, which previously reported yaws. Different doses of azithromycin are used in community mass treatment for yaws. Yaws eradication appears an achievable goal. The programme will require considerable support from partners across health and development sectors. Studies to complete baseline mapping, integrate diagnostic tests into surveillance and assess the impact of community mass treatment with azithromycin are ongoing.

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