Yaws

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Yaws is an infectious disease caused by *Treponema pallidum pertenue*—a bacterium that closely resembles the causative agent of syphilis—and is spread by skin-to-skin contact in humid tropical regions. Yaws causes disfiguring, and sometimes painful lesions of the skin and bones. As with syphilis, clinical manifestations can be divided into three stages; however, unlike syphilis, mother-to-child transmission does not occur. A major campaign to eradicate yaws in the 1950s and 1960s, by mass treatment of affected communities with longacting, injectable penicillin, reduced the number of cases by 95% worldwide, but yaws has reappeared in recent years in Africa, Asia, and the western Pacific. In 2012, one oral dose of azithromycin was shown to be as effective as intramuscular penicillin in the treatment of the disease, and WHO launched a new initiative to eradicate yaws by 2020.

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Introduction

Yaws is an infectious disease caused by *Treponema pallidum pertenue*. Unlike syphilis, which is caused by the almost identical *Treponema pallidum pallidum*, yaws is not sexually transmitted, but is spread by skin-to-skin contact in warm humid environments, mainly among children. The disease is one of the endemic, non-venereal treponematoses. The other treponematoses are bejel (ie, endemic syphilis), which used to be prevalent in parts of northern Africa, eastern Europe, and the Middle East, and pinta, which is confined to South America. All these diseases affect poor, rural populations.

The term yaws—from either the Carib word for sore or lesion *yaya*, or the African word for berry *yaw*—was in common use by the 17th century, when the Dutch physician Willem Piso provided one of the earliest recorded clinical descriptions of the disease in South America.[1] In his 1679 epistle on venereal disease,[2] Thomas Sydenham clearly described yaws—believed to be common among African slaves—and thought that it was the same disease as syphilis. In 1905, Castellani discovered spirochaetes in the ulcers of patients with yaws in Ceylon.[3] Because the lesions of yaws resemble raspberries, the disease was also known as framboesia tropica, from the French word for raspberry (*framboise*).

Bone changes typical of yaws have been found in skeletons of *Homo erectus* in Kenya dating from 1·6 million years ago.[4,5] Phylogenetic analyses identify the yaws subspecies as the oldest of the treponemal diseases, and suggest that the bejel and syphilis subspecies evolved subsequently.[6,7] This finding supports the so-called unitarian hypothesis put forward by Hudson, who believed that venereal syphilis in Europe arose from yaws, which was introduced into Europe in the 15th century as a result of the slave trade.[8] Strains of *T pallidum pertenue* that are almost indistinguishable from human isolates with molecular analysis have been isolated from wild non-human primates in central Africa, suggesting a possible animal origin of yaws.[9–11] However, the genetic data used to build the phylogenetic tree are scarce because of the few available strains, and some evidence suggests a fairly parallel evolution of the three subspecies.[12] Therefore, conclusions about how old yaws is and where it came from should be made with caution.[13]

Causative agent

T pallidum pertenue belongs to a family of Gram-negative, spiral-shaped bacteria, the Spirochaetaceae, and is closely related to other pathogenic subspecies of *T pallidum*, from which it is morphologically and, up to now, serologically identical.[13] *T pallidum pallidum*, *T pallidum endemicum* (bejel), and *Treponema carateum* (pinta) can be differentiated from *T pallidum pertenue* by the clinical manifestations of their respective diseases and, more recently, by identification of minor genetic differences.[14,15] Most of our knowledge of the ultrastructure, physiology, microbiology, and genetics of *T pallidum pertenue* comes from five strains—CDC-1, CDC-2, Gauthier, Samoa D, and Samoa F, cultured in rabbits[15]— and from preserved non-viable cells from other strains. *T pallidum pertenue* has a length ranging from 10 to 15 µm and a diameter of 0·2 µm, which makes it invisible by light microscopy except under dark-field illumination.[16] The bacterium is surrounded by a cytoplasmic membrane that is enclosed by a loosely associated outer membrane.[17] Although *T pallidum* is thought to have fewer integral outer-membrane proteins than do other bacteria, several proteins have been identified with new methods (eg, cryo electron tomography), and opsonic activity against some of these proteins has been shown.[18,19] Treponemes have characteristic corkscrew motility attributable to endoflagella,[20] and can swim efficiently in gel-like environments—eg, connective tissue.[21] This virulence plays a part in the widespread dissemination of yaws infections and the establishment of chronic disease.[22] *T pallidum* is killed easily by drying, raised temperature,

Search strategy and selection criteria

We searched Medline, Cochrane Library, and WHO databases from Jan 1, 1905, to Sept 1, 2012, in all languages. Many articles were identified through searches of the files of the authors and reference lists from relevant review articles. Search terms were "yaws", "pian", "endemic treponematoses", "Treponema pallidum pertenue", and "eradication". Data from original articles, reviews, and book chapters published in English, French, Spanish, and Portuguese are summarised in this Seminar.

and oxygen exposure. The organism multiplies very slowly (once every 30–33 h),[23] does not survive outside the mammalian host, and cannot be grown in culture.[23] Rabbits and golden hamsters have been the preferred animals for investigation of experimental yaws and antibiotic-resistance testing.[24] Scarce in-vitro susceptibility laboratory data exist for the non-venereal treponematoses.[25] With an in-vitro assay to assess the effect of antibiotics on treponemal protein synthesis,[26] Stamm and colleagues[27] showed that *T pallidum pertenue* was sensitive to penicillin, tetracycline, and erythromycin at concentrations achievable in the serum of patients receiving the drug according to recommended regimens. The same in-vitro system showed insensitivity to streptomycin (up to 500 µg/mL) and rifampicin (up to 100 µg/mL).[28,29]

Genomics: yaws versus syphilis

The *T pallidum pertenue* genome was sequenced in 2010,[15] and was compared with *T pallidum pallidum* strains. The genome size—roughly 1139 kilobases—was much the same, and the gene structure of *T pallidum pertenue* was identical to that of *T pallidum pallidum*. The overall sequence identity between the two genomes was 99·8%, which suggests that the two pathogens are very closely related.[30] Most of the differences between subspecies are localised to six genomic regions, which probably contribute to the observed differences in pathogenicity in human beings, although this hypothesis has not been proven.[15] Regions of sequence divergence could be used for molecular detection and differentiation between syphilis and yaws strains; however, this option is not possible with available diagnostic tests. Several genetic differences between *T pallidum pallidum* and *T pallidum pertenue* have been discovered, including a one base pair difference in the flanking regions of the *tpp15* gene (encoding a lipoprotein),[31] a one nucleotide substitution in the *gpd* gene (encoding a hydrolase enzyme),[32] a base pair deletion in the *tp92* gene (coding for a surface protein),[33] allelic variations in members of the *tpr* gene family (which code for outer-membrane proteins),[14,34] sequence variation in the *arp* gene (for an acidic-rich protein),[35] and sequence variation of the intergenic spacer IGR19 (between the *fliG* and *hlyB* genes).[36] Similarly, Noordhoek and colleagues[37] detected a base pair difference in the *tpF1* gene of the Haiti B strain that was originally identified as *T pallidum pertenue*, but which is now regarded as a *T pallidum pallidum* strain.[31]

Pathogenesis

T pallidum pertenue presumably enters the human host through small breaks in the skin.[38] Treponemes move through epithelial cells via tight junctions and invasively attach to fibronectin-coated surfaces on the extracellular matrix of host cells.[39] In the hamster model, rate of appearance and resolution of cutaneous lesions varies with the size of the inoculum, and the minimum infective dose is about 10^3–10^4 bacteria.[40,41] The organisms appear in lymph nodes within minutes and disseminate widely within hours. The infected lymph nodes increase substantially in weight, and teem with treponemes for several weeks.[41] The skin pathology of yaws is much like that of venereal syphilis; early lesions consist of epidermal hyperplasia and papillomatosis, often with focal spongiosis and intraepidermal collections of neutrophils. However, skin biopsy samples from patients with yaws show many plasma cells in the dermis, but few T and B cells.[42] Vascular changes in yaws are less marked than in syphilis, and are often absent.[43,44] The yaws treponemes are found mostly in extracellular clusters in the upper regions of the epidermis, unlike treponemes in the subspecies *pallidum*, which are located mainly in the dermis and dermal–epidermal junction (figure 1).[17,45]

The host responds to yaws infection with both humoral and cellular immune responses. Phagocytosis of treponemes by macrophages—which is increased by opsonisation with immune serum—plays a key part in this response.[41,46] In a hostile host environment, bacteria

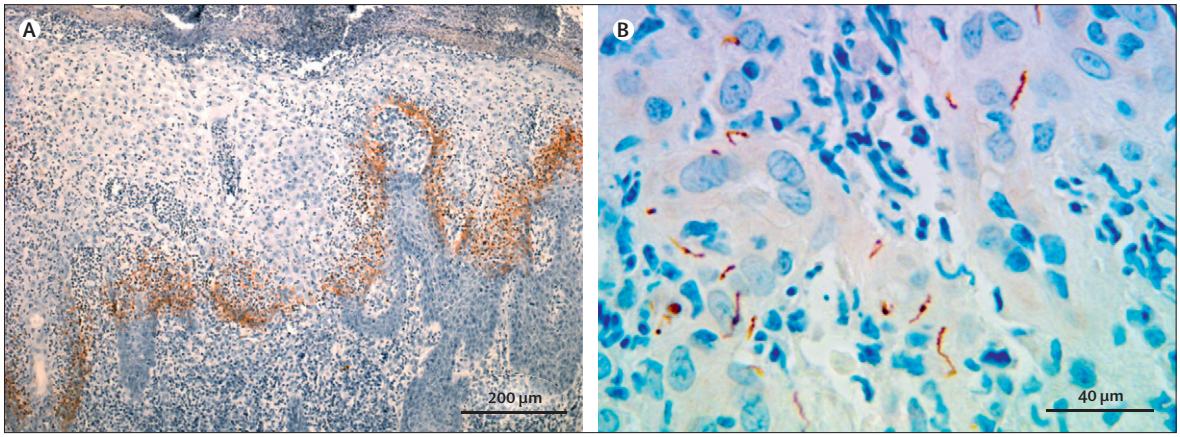

***Figure 1*: Micrographs of tissue specimens from patients with yaws**
(A) Haematoxylin and eosin-stained tissue section (×200) from a yaws lesion with a markedly psoriasiform epidermis. (B) Immunohistochemistry with anti-*Treponema pallidum* antibodies (×1000) shows numerous spiral-shaped organisms in the spinous layer of the epidermis.

can have several survival mechanisms: *T pallidum pertenue* can induce depression of the mitogenic response of normal lymphoid cells,[47] or might stimulate trafficking of T cells out of the peripheral blood circulation (as reported in *T pallidum pallidum*);[48] the organism can exploit its low metabolic rate to maintain infection with very few viable cells, and thereby avoid immune response stimulation during latent disease;[49] and antigenic variation in candidate outer-membrane protein antigenic targets (eg, TprK) could also have a role in immune evasion.[50] In the rabbit model of *T pallidum* infection, untreated animals with latent infection cannot be superinfected with the same strain.[49] The epidemiology of yaws in human beings–in whom new skin lesions are rarely found in adults—suggests that untreated individuals can develop immunity to reinfection, which might be strain-specific. Similarly—as described by Abraham Colles[51] in the 19th century—mothers breastfeeding syphilitic babies do not develop chancres of the nipple, whereas healthy wet nurses who feed syphilitic babies often do.

Epidemiology

Yaws is transmitted by direct skin-to-skin, non-sexual contact with infectious lesions. Because *T pallidum pertenue* is temperature and humidity dependent, yaws is found in warm, moist climates, mainly in forested tropical regions. The incidence of yaws skin lesions is higher in the wet season than in the dry season;[52] high humidity promotes exuberant growth of papillomata and survival of treponemes in serous exudates, which increases infectiousness and transmission. Yaws predominantly affects children; 75% of new cases are in individuals younger than 15 years,[52,53] and children (aged 2–15 years) are the main reservoir of infection. Breach in the skin of the recipient, such as a scratch or an insect bite, can make transmission easier. Indirect mechanical transmission by non-biting flies has been suggested on the basis that *Musca* spp and *Hippelates* spp flies produced an infection in experimental animals after being fed on scrapings from yaws;[54,55] however, no definite experimental or epidemiological evidence in human beings exists. The disease can be clustered in households, but transmission also happens between children in the community, schools, and other public places.[56]

The *pertenue* subspecies has been identified in non-human primates in Africa (17% of a wild gorilla population in Democratic Republic of the Congo carried the subspecies),[57] and studies show that experimental inoculation of human beings with a simian isolate causes yaws-like disease.[9,58] However, no evidence exists of cross-transmission between human beings and primates, or of a resurgence of yaws in countries such as Cambodia, Malaysia, and Vietnam, where contact between people and monkeys is common. The yaws eradication programme by WHO and UNICEF in 46 countries led to a reduction in the number of cases from an estimated 50 million in 1952, to 2·5 million in 1964. In the late 1970s, the disease started to re-emerge, which resulted in a World Health Assembly resolution in 1978 to renew efforts to eradicate the disease.[59] However, renewed control efforts—especially in west Africa in the 1980s—failed after a few years because of insufficient political will and resources.[60] Except for the WHO south Asia region, which kept yaws

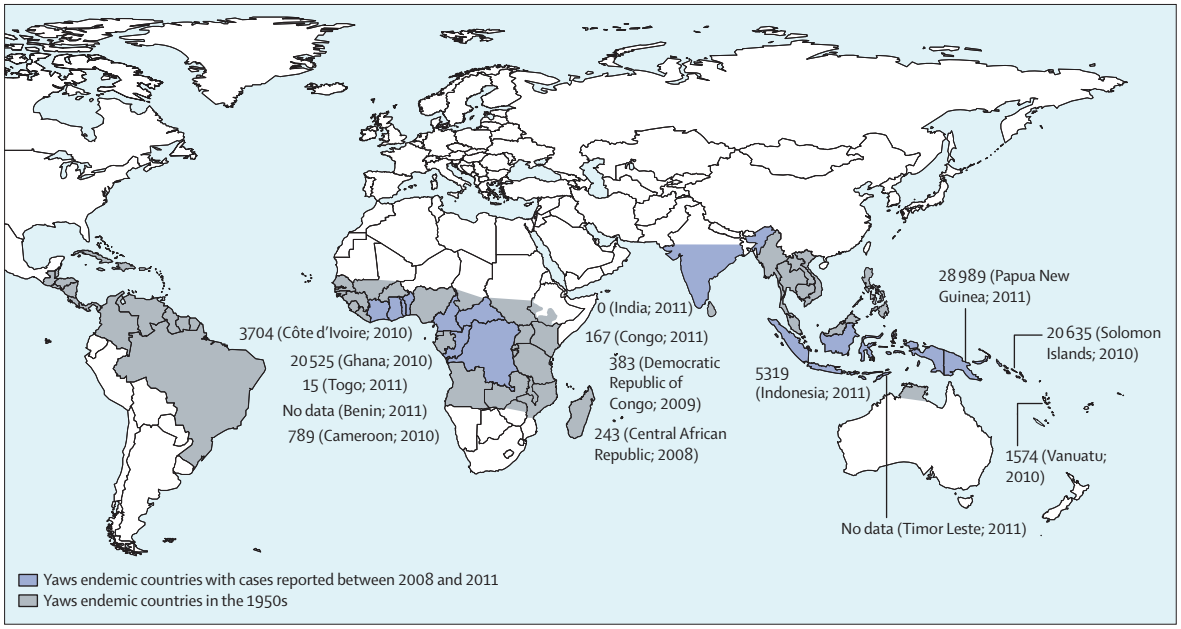

Figure 2: **Global distribution of yaws in the 1950s and countries with recently reported data for yaws, 2008–11**[75]
India interrupted transmission in 2004, and declared elimination of yaws in 2006. Since 2004, no new cases have been reported. In the renewed eradication efforts—in addition to the 14 known endemic countries—the status of the other endemic countries of the 1950s should be established.

on its agenda, yaws was not deemed a priority, and the epidemiological status of yaws worldwide remains uncertain. There is growing evidence that the number of cases in some countries continues to increase.[61–74]

Figure 2 shows the most recent data[75] from routine surveillance in yaws endemic countries compared with the global distribution in 1950.[76] Because the reporting of yaws is not mandatory, these figures suggest only the presence of the disease, and under-reporting is likely. Since no process for certifying countries exits, whether endemic countries of the 1950s have eradicated the disease or are just not reporting is unclear. Yaws remains endemic in communities living in poor, overcrowded, and unhygienic conditions, mainly in remote rural areas of Africa, southeast Asia, and the Pacific. Limitied recent information about yaws in the Americas exists, except for two reports published in 2003; one reported the elimination of yaws in Ecuador,[73] and the other a 5·1% prevalence of active yaws in rural Guyana.[74]

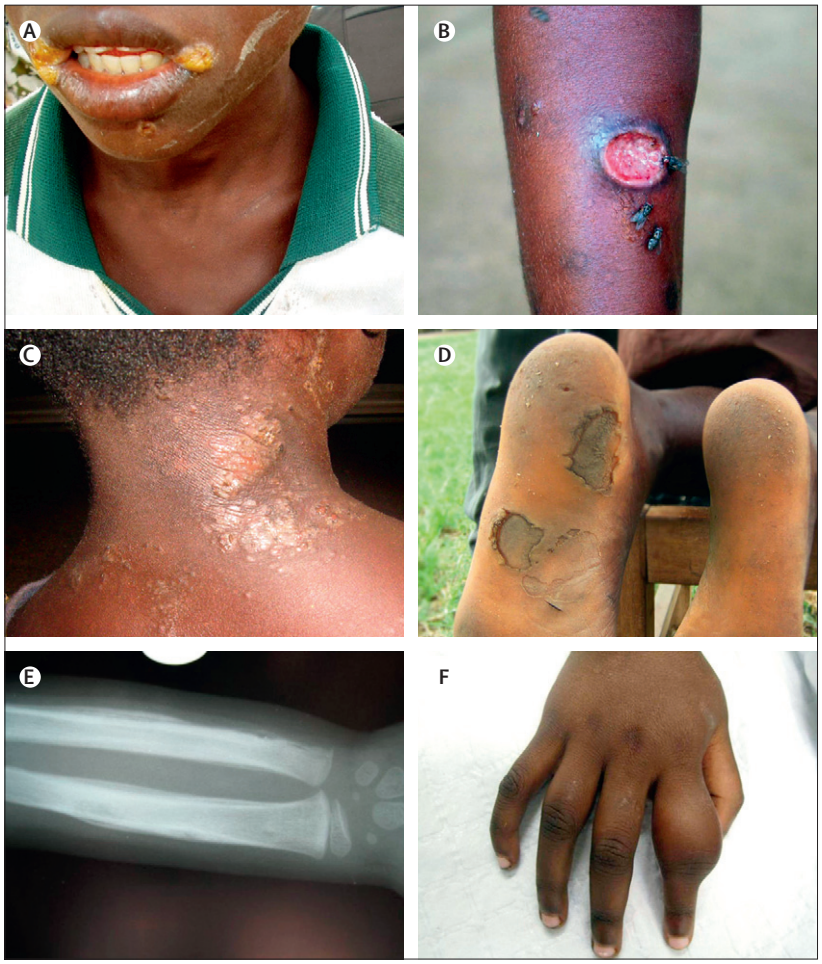

***Figure 3*: Common yaws lesions in 2013**
(A) Papilloma with yellow crust in the peribuccal area of a patient with primary yaws. (B) Early stage ulcer, round in shape with raised margins and a reddish, friable bed. (C) Scaly patches on the skin of a patient with secondary yaws. (D) Cracks and discoloration of the soles of the feet of a patient with secondary yaws. (E) Loss of clarity of the cortex of the distal radius and ulna and organised periosteal reaction (widespread onion layering) in a patient with osteoperiostitis. (F) Fusiform swelling of the second digit of a patient with dactylitis. Copyright for images belongs to Oriol Mitja and Kingsley Asiedu.

Clinical features

As for syphilis, the clinical manifestations of yaws arise in three distinct stages (figure 3). The initial or primary lesion—so-called mother yaw—appears at the site of inoculation on an exposed part of the body.[54,77] The scarce experimental data suggest that the incubation period of yaws could be between 10 and 90 days (mean 21 days).[54] Similar results on the incubation period were reported in a cohort of uninfected individuals with a wound or breach of the skin surface who were continually observed until a primary lesion appeared.[77] The primary lesion is usually a localised papule, which can develop into a large papilloma 2–5 cm in diameter, or a solitary non-tender ulcer with a red, moist base. The primary lesion is most commonly found on the legs and ankles (65–85% of cases),[78,79] but can be on the buttocks, arms, hands, and face. The lesion usually heals after 3–6 months, and regresses into a pitted scar with dark margins;[80] and only a few patients (9–15%) have a primary lesion that persists at the onset of the secondary stage.[77,79]

Secondary lesions result from lymphatic and haematogeneous spread of organisms, and can appear from a few weeks to 2 years after the primary lesion. Arthralgias and malaise are probably the most common, albeit non-specific symptoms of secondary yaws; up to 75% of children younger than 15 years with yaws presented with arthralgia in Papua New Guinea.[79] Secondary skin lesions consist of many smaller excrescences that often resemble the initial papilloma, or scaly lesions that are irregular or discoid in shape. Hyperkeratotic plaques can form on the palms and soles, and fissure into painful secondary infections that cause a characteristic 'crab-like' gait.[81]

In secondary yaws, early osteoperiostitis of the proximal phalanges of the fingers (ie, dactylitis) or of long bones (ie, forearm, tibia, or fibula) might result in nocturnal bone pain and swelling. Early bone changes are usually visible by plain radiography (eg, so-called onion layering periosteal reaction or loss of clarity of the cortex) and periosteal thickening is often palpable.[82,83] Yaws changes the appearance of bones in a highly specific manner; it is a polyostotic disorder—the mean number of affected bones is three—and involvement of the hands and feet is common.[84] All secondary yaws lesions are generally reversible after treatment, subside in weeks to months, and heal with or without scarring. The patient can enter latency at any time, with only serological evidence of the infection remaining, although infectious relapses can happen for up to 5 years and, rarely, 10 years.[85,86]

Unless treated in the early stages, yaws can become a chronic, relapsing, and disfiguring disease and can lead to severe deforming bone lesions in the long term. Although not common nowadays, about 10% of patients develop tertiary stage lesions after 5 years or more of untreated infection.[52] Late-stage skin lesions are charac-

terised by gummatous nodules with massive necrotic tissue destruction, which are followed by debilitating scarring and contracture. Destructive osteitis can result in ulceration of the palate and nasopharynx (ie, gangosa)[87] or bowing of the tibia (ie, sabre shins). Hypertrophic periostitis at periarticular sites can lead to exostosis of the paranasal maxillae (ie, goundou).[88] Unlike syphilis, *T pallidum pertenue* is not known to cause congenital infection, possibly because most new yaws infections occur in children rather than in women of childbearing age. Tertiary yaws is generally believed to not result in cardiovascular or neurological disease.[86] However, analysis of 3645 autopsies in the Gold Coast—now Ghana—between 1921 and 1953 showed that aortitis, identical to that caused by syphilis, was the most common cardiovascular disease identified, whereas congenital syphilis was not seen in autopsies of 259 infants who died in the first week of life. This discovery led the pathologist George Edington[89] to conclude that tertiary yaws can cause cardiovascular disease. Neurological and ophthalmological abnormalities—possibly caused by yaws—have been reported, but no firm evidence of a causal relationship exists.[58,90]

In areas of reduced transmission—caused by climate conditions or after mass treatment—the clinical expression of yaws can be much milder than in areas with high transmission (ie, attenuated yaws).[91] Symptoms can consist of one papilloma or scattered scaly maculae, and many infected people can be asymptomatic.[91–93] A marked reduction in the percentage of late-stage cases with destructive lesions has been noted in recent years.[66] This fall is probably the consequence of more accessible health systems, which results in early diagnosis and widespread use of antibiotics.

Diagnosis

Clinical diagnosis of yaws is generally straightforward in known endemic communities, although the diagnosis of attenuated yaws can be more challenging. Yaws can be confused with several diseases that are common in the tropics—eg, tropical ulcer or cutaneous leishmaniasis in a patient with cutaneous ulcers, scabies or fungal infections in a patient with squamous maculae, and tuberculosis or sickle cell disease in a patient with dactylitis. Health-care workers who are not familiar with the diseases might under-report or over-report yaws unless the diagnosis is confirmed by laboratory techniques.[65] Treponemes can be identified in a wet preparation of the material from early lesions with dark-field microscopy, in biopsy material stained by the silver impregnation technique, or by immunohistochemistry with anti-*T pallidum* antibodies.[86,94,95] However, these methods are impractical and their sensitivity can be severely decreased when the bacterial load is low or viability of the treponemes is reduced by oral antibiotics or topical antiseptics.[96] Because rapid serological tests are available, dark-field microscopy is rarely used to diagnose treponemal infections.[97]

The same serological tests can be used to diagnose both yaws and syphilis. The non-treponemal agglutination tests—rapid plasma reagin and venereal disease research laboratory—are positive in untreated cases, and can be used as a test of cure because they usually revert to negative after successful treatment. Both are simple to do; rapid plasma reagin can be read with the naked eye, whereas the venereal disease research laboratory test needs a microscope. The non-treponemal tests can give rise to false positives in patients with other disorders, including malaria, leprosy, and rheumatological diseases.[98] The tests are often undertaken on serial dilutions of serum, and give a quantitative readout or titre, defined as the highest dilution that gives a positive result. The tests become positive within 2–4 weeks of the appearance of the primary lesion.[99] A negative correlation between the duration of yaws and the titre exists, and non-treponemal tests can even become non-reactive in end-stage disease. Large serological cohort surveys of yaws have shown an association of low non-treponemal titres (<1:32) with secondary stage cases (70–83%), by contrast with primary stage cases (30–49%).[56,99,100]

The treponemal tests (*T pallidum* haemagglutination assay, *T pallidum* particle agglutination assay, and the fluorescent treponemal antibody absorption)[101,102] are more specific, but remain positive for life, even after successful treatment. New, simple, and rapid point-of-care treponemal tests have been developed in recent years in the form of immunochromatographic strips, and are very useful because they can be used with whole blood and do not need refrigeration.[103,104] In 2010, a combined point-of-care test that detects both treponemal and non-treponemal antibodies was assessed for the diagnosis of syphilis, and is promising.[105] In a multi-site study evaluation in China, the performance of the combined rapid test in outreach settings was as good as that in the clinic settings, and the performance was no different between whole blood, serum, and plasma.[106]

The inability to serologically differentiate yaws and syphilis can be an issue in countries where yaws is endemic and the prevalence of syphilis is high, since existing serological tests cannot distinguish between these diseases.[107,108] An important area of research into treponematoses is analysis of the *T pallidum* genome to identify target peptides so that serological tests that can distinguish between the subspecies can be developed. New diagnostic PCR tests to establish whether the organisms in a lesion are truly *T pallidum pertenue* are also in development. Genetic signatures of *T pallidum pertenue* have been identified,[14,31–35] but DNA sequencing to confirm yaws in a patient with active skin lesions has been described only once in a 10-year-old boy from Democratic Republic of the Congo.[36] Real-time PCR is useful to identify *T pallidum pertenue* as the unknown organism, and would be a good test to differentiate between the *T pallidum* subspecies in one assay. However, such methods are expensive, and are unlikely to be available outside reference

laboratories. For routine purposes, the diagnosis of yaws will continue to depend on results of traditional and rapid serological tests and clinical manifestations, while carefully taking into account the epidemiological and demographic characteristics of yaws.[34,109]

Management

Longacting penicillin, given as one intramuscular dose, was shown to be effective in 1948,[110] and has been the mainstay of yaws treatment and eradication efforts for the past 60 years.[111] A single intramuscular dose of 1·2 MU and 0·6 MU of benzathine benzylpenicillin for patients older than 10 years, and younger than 10 years, respectively, is the recommended regimen.[86] Larger doses are recommended in syphilis because venereal treponemes invade tissues that are difficult for penicillin to penetrate.[86] Cure rates for patients with early, active yaws lesions are more than 95%. A few reports of possible penicillin treatment failures in Papua New Guinea and in Ecuador exist,[73,112] but this finding could not be proven microbiologically because *T pallidum* could not be cultured. The distinction between reinfection and true resistance is difficult, but clinical failures do not seem to have had a major effect.[25] Indeed, although three putative penicillin-binding proteins and a lipoprotein with β-lactamase activity have been identified in *T pallidum*, the development of penicillin resistance is unlikely because it would need a multistep mutational process or acquisition of new genetic information.[25]

One oral dose of azithromycin (30 mg/kg; maximum 2 g), which is safe and easy to give, is as effective as intramuscular benzathine benzylpenicillin in the treatment of yaws.[113] In a meta-analysis of antibiotic treatments for trachoma, investigators reported no serious adverse events after one 20 mg/kg dose of azithromycin.[114] In the studies that reported minor side-effects, such as nausea, vomiting, and other gastrointestinal disturbances, incidence ranged between 10% and 15%. WHO revised policies for the treatment of yaws in 2012,[75] specifically responding to the growing evidence of resurgence of yaws and the need to develop new strategies for eradication. On the basis of the trial in Papua New Guinea,[113] azithromycin is now recommended as equivalent to the standard regimen of benzathine benzylpenicillin for yaws treatment, control, and eradication. Little information about the use of drugs other than injectable penicillin and azithromycin to treat yaws exists. Oral tetracycline (500 mg every 6 h; 15 days) or doxycycline (100 mg every 12 h; 15 days) have been used as alternative agents for the treatment of yaws in non-pregnant adults;[115–117] and oral erythromycin (8–10 mg/kg every 6 h; 15 days) for penicillin-allergic children younger than 12 years.[118] The adverse effects and difficult dosing schedules needed for these second-line antibiotics can result in poor compliance and therefore higher rates of treatment failure than in patients given single-dose, supervised treatments.

Alteration of the recommended treatment from a painful injection to single-dose oral treatment has substantial advantages: no trained staff are needed to treat cases in remote areas, infection and anaphylactic shock control measures are not necessary, and treatment is more acceptable to communities who need it.[119] However, potential bacterial resistance because of antibiotic pressure serves as a note of caution.[120] In the USA, patients with syphilis who had received macrolides in the previous year for unrelated infections (mainly respiratory) were roughly twice as likely to have a resistant strain of *T pallidum pallidum*, compared with patients who had not taken macrolides.[121] For *Mycoplasma genitalium*, which has the same resistance mutations as *T pallidum*, Ito and colleagues[122] tested samples before and after treatment and showed that low-dose azithromycin can induce development of resistance. Macrolide-resistant *T pallidum pallidum* has not been found in Uganda,[123] Tanzania,[124] or Madagascar[125]—countries where macrolides are not widely used.[119]

Macrolide resistance in *T pallidum* is associated with changes in the target site because of point mutations at positions Ala2058[126] or Ala2059[127] of the 23S ribosomal RNA gene.[128] Although these mutations have not yet been found in *T pallidum pertenue*,[126] surveillance for treatment failure and biological markers of resistance will be essential if azithromycin is widely used for the eradication of yaws. To address this issue will need an effort along several fronts: misuse or diversion of macrolides for other purposes should be tracked and the correct dose should be given to each eligible individual during eradication campaigns; patients should be monitored for treatment failure and switched to benzathine benzylpenicillin in such cases; molecular analysis should be done in designated reference laboratories to detect mutations in clinical specimens from patients who do not respond to treatment.[120]

Panel 1: **A milestone for India in yaws eradication**

- "In 1887 a coolie woman came from Ceylon with three daughters, the youngest being infected with yaws. The other two girls in turn became infected and were constant visitors to the lines in which cases of yaws were first seen", wrote Arthur Powell who was assigned to British India.[77] Yaws has a history of more than 150 years in India; it was first noticed in tea workers in Assam in the late 19th century.[77] From Assam, yaws spread to the states of Orissa, Chhattisgarh, Madhya Pradesh, and other areas.
- The India Yaws Eradication Programme, which lasted nearly 15 years, began in 1996 and targeted ten states covering 49 districts.[133] Within the first year, the number of yaws cases fell from 3571 in 1996, to 735 in 1997. Scorecards, posters, and other illustrated material were widely distributed among health workers and the general population to help to identify remaining cases. Cash rewards were given to residents who had reported suspected cases that were serologically confirmed.
- A very aggressive campaign including intense serological surveillance, supported by strong political commitment, enabled India to declare yaws as eliminated in September, 2006. Continuing clinical and serological surveillance has identified no new cases since 2004. India's achievement is a great example and a benchmark.

Prognosis and follow-up

Yaws lesions become non-infectious within 24 h of treatment; joint pains usually disappear in 24–48 h, and complete healing of the primary and secondary lesions usually happens within 2–4 weeks after treatment.[113,129] Although treatment in early stages results in cure in almost 100% of patients, it will not reverse destructive changes in the late tertiary stage. An early-stage lesion that has not healed in 4 weeks must be regarded as a treatment failure. In such cases, a serological test to confirm the diagnosis of yaws is important. If the result is negative, an alternative diagnosis should be considered and appropriate treatment given.[130]

Rapid plasma reagin or venereal disease research laboratory titres fall within 6–12 months, and usually become negative in less than 2 years. Seronegativity or a four-fold reduction in serological titre was attained 12 months after treatment in roughly 95% of all cases of larger historical yaws cohorts.[56,99,129,131] However, in some cases, especially if treated in late stages, the rapid plasma reagin or venereal disease research laboratory can remain positive, albeit at low titre (less than 1:8).

Eradication strategy: lessons learnt from the past

The history of disease eradication is closely related to that of yaws. After the founding of WHO in 1948, yaws was the first disease to be targeted for global eradication, on the basis of a previous attempt at elimination in Haiti.[129] Although mass treatment campaigns greatly reduced the number of cases of the disease worldwide, the subsequent complacency led to gradual dismantling of the vertical control programmes, and premature integration of yaws control activities into primary health-care systems that were either weak or non-existent in many of the places where yaws was endemic. Additionally, the resources and commitment for yaws activities disappeared in many regions. A notable exception was India, where a vigorous yaws elimination programme introduced in the 1990s resulted in the elimination of yaws in 2006 (panel 1).[77,132]

The 1950s eradication effort[52] emphasised the importance of subclinical or latent cases as a source of reinfection, caused by the reactivation of infectious skin lesions. The ratio of clinically apparent to latent cases was estimated to be as high as 1:6, and treatment of active cases only had little effect on the prevalence of yaws in the community 1 year after mass treatment.[133] Most of the active cases detected at resurveys were in people originally in the latent stage and who had not received treatment.[134] By contrast, when high-coverage mass treatment is used, transmission can be interrupted in 6–12 months, as was shown in the Nsukka district of Nigeria (table 1).[86,135] In 2007, yaws was included in the list of diseases covered by the WHO Department of Control of Neglected Tropical Diseases.[136] Experts and delegates from endemic countries agreed on a renewed effort to assess the burden of yaws and to restart activities to control the disease. In 2012, WHO issued a roadmap for neglected tropical diseases, with a goal to eradicate yaws worldwide by 2020.[137,138] At its meeting in November 2012, the International Task Force for Disease Eradication endorsed the eradication of yaws.[139] New inexpensive methods are available for these eradication programmes, including a single-dose oral

	Treatment strategy
>10%	Total mass treatment (whole community)
5–10%	Juvenile mass treatment (all prepubertal children and household and other contacts of infectious cases)
<5%	Selective mass treatment (all household and other contacts of infectious cases)

Table 1: **Recommendations for community-based treatment for yaws eradication in the 1950s**[86]

	Recommendations
Initial assessment	In areas with restricted information about yaws: • Review existing information • Undertake surveys and map clinically and serologically endemic villages or communities
Treatment policies	
First round	Total community treatment: • Initially treat the entire endemic village or community (recommended treatment coverage of 100%)
Resurveys and retreatment	3–6 monthly until no clinical cases: • Total targeted treatment; treat all active clinical cases, and their contacts (household, classmates, and playmates) • Repeat total community treatment if coverage in the initial treatment was less than 90% or access to the endemic communities is difficult
Strengthen health and community systems	• Community mobilisation and information about yaws • Diagnosis and treatment of patients who present to health care (passive case finding) • Active case finding (eg, by village volunteers or schoolteacher) • Trace and treat contacts
Post-zero case surveillance	Duration for declaration of 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 (no cases should be reported) • Yearly serological surveys in children younger than 5 years

Table 2: **New WHO yaws eradication strategy and treatment policies for yaws with azithromycin**[75]

Panel 2: **Unanswered research questions**

Epidemiology
- Inadequate epidemiological information about location of cases: what is the best strategy for identification of endemic foci and their mapping?
- Prevalence of asymptomatic infection is poorly documented: how common is asymptomatic infection?

Transmission
- Inadequacy of information to discount the existence of an animal reservoir of yaws in baboons, chimpanzees, and gorillas: is the evidence of yaws in non-human primates epidemiologically relevant for human infection?

Diagnosis
- Serology is unable to differentiate syphilis and yaws: what are the most suitable targets for development of specific serological tests?
- The dual point-of-care syphilis test would result in the ability to screen and confirm the serological status of patients: what is the diagnostic accuracy of new rapid serological combined tests for yaws?

Treatment and prevention
- Azithromycin is effective in children with active yaws in Papua New Guinea and Ghana: is mass administration of oral azithromycin effective in the elimination of yaws in all treated communities?
- Syphilis has rapidly developed resistance to macrolides in developed countries where azithromycin is widely used: what is the risk of macrolide resistance in yaws endemic countries?

Mass administration
- One round of mass drug administration with azithromycin can have a huge effect on yaws but only with very high coverage (>90%): how can high coverage be achieved?
- Movement of populations poses a threat to eradication, with potential reintroduction of clinical and latent cases: how can the effect of population movements be evaluated and mitigated?
- A system for serological surveillance to certify interruption of transmission is needed: what is the best strategy for assessment of effect?
- The difference in recommended dose for trachoma and yaws (20 mg/kg compared with 30 mg/kg) should be researched: what is the effect on yaws of mass drug administration with azithromycin in trachoma control programmes?

Population knowledge and attitudes to yaws
- The knowledge and attitudes of the affected populations towards yaws are important for eradication: what will be the best approach to changing attitudes and sustaining communities' support for yaws eradication?

Social and economic effect of yaws
- Assessment of the social and economic effect of yaws: what are the social and economic effects of yaws on the affected populations?
- The costs of eradication campaigns need to be estimated according to the geographic extent: how much will yaws eradication cost?

treatment and a rapid point-of-care serological test; however, new challenges have arisen in the past 50 years, such as increasing population mobility and gaps in the knowledge of yaws in health-care workers.

Table 2 summarises the key recommendations from a WHO meeting of experts held in Morges, Switzerland, in 2012, for a new yaws eradication strategy.[75] The recommended treatment is one dose of oral azithromycin (30 mg/kg; maximum 2 g) to be given to entire populations in areas known to harbour yaws. Benzathine benzylpenicillin is still important in the treatment and eradication of yaws; it can be used as an alternative in individuals who cannot be treated with azithromycin, or for mass treatment in places where azithromycin is not available. The initial mass treatment will be followed by resurveys every 3–6 months to detect and treat remaining cases. Between the resurveys, the health facilities serving the endemic communities will follow up and treat infected people and their close contacts. The eradication of yaws will be declared when no new active cases are reported over 3 successive years, supported by evidence of no transmission among children younger than 5 years. The aim of the new policy is to ensure a more pragmatic, aggressive approach to the management of cases, contacts, and latent infections, so that transmission can be interrupted quickly and yaws can be eradicated worldwide.[75] The cost of drug acquisition and administration of a low-cost generic preparation of azithromycin is estimated to be US$0·72 per person. With good planning and high coverage, one main mass treatment followed by mop-up treatments is sufficient, so the cost can be kept to a minimum. Past experience suggests that health education and improvement of social conditions can contribute to halting the spread of the endemic treponematoses.[140] Supportive measures for the eradication of yaws are: strengthening of accessibility to primary health care; health education; improvement in the standard of living and in personal hygiene; and provision of soap, water, and clothing to children.[141]

Unanswered questions

To eradicate yaws, some unanswered questions will need to be addressed (panel 2). First, the true geographical extent of the disease needs to be established with careful mapping of populations in whom yaws is known or suspected to be endemic. Remarkably few recent data for the prevalence of pinta and bejel exist, although sporadic cases are still reported.[142,143] Communities in which these infections are endemic are also candidates for eradication campaigns. Second, the effect of mass treatment with azithromycin needs to be established, with careful follow-up of suspected cases of treatment failure to monitor the potential development of macrolide resistance. Strategies will need to be developed to ensure high coverage and to minimise the re-introduction of disease by those missed during the mass treatment and new entrants into the village. Most importantly, free availability and accessibility to azithromycin, funding, and political commitment from endemic countries will be needed. Finally, strong support from the private sector, donors, and research community is essential.

Contributors
OM, KA, and DM did the literature search, and developed, wrote, and revised the Seminar.

Conflicts of interest
We declare that we have no conflicts of interest.

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