Epidemiological study on yaws disease in Umunzim Okoye's family Eziama Ikeduru local government area Imo State Eastern Nigeria.

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Abstract

Yaws is a rare skin disease endemic to tropical countries caused by *Treponema pertenue*. It is highly infectious and spreads through physical contact. It is a poverty-related chronic disease characterized by primary and secondary skin lesions, with latent infection and a chronic stage, which could include a destructive process of bones and joints. Early detection and treatment can avoid gross disfigurement and the associated stigma. Currently, the treatment with a single dose of oral azithromycin has proven effective. This systematic review shows that in the Americas there is a need to update the epidemiological situation of yaws and if needed, to implement and optimize the best public health recommended interventions to interrupt transmission and then verify elimination of transmission. WHO guidelines define the methodology for monitoring and evaluating yaws control programs. Yearly surveys of pre-school children, though logistically complex, are needed in the post-zero case surveillance. Due to its rarity, the disease often goes unrecognised and misdiagnosed. A key determinant for the success of the eradication campaign is good understanding of the disease epidemiology.

Keywords: *Treponema pertenue*, Physical contact, Treatment, Transmission, Azithromycin.

Introduction

Yaws, is a long-forgotten tropical skin infection caused by a highly infectious gram-negative spiral-shaped bacterium known as *Treponema pertenue* [1]. It spreads *via* direct skin-to-skin contact with an infected lesion and is most prevalent in children between the ages of 2 and 15 years old. Boys are reportedly more prone to infection because they are physically active and more likely to acquire abrasions in the lower limbs [2]. Boys are reportedly more prone to infection because they are physically active and more likely to acquire abrasions in the lower limbs. It is also known as a poor man's disease because it mainly affects populations living in the isolated and rural areas of tropical countries, where the climate is warm and humid [3]. Yaws is frequently missed due to healthcare providers' inexperience. It is diagnosed clinically and requires serological confirmation [4]. The fact that it spreads through physical contact makes it highly contagious, especially among family members. Treating patients whilst also administering prophylaxis and contact screening household members is of great importance.

The disease is characterized by an acute phase followed by a chronic, relapsing course in a minority of patients. Clinically, the disease is comprised of distinct stages similar to venereal syphilis with cutaneous findings in early stages, and after a latent period, late yaws may manifest as gummatous nodules, scarring, and destructive bone lesions. Treatment was traditionally benzathine penicillin-G, but as a single dose of azithromycin has been found to equally effective for primary and secondary stages, the latter has become the cornerstone of therapy [5,6].

Treponema pertenue disseminates through the bloodstream and lymphatic system and can lead to extensive ulcerative or papillomatous lesions and progressive damage to cartilage or bone. In eradication campaigns that ran during 1948–1964, over 300 million persons were assessed for yaws and over 50 million were treated with injectable benzathine penicillin, reducing global prevalence by as much as 95% [7]. Despite this achievement, interest in yaws eradication waned and the disease resurged in several countries in Africa, the Pacific, and Southeast Asia by the 1970's. In 2012 the World Health Organization (WHO) relaunched eradication efforts based on total community and targeted treatment with single-dose azithromycin, termed the Morges strategy [8].

Historically, 103 countries have reported cases of yaws, but as of 2018 only continued to report confirmed cases to WHO. It remains unclear whether this reflects true absence of disease or rather inadequate surveillance and loss of disease-specific expertise. A recent modeling study suggested that more than two thirds of countries without recent data would be highly

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unlikely to report yaws without dedicated active surveillance [9]. Furthermore, since the launch of the Morges strategy, the Philippines remains the only country that previously reported cases to subsequently confirm autochthonous transmission. Surveillance activities are challenging because of low population-level prevalence with cases clustered among poor rural populations with low accessibility, although there is a lack of objective data on yaws-endemic communities [10]. Consequently, no standardized approaches exist to efficiently identify cases in areas of unknown burden. One approach proposed by WHO to is to integrate active surveillance for multiple Neglected Tropical Diseases (NTDs) that affect the skin (skin NTDs), including yaws, an approach recently adopted by several countries in West Africa [11].

Data that can be used to identify the burden of yaws in a community include the prevalence of active infectious yaws (*i.e.*, ulcers or papilloma), which shows the intensity of yaws transmission, and the prevalence of latent yaws (*i.e.*, seropositivity in healthy individuals), which shows the extent of latent or hidden infection in the community. Clinical surveys for active yaws lesions can be done without any sophisticated laboratory test through interviews and physical examinations, whereas serological tests measuring yaws antibody (treponemal and non-treponemal) are needed for surveys of latent disease. Another important source of information is national routine surveillance data, which allow estimation of the incidence of yaws at country and regional levels; countries report the number of cases at the first administrative level.

Early detection and treatment can avoid gross disfigurement, which occurs in about 10% of the cases [12]. Nevertheless, yaws remains a cause of disability and associated stigma in much of the developing world, primarily affecting those who reside in tropical regions, in rural and overcrowded communities, living in substandard hygiene conditions, with lack of knowledge of the risk factors for infection, and limited access to healthcare. Diagnosis should include patient examination and laboratory confirmation with a combination of treponemal and non-treponemal serological tests as the serological tests are indispensable for diagnosing latent disease. It is however also necessary to take into consideration the epidemiological context because the serological tests cannot differentiate between yaws and other treponematoses. In 1950 the World Health Organization (WHO) estimated that 50 million people were infected with yaws. A review of historical documents from the 1950's shows that over 85 countries and territories were endemic for this disease. The WHO and the United Nations Children's Fund (UNICEF) provided technical assistance to 46 of these countries between 1952 and 1964, with the consequent drastic decline of yaws prevalence in the endemic areas. Since then, disease control activities were reduced in most countries, and a surveillance phase began, but yaws has not been eradicated [13]. Reporting of yaws to the WHO has not been mandatory since 1990 and therefore the availability of up-to-date data on yaws infection is limited. According to WHO, in the Americas, 26 countries were previously considered endemic, and their current status is unknown, seven countries do not have previous history of yaws, and one country–Ecuador–has claimed the interruption of the transmission but it is still necessary to formally verify this achievement. Treatment with a single dose of oral azithromycin has proven effective and has renewed optimism that eradication can be achieved through a new treatment policy, the socalled Morges Strategy. This should be implemented along with efforts to facilitate access to clean water, improve sanitation, and promote health education within the community. Yaws is targeted for eradication, defined as the complete interruption of transmission (absence of new cases of yaws) globally, by 2020 resolution of the World Health Assembly and by the WHO roadmap on Neglected Tropical Diseases. The Directing Council of the Pan American Health Organization (PAHO) adopted the eradication goal in the resolution and the plan of action for the elimination of neglected infectious diseases and post-elimination actions [14]. WHO details the procedures for verification and certification of interruption of yaws transmission. To guide the process towards successful eradication, a better knowledge of the historical and current epidemiological status of yaws in the Americas is needed.

We will now return to the immunological features which characterise yaws. Flocculating and complement-fixing lipoidal antibodies, as well as fluorescent, and immobilising treponemal antibodies, are produced by the host in response to infection with *Treponema pertenue*, in much the same way as in syphilis and pinta. The same serological tests are uscd (e.g., VDRL, WR, FT A, TPI) in immunological studies. No routinely useful serological test is available to differentiate between yaws and syphilis (or pin ta). No differences have been elicited by the cross-use of *Treponema pertenue* as antigens in the FTA or TPI tests in syphilis or in yaws. It is, however, possible in scientific expcrimentation, to differentiate between these treponemal infections in certain laboratory animals (e.g., the golden hamster).

Aim of study

The aim of this study is to provide a better characterization on YAWS epidemiology.

Objective

- To identify a single case of yaws disease in Umunzim Eziama Ikeduru local government area of Imo State.
- To determine the prevalence case of yaws diseases among individuals of Umunzim Eziama Ikeduru local government area of Imo State.
- To access awareness of people on the severity of yaws (KAP).

Materials and Methods

It is estimated that there were 50 to 150 million cases of active yaws worldwide in the early 1950's. In the 1970's, resurgence was reported in many of the formally endemic areas. Despite efforts to renew the commitment to yaws control and to reengage the international community (e.g., World Health Assembly Resolution 31.58 of 1978 on yaws; global and

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regional meetings in the early 1980's), yaws persisted in many parts of the world, with the largest number of cases found in west and central Africa. Haiti and Jamaica were the two countries with the highest number of papers (14.7% and 12.0%, respectively). Three-quarters of the studies were conducted before 1970. Thirty-three countries reported yaws case count or prevalence data. The largest foci in the history were described in Brazil and Haiti. The most recent cases reported were recorded in eight countries: Suriname, Guyana, Colombia, Haiti, Martinique, Dominica, Trinidad and Tobago, and Brazil. Gaps in information and heterogeneity were detected in the methodologies used and outcome reporting, making cross-national and chronological comparisons difficult [15]. In Ecuador, a survey in the northern region of Esmeraldas documented a prevalence of active yaws of 16.5% (95% CI: 14.9–18.3) in 1988. A continuous long-term community-based surveillance program was therefore put in place focusing on yaws as one of the sentinel diseases. The successful results of this intervention were consistently reported in a second survey in 1993, showing a reduction in the prevalence of clinical cases to 1.4% (95% CI: 0.88–2.3) [16]. This is the second epidemiological study conducted in the Philippines to ascertain the status of yaws and to provide a basis for the type of yaws control and eradication program that the Philippine government will undertake. The first study in 2016–2017 confirmed the presence of active, latent, and past yaws in selected municipalities of the Liguasan Marsh area of Mindanao, within Cotabato, Sultan Kudarat, and Maguindanao provinces [17]. The current study focused on the Luzon and Visayas Island groups and succeeded in confirming the presence of active, latent, and past yaws in the Luzon Island group but not in the Visayas Island group. This is also the first report of confirmed yaws cases outside the Mindanao Island group and among indigenous people in Luzon. The total number yaws cases reported after 1973 is at least 250, including the new cases detected in the current study. In Ecuador no yaws cases were identified between 1993 and 1998; therefore, the disease is also regarded as being eliminated. The current study confirmed the presence of yaws in the Luzon Island group in one study site with indigenous people, the Aetas. When tinea imbricata cases were reported by the RHU physician in August 2019 and a skin outreach mission was conducted by this investigator (BLD), it was the first opportunity to confirm tinea imbricata and to screen the Aetas for possible yaws. Three yaws cases (one latent, two past yaws) also had tinea imbricata. The RHU physician performed the serologic confirmation of *T. pallidum* antibodies and nontreponemal antibodies using the DPP test kits in October 2019, after which the investigators began the process of securing permission from NCIP for the yaws case detection study to be conducted among the Aetas [18]. In Guyana, following the implementation of a control program in 2000, a resurvey conducted the following year showed a drop in prevalence of yaws skin lesions from precampaign 5.1% (95% CI: 3.9–6.6) to postcampaign 1.6% (95% CI: 0.08–0.3). In Cook Islands, 99% of the population were screened in 1960, and in Vanuatu, an initial mass treatment survey conducted in 1958 covered 94% of the indigenous population [19]. The results of these surveys were also utilized to determine appropriate control methods. In most cases, further surveys were conducted to identify and treat previously untreated cases and their contacts. Geizer reported that only 6 cases were found in Niue in 1957, while the disease was widely spread earlier. According to Geizer, only 3 cases were diagnosed between 1964 and 1984 in Fiji, the last one being in 1983, while initial surveys conducted in 1954 found 10% to 70% prevalence of reactive serology. In Tonga, the last 7 cases were reported in 1976 while 7,452 cases were reported in 1962 when the eradication campaign was launched. Several authors reported that yaws control activities were then gradually integrated with other communicable disease programs into basic health services without providing further details. In 1985, Meheus and Hopkins discussed integration of yaws control activities into Primary Health Care (PHC) interventions [20,21]. In the South Pacific, records show that yaws was highly prevalent prior to mass treatment campaigns carried out in the late 1950's and early 1960's. Following mass treatment campaigns, the number of reported cases dramatically declined, and yaws was considered eliminated in most areas of the South Pacific. Since the late 1970's, however, suspected cases of yaws were reported in various areas of Papua New Guinea the Solomon Islands and Vanuatu. While available records suggest that these countries remain endemic to this date, the extend of the current burden due to yaws is not well known. In 1998, following a study in 39 children with clinical yaws in Karkar Island, reported that while initial clinical and serologic responses to benzathine penicillin were satisfactory in more than 90% of the children, 11 (28%) later showed clinical and/or serologic evidence of relapse or reinfection. These authors concluded in favor of treatment failures due to reduced susceptibility to penicillin because reinfection was unlikely in this particular community and under the circumstances of the study. To our knowledge, this possible reduction in susceptibility or tolerance to benzathine penicillin of *Treponema pallidum* subsp. pertenue has not been further documented, and additional data to support the finding could not be found in the South Pacific. In most cases, diagnosis was based on clinical criteria during the 1950's and 1960's. With the disappearance of yaws in a number of countries and the progressive retirement of those who were involved in the eradication campaigns in the 1950's and 1960's, some authors suggested that most health workers have never seen the disease and may not be able to make a clinical diagnosis.

A nationwide mass treatment targeting the entire population of PNG took place between 1953 and 1958 under the Australian administration covering more than 90% of the population. Many of the untreated individuals were residents of remote and isolated areas of the country where campaign reach was limited. The campaign was successful; only 2,352 cases were reported in 1959, and fewer than 500 cases were reported each year until 1973. A slight increase in the number of cases was recorded between 1973 and 1978. However, it did not exceed 1,000 cases per year, and most of them occurred in rural areas, in Bougainville, and around Rabaul in New Britain. The disease was rare in the Highland districts and reported to be nonexistent in the Central Province and Port Moresby.

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Consequently, yaws was removed from the national list of reportable diseases. The clinical appearance of yaws observed during this time period was milder (fewer lesions, plantar lesions, and bone involvement rarely observed) than in the 1950's, and these milder cases were described as attenuated cases. In 1964-65, a serological survey for treponemal disease involving 844 sera was conducted in the Eastern Highlands of PNG. No clinical case of active yaws was found in the population, but some of the elderly were identified with clinical evidence of old yaws lesions. The seroprevalence reported by the authors varies from 3.9% to 79.2%. In 3 out of the 10 census units surveyed, the prevalence in children below 15 years ranged from 14.3% to 40%, and the authors concluded that the treponemal disease involved was yaws. In 1988, another outbreak was reported on Karkar Island in the village of Takia. Among 632 children aged 0 to 15 years, 39 (6%) presented early lesions. All villagers were subsequently treated with benzathine penicillin. Blood samples were repeatedly collected from the clinical cases over 22 months following the initial treatment, and the authors found that 13% of the cases remained or became serologically positive again at 22 months despite the fact that many of the initial cases were treated multiple times. Clinical relapse among the initial clinical cases was reported to be 8% at 22 months. This incidence suggested that yaws cases in this area had decreased sensitivity to penicillin. However, the finding needs to be confirmed. Between April 2000 and September 2001, the Nine Mile Clinic in Port Moresby identified 494 cases confirmed by serological tests (TPHA and VDRL) through clinic-based case detection. The clinic serves approximately 20,000 individuals in the periurban population of northeast Port Moresby, where many live in squatter settlements with poor access to water and electricity. Yaws cases were seen at the clinic as early as 1995, and a yaws register was created in April 2000 after an increase in numbers was observed in 1999. The clinic also conducted a prevalence survey in 2001 at settlements near the clinic where prevalence was expected to be high. Among 227 children under the age of 17 examined, 33 had active yaws lesions as diagnosed by experienced medical staff. It is not clear whether these cases were later treated. Yaws cases had been rare in Port Moresby, and thus, this finding suggests that the cases observed at the clinic may have contracted yaws outside Port Moresby or from persons with yaws who migrated from other parts of the country. The population in Port Moresby is young and rapidly growing with a continuous migration of people throughout the country. With poor hygiene, crowded environments, and a large number of people previously unexposed to yaws, the population provides an ideal environment for yaws transmission.

A nationwide mass treatment campaign was carried out in the British Solomon Islands Protectorate between 1956 and 1958, covering all main islands and most of the other inhabited islands. An initial survey prior to the treatment campaign found the prevalence of active yaws cases above 14.5%. The campaign was successful, and only a few cases were reported (from Malaita) following the campaign. The national yaws elimination project was then completed in 1963. A small number of cases were sporadically reported until 1970.

No cases were documented from 1970 until 1981 when an outbreak of cases was reported in the Western Province. The cases were initially misdiagnosed as tropical ulcers until suspected cases presenting large leg ulcers were serologically confirmed as yaws in 1984 (serology done in Australia). Following the confirmation, a mass treatment of the entire population was carried out in the islands of Gizo, Vella la Vella, Ranonga, Simbo, New Georgia, Kolombangara, and North Choiseul. By the end of the campaign, 3,994 out of 29,235 persons examined (13.7%) were found to have active yaws. The disease was more prevalent among children under the age of 15; 28% of children under 15 examined were diagnosed to have yaws. Yaws was diagnosed clinically in the field by medical staff involved in the previous mass campaign in the 1950's. Follow-up visits in selected villages did not find any additional cases. A higher prevalence was reported in the islands of Vella la Vella, Ranonga, and Simbo. No case had been reported in the Shorthand Islands, despite its proximity to PNG.

In 1981 and 1985, mass treatments were carried out in several villages in Northwestern Tanna where clinical cases had been reported. Despite these efforts, yaws continued to reappear in Tanna, and a large-scale treatment campaign was planned in 1989. A survey conducted prior to the mass treatment found 116 (16.5%) clinically suspected cases out of 704 treatment participants in 13 villages and 1 school in Tanna. Among the 97 clinically suspected cases, 34 showed VDRL titer above 1: 4. Based on this finding, the mass treatment was planned to cover the entire population of Tanna, about 20,700 people. Approximately 90% of the population were treated, although children under the age of 3 months were excluded from examination and treatment. During the mass treatment, 348 clinically suspected cases were recorded. A large proportion of clinical cases (79.3%) were under the age of 15, and 32% of blood samples from 189 suspected cases had positive VDRL results. Following the campaign, only a few cases were reported in 1990. However, by 1992, a number of cases were reported from villages that previously had not participated in the treatment campaign. The laboratory reports between 1995 and 1998 also indicated that yaws was still not eliminated from the island.

In Australia, the most recent information we found is from Garner, who reported in 1972 results from a serological survey in the aboriginal population of the Northern Territory. They concluded that while no case of active treponemal infection was found, the prevalence of treponemal infection varied from 3.4% to 58% indicating that yaws, endemic syphilis, and probably venereal syphilis were present in the aboriginal population.

Furthermore, yaws-like infections have been identified in nonhuman primates in Africa, in particular in the Republic of Congo where 17% of a wild gorilla population have been found with typical yaw lesions, leading the authors to speculate that yaws infections in gorillas and humans living in tropical rain forests might be due to the same bacterium *Treponema pertenue*. Considering that in humans and gorillas *T. pertenue* spreads by direct contact with infected lesions and that flies

also play a role in transmission of the bacterium, a risk of contamination between humans and other primates might exist. These findings argue in favor of a potential role of yaws-infected nonhuman primates in humans' infections. However, there is no evidence of such transmission in the literature, and the actual significance of these findings to human is not known. Surveys carried out in Ghana in 2008 showed a national clinical prevalence of yaws lesions at 0.68%; however, prevalence in some rural communities was as high as 20%. In 2012, a survey to determine the current prevalence of yaws lesions in the Lomié health district showed that yaws remains highly endemic among Baka indigenous populations as well as Bantu communities, with a prevalence rate of yaws lesions of 9% (95% CI: 7.5–10.9). Coldiron, et al. conducted a screening and treatment program in two districts of Likouala region (Bétou and Enyellé) in 2013. The program reached some 6,000 children and identified 485 clinical cases with yaws-like ulcers. 183 subjects had confirmed reactive serology, representing a 2.9% (95% CI: 2.6–3.4) prevalence of clinical yaws. Touré, et al. had reported that active yaws prevalence in Côte d'Ivoire was 0.5% (95% CI: 0.28–0.90) in 2007 based on available hospital statistics and a cross section investigation. A yaws outbreak was reported in Northeastern Nigeria in 1998 by Akogun, despite the official position that yaws had been eradicated in Nigeria. A more recent study by Nnoruka, however, failed to identify any yaws-affected individuals among 2,871 consecutive patients at the dermatology clinic of the University of Nigeria in Enugu (approximately 500 miles from the more rural area of Garkida, where Akogun conducted his research). In this study, however, most of the patients were adults, diagnosis was based on the patient's history and physical examination, and no tests to specifically identify treponemes or treponemal infection were performed.

Table 1. *Countries with available information on yaws 2008-2012.*

Country	Number of cases		Prevalence of yaws lesions in cross-sectional surveys		
	Year of report	Number	Year of survey	Sample size/district	Prevalence, % (95% CI)
Africa					
Benin	2012	11	2013	900 (Toffo, Ze, Allada)	1.1 (0.8–1.3)
Cameroon	2012	16	2012	1,075 (Lomie)	9 (7.5–10.9)
Central African Republic	2012	230	2012	2,030 (Lobaye)	11.3 (10.2–12.8)
Republic of the Congo	2012	197	2013	6,215 (Bétou, Enyelle)	2.9 (2.6–3.4)
Côte d'Ivoire	2012	2,864	2007	2,182	0.5 (0.28–0.90)
Democratic Republic of the Congo	2008	383	2012	1,176 (Wasolo)	4.7 (3.7–6.1)
Ghana	2012	9,356	2008	ND	0.68 (NA)
Togo	2012	5	1994	ND	0.23 (NA)
South East Asia					
Indonesia	2012	3,476	1991	37,000 (Sumatra)	0.31 (0.26–0.37)
Timor Leste	NA	ND	2010	1,535 (Oe-cusse)	0.39 (0.18–0.85)
Pacific					
Papua New Guinea	2012	17,560	2001	227 (Port Moresby)	14.5 (10.5–19.7)
Solomon Islands	2012	12,372	2007	ND	0.4 (NA)
Vanuatu	2012	1,718	1989	20,200 (Tanna)	2.3 (2.1–2.5)

Note: CI: Confidence Interval; NA: Not Applicable; ND: No Data.

Etiology

The genus of *Treponema* includes several uncultivable spirochete pathogens notably including but not limited to *T. pallidum*, the causative agent of syphilis, *Treponema endemicum*, the causative agent of bejel, related *Treponema carateum*, the causative agent of pinta, and *Treponema pertenue*, the causative agent of yaws. The first genome mapping off *T. pallidum* in 1998 led to the further genomic sequencing of twelve treponemal pathogens and this notably revealed minimal variability between sub-species. Despite this *T. pertenue* and its associated disease, yaws presents with a distinct history and clinical features. Unlike syphilis, yaws is neither sexually transmitted nor transmitted from mother to baby. Disease is most commonly seen in children and is transmitted from skin to skin contact. In 1954 the WHO and

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the United Nations Children's Fund put forth a dramatic effort to address yaws in endemic areas. Over the next 20 years, the annual incidence fell from 140.85 to 1.25 per 100,000. As the disease continues to decline and efforts to treat all cases reported is hoped disease can be eradicated.

Epidemiology

Yaws is found in tropical regions with warm and humid environments. The disease mostly affects children between the age of 2 to 15 who also serve as reservoirs for the spirochete. Infection is spread by direct skin to skin contact, and there has been a consideration for fly vectors although the latter is unproven. And though primate species also carry treponemal infections closely related no evidence of zoonotic transmission exists.

Treponema pertenue is found to cause disease in Africa, Asia, and the South Pacific. Between 2008 and 2012 over 300,000 cases were reported to the WHO endemic countries exist and include Benin, Cameroon, Central African Republic, Republic of the Congo, Cote d'Ivoire, the Democratic Republic of the Congo, Ghana, Togo, Indonesia, Papua New Guinea, Solomon Islands, and Vanuatu. Two countries that used to harbor disease now boast eradication and those are India and Ecuador. These reports and other systematic reviews evaluating epidemiology show slight progress since 1992, but now notably the vast majority, up to 84% of all cases, are from only 3 countries: Papua New Guinea, Solomon Islands, and Ghana.

There have been suggestions that flies may act as a vector for yaws but there is no definitive proof that this occurs. Treponemal infections closely related to yaws and syphilis have been identified in primates, but there is no evidence to suggest that zoonotic transmission between humans and non-human primates occurs. Children born to mothers affected with yaws are generally unaffected, and most evidence seems to indicate that the disease is not acquired congenitally. The early lesions of yaws are most infectious. It is estimated that patients are infectious for up to 12–18 months following primary infection but relapsing disease can extend this period. The destructive lesions of late yaws are not infectious. In studies in both Papua New Guinea and the Solomon Islands, endemicity at the village level has been identified as the major risk factor for infection and re-infection following treatment. The disease primarily affects rural communities with low standards of hygiene, with incidence declining as social and economic status rise. In the mid-20th century, yaws was reported to affect ~50 million individuals and to be endemic in at least 90 countries in South America, the Caribbean, Africa, Asia and the Pacific. The WHO launched a major eradication effort in the 1950's based on mass screening and treatment with injectable penicillin. The campaign examined some 300 million individuals of whom 50 million were treated. Although yaws was not eradicated, by the end of the major campaign in 1964, the burden of yaws had been significantly reduced to ~2.5 million cases. Following this initial success of the WHO campaign, yaws dropped down the public health agenda internationally and domestically in many countries. In the 1970's and 1980's, there was a resurgence of cases in some countries in West and Central Africa. This led to a renewal of control efforts, which again reduced the burden of the disease but did not eradicate it. Over the past 20 years, there has been a further resurgence of yaws in previously endemic countries, and the disease is now thought to be endemic in at least 12 countries in West Africa, Southeast Asia and the Pacific. 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. Most yaws cases are concentrated in just three countries: Ghana, Papua New Guinea and the Solomon Islands have each reported >15,000 cases annually within the last 3 years. In another eight countries, transmission occurs in focal communities. Despite being deprioritized in international health fora, both India and Ecuador have reported eliminating yaws in recent years with prolonged campaigns based on case identification.

Pathogenesis

Treponema pallidum subspecies *Pertenue* is transmitted intradermally between humans by the transmission of puss through an open lesion. The puss contains treponemes, which enter the host through open abrasions of the skin or mucous membrane. Treponemes move through epithelial cells *via* the tight junctions between cells and invasively attach to fibronectin-coated surfaces on the extracellular matrix of host cells. Attachment to the fibronectin causes increased synthesis of fibroblasts in the cell. Antibodies in the circulating blood attach to antigens on the treponemes and ignite an inflammatory immune response that increases the swelling of the lesions.

Low concentration of antigen epitopes expressed on the cell surface of *T. pertenue* is the predicted cause of the pathogenesis of the bacteria because the limited amount of surface antigens decreases the likelihood of a host cell antibody recognizing the antigen. One-dimensional Radioimmunoprecipitation (RIP) confirmed that subspecies pertenue had a decreased amount of proteins expressed on the cell surface compared to subspecies *Pallidum*.

The antigen that is thought to be immunodominant in *T. pertenue* is the 47-kDa antigen, which is present in all *T. pallidum* subspecies. Monoclonal antibodies 11E3 and 13C6 react with this antigen on the bacterial cell surface in the immune response against the bacteria. In comparison study between *T. pallidum* and *T. pertenue*, a binding assay and electron microscopy study were done and showed that the antigen was abundant on the cell surface of *T. pallidum* but had reduced presence on the surface of *T. pertenue*. This study indicated that the reduced presence of the 47-kDa antigen allowed for greater pathogenesis of the cell by reducing its ability to be recognized by host antibodies.

The contrast in the presence of the Immunoglobin M (IgM) and Immunoglobin G (IgG) antibodies in the immune system of neonate and adult guinea pigs indicates a greater risk of infection in children, which validates the prevalence of yaws in children under 15. In a study, adult guinea pigs expressed five

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times the amount of antibodies after exposure to *T. pertenue* compared to neonates. Additionally, the presence of antibodies was greatest in adults three to six weeks after infection, while neonates did not reach their peak presence until six to nine weeks after exposure.

While the limited presence of antigens aids the pathogenesis of the bacteria, the limited surface proteins also inhibit it. Specifically, the surface proteins P1 and P3, which are fibronectin-binding proteins, are very limited in presence on the cell surface. The absence of these proteins limits the number of host cells that the bacteria can bind to, therefore limiting the exposure of bacteria to the host cells. Fibronectin-binding surface proteins P2, P4, and P5 are not limited in their presence on the cell surface, however, which increases the pathogenesis and contributes to the effectiveness of the bacteria.

Many aspects of the pathogenesis of *T. pertenue* are still unknown and being studied, but the differences in the presence of antibodies, antigens, and other surface proteins provide some insight to the complex pathogenesis of this subspecies of *T. pallidum*.

Pathophysiology

Treponema pertenue are spirochetes that cannot be cultured *in vitro*. All subspecies are morphology and serologically indistinguishable. These organisms reproduce every 30 hours and with corkscrew motility these move through connective tissue. These spirochetes are fragile outside of their host vectors and are rapidly killed by exposure to heat, oxygen, and drying. As yaws is contracted, most commonly from skin-to-skin contact poor hygiene has been a risk factor for transmission. Poverty, crowding, rural settings, and a climate of heavy rainfall and high humidity are also linked to increased prevalence.

Histopathology

Treponema pallidum, as a group, are not viable *ex vivo*, and therefore, diagnostic methods are limited. Darkfield microscopy does allow direct visualization of spirochetes; however, equipment is often not available in endemic areas. Combinations of serologic assays and nucleic acid amplification tests have been used as the primary mode of identification.

Ecology

Sociological and geographical factors have caused a potential problem in some regions of the world that had expanded to be sources of other predicaments economically and politically. At this time, mass serological testing had revealed a high number of cases of yaws around the world. This led to the search for solutions and medical responses to eradicate the spread of yaws.

Environmental factors revolved mainly around the moisture content and temperature in tropical and sub-tropical areas. High humidity specifically targets high moisture in the skin and an increase in skin infections from diseases and bacteria. However, during the winter season, when temperatures have fallen to approximately 65°F on average, yaws had a higher tendency to resemble syphilis, where it may change its form and be nurtured. During the winter months, it was rare to see the painful lesions and the characteristic yellow-encrusted yaws on the skin that usually occurs in warm, moist regions. These attributes were frequently mistaken as syphilitic.

There is also an increase in the number of cases where rainfall was heavy, particularly during the rainy seasons. An increase in new cases and an increase in relapse cases are caused by the heavy rainfall of wet seasons, based on altitude and its soil characteristics.

Economically, a lack of proper sanitation is a large issue in populations where there was a lower standard of living. Overcrowding in huts became very common in large populations and poor personal hygiene was assumed to be one of the main causes of yaws. The prevalence of yaws declined in these regions when clothes and shoes were worn more often, which helped maintain personal hygiene and sanitation. This served as a protection barrier from being exposed directly to bacteria-rich objects, including exposure to open sores on infected people.

The availability of food was also scarce during the 1950's, which contributed to the low economic status and poor diet of the people. The diets were generally unbalanced: Fresh fruit, vegetables, milk, and eggs are not readily available year-round. The water supply was also tainted by overuse, further contributing to poor hygiene. Malnutrition and poor sanitation played a major part in the proliferation of yaws in the world.

Clinical features

As with other treponemal diseases, the clinical features of yaws may be conveniently divided into primary, secondary and tertiary disease. Although this classification is clinically useful, it should be remembered that patients may present with a mixture of clinical signs. The primary stage involves the entry and initial development of *T. pertenue*. The secondary stage is characterized by varying skin lesions and is highly infectious. Secondary lesions may go on to develop into tertiary stage, during which secondary lesions may come and go.

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. 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. Primary lesions may still be present in patients who present with secondary yaws.

Secondary yaws: After a period of 1–2 months (sometimes up to 24 months), haematogenous and lymphatic spread of treponemes may result in progression to secondary yaws,

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which predominantly affects the skin and bones often with general malaise and lymphadenopathy. As with venereal syphilis, a wide range of skin manifestations has been described in secondary yaws. Patients may develop disseminated papillomatous or ulcerative lesions, scaly macular lesions or hyperkeratotic lesions on the palms and soles. Hyperkeratotic lesions can crack and become secondarily infected, resulting in severe pain and a crablike gait (crab-yaws). Mucous membrane involvement is uncommon in secondary yaws. 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. In most patients, multiple bones can be affected. In a study from Papua New Guinea, 75% of children with secondary yaws had joint pain. Following treatment of primary or secondary yaws, skin lesions usually resolve within 2–4 weeks and bone pain may begin to resolve in as little as 48 hrs. As in all treponemal infections, untreated patients may develop latent infection, with positive serology but no clinical signs. Latent cases can relapse, usually in the first 5 years (rarely up to 10 years) after infection. Relapsing lesions tend to occur around the axillae, anus and mouth.

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. Gangosa, a destructive osteitis of the palate and nasopharynx, results in mutilating facial ulceration. Goundou, which was rarely reported even when yaws was hyperendemic, is characterized by exostoses of the maxillary bones. Unlike syphilis, yaws is not thought to cause cardiovascular or neurological disease. Post-mortem studies in a yaws endemic community in Ghana found that aortitis, histologically similar to that found in tertiary syphilis, was the most common cardiovascular abnormality, but definitive evidence that this was due to yaws is lacking.

Treatment/management

Treatment in the 1950's, during the initial eradication of *T. pertenue* and yaws, began with penicillin aluminum monostearate. Benzathine penicillin subsequently supplanted this as it was found to have prolonged treponemicidal levels and convenient dosing. Treatment dosing was determined by age with 600,000 units for age younger than 6 years old, 1.2 million units for children 6 to 14 years, and some sources reporting similar dosing of 1.2 million units for adults. This dosing is lower than used in venereal syphilis.

Prolonged oral penicillin and tetracyclines may be effective; however, azithromycin 30 mg/kg became the primary alternative after it was shown to be non-inferior when compared to penicillins maintaining a 96% cure rate at 6 months. In 2012, the WHO re-duplicated efforts for eradication and implemented single mass dosing of oral azithromycin in endemic areas and case detection monitoring with subsequent treatment. It is through this they hope to eradicate the disease by the target date of 2020, as stated above. Resistance to macrolides is a concern, however, as *T. pallidum* is notoriously resistant, and concerns about the similar organism of yaws have been discussed.

Study area

Imo State is a state in the South-East geopolitical zone of Nigeria, bordered to the North by Anambra State, Rivers State to the West and South, and Abia State to the east. It takes its name from the Imo River which flows along the state's eastern border. The state capital is Owerri and its state nickname is the "Eastern Heartland. Of the 36 states, Imo is the third smallest in area but is fourteenth most populous with an estimated population of over 5.4 million as of 2016 census. The state lies within latitudes 4°45'N and 7°15'N, and longitude 6°50'E and 7°25'E, with an area of around 5,100 sq km.

Eziama is a village located in Ikeduru. It has a latitude of 5° 32' 59" N and longitude of 7° 9' 0" E. Housing conditions and sanitary standards are still primitive. Most compounds consist of a variable number of mud-walled houses with the roof made of stick rafters and grass-thatching cover. The huts are dark, badly ventilated, and difficult to keep clean. The major occupation of people living in that area is farming.

A community-based survey was designed using a quality assurance sampling method to classify the prevalence of active yaws in the given area of study. The classification into high, moderate, or low yaws prevalence corresponded to World Health Organization prevalence thresholds for identifying appropriate operational treatment strategies. Active yaws cases were defined by suggestive clinical signs and positive rapid plasma reagin and *Treponema pallidum* hemagglutination serological tests.

The questionnaire

The questionnaire will capture key clinical signs and symptoms of yaws, especially those differentiating it from syphilis–its closest counterpart. Thus, those respondents' questionnaires indicating possibility of yaws will be blood sampled for serological test. The questionnaire consists of three sections; A) Demographic data, B) Potential clinical signs and symptoms of yaws and C) Consideration for serological test. Data will be collected on demographics, including gender, ethnicity, religion, age, marital status, education achieved and occupation. Signs such as presence of papule, its characteristics like moist red base, yellow crust, associated fever, fever duration, papule association with raining season and method of treatment if any. Also considered is the habit of antibiotics usage either for papule treatment or for any other reason and leisure activities to establish route of spread. It spreads by skin-to-skin contact. Section C is assess by the research assistant based on symptoms observed in section B, whether it is presume yaws case, if yes, then blood will be sampled for serology. Prior to conducting the fieldwork, research assistants will receive training on how to approach and penetrate the

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community in addition to teamwork skills to work with the community assistant corps. They will also receive technical know-how on administering the questionnaire. The questionnaire will be written in English Language, however, where necessary, it will be explained in local language for proper information presentation.

Ethical approval

This study was reviewed and approved by the Federal Ministry of Health Research Ethics. Written informed consent forms was obtained from the respondents, their parents or representatives, because some of the respondents may not be able to read. However, their verbal consent was obtained from them. The data collection instrument for this study was self-administered questionnaire, which was carefully filled and confirmed by a research assistant. Privacy and confidentiality of all information obtained was ensured both during and after the study process. Information obtained was used strictly for the purpose of the research.

Sample collection

Samples were collected from patients that are suspected to harbour characteristics of yaws infection. Blood samples and samples from areas of Infection were collected. Subsequently, samples were labeled and put into icebox and then transported to the laboratory for analysis. The analysis was performed after sampling.

Data analysis

Data was analysed with the use of descriptive statistics. Categorical variables were transformed to dummy variables for the analyses. Multiple linear regression were used to predict relationships between 'presumptive case' of yaws and demographic variables, including age, gender, level of education, occupation as well as use of antibiotics and also predict their effect on the presumption of yaws cases.

Diagnosis

Yaws is diagnosed clinically, with laboratory confirmation of disease. Serologic evaluation can be used for confirmation of the diagnosis however cannot differentiate between syphilis and yaws subspecies. Dark field microscopy can be used for detection but also cannot differentiate between the two. The available testing includes the RPR, Fluorescent Treponemal Antibody Absorption (FTA-ABS) test, VDRL test and *T. pallidum* hemagglutination assay (TPPA). Currently, the search for a sensitive and specific rapid diagnostic test that allows accurate point-of-care results is underway for diagnostic confirmation. The search for a cost-effective rapid screening test in asymptomatic patients remains to be seen, however, does serve a useful function in post-mass drug administration monitoring.

Treponemal rapid tests are widely available and cheap; however, they cannot distinguish between past and current infection and therefore have limited use in monitoring interruption of transmission. Dual path platform syphilis screen and confirm assay can detect both past and present infection. Because of the high cost of the DPP test, initial screening of suspected yaws cases can be done by the treponemal tests and positives confirmed by the DPP. However, countries may choose to use only DPP if affordability is not a problem.

Polymerase Chain Reaction (PCR) technology is used to definitively confirm yaws by detecting the DNA in the skin lesions. It can also be used to monitor azithromycin resistance. This will be useful after mass treatment and post-elimination surveillance.

Results

A total of 25 individuals participated. Male (n=14, 56%) were included than female (n=11, 44%), and of children (aged 15 and below, n=18, 72%) while adults (above 16, n=7, 28%). Despite high presumptive cases of yaws (n=15, 60%), only 24% (n=6) was reactive to serological test strip and (n=19, 76%) showed no symptoms (Table 2). Formal education showed that 11 (44%) attended primary school, were as 5 (20%) attended secondary school and 9 (36%) attended university. Marital status among individuals showed that 8 (32%) were married, 4 (16%) divorced, 10 (40%) are single and others 3 (12%) (Tables 3 and 4).

Table 2. *Demographic characteristics.*

S/N	Characteristics	Variables	Number (n)=25	Percentage (%)
1	Gender	Male	14	56
		Female	11	44
2	Age	Children (<15)	18	72
		Adults (16>)	7	28
3	Presumptive case	Yes	15	60
		No	10	40
4	Serologically reactive	Yes	6	24
		No	19	76

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5	Occupation	Farmer	6	24
		Students	8	32
		Others	2	8
		Civil servants	3	12
		Business owners	2	8
		House wives	4	16
6	Formal education	Primary	11	44
		Secondary	5	20
		Tertiary	9	36
7	Marital status	Married	8	32
		Divorce	4	16
		Single	10	40
		Others	3	12

Table 3. *Descriptive analysis of the yaws cases.*

S/N	Characteristics	Variables	Number (n)=10	Percentage
1	Gender	Male	6	60
		Female	4	40
2	Age	Children (<15)	5	50
		Adults	5	50
3	Presumptive case	Yes	7	70
		No	3	30
4	Serologically reactive	Yes	10	100
		No	0	0
		No symptoms	0	0
5	Occupation	Farmer	4	40
		Students	3	30
		Others	0	0
		Civil servants	1	10
		Business owners	1	10
		House wives	1	10

Table 4. *Knowledge and practices of participants.*

S/N	Characteristics	Variables	Number (n)=10	Percentage
1	Clinical examination	Papiloma/papules	4	40
		Ulcer	3	30
		Bone swelling	2	20
		Hyper keratosis of the palm	1	10
		None		

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2	Causes of infection	Insect bite	4	40
		Drinking	1	10
		The Gods/evil spirit	2	20
		Bathing cold water	0	0
		Enemies	3	30
		Others	0	0
3	Treatment	Clinics	3	30
		Chemist store	2	20
		Herbalist	3	30
		Oracle consults	1	10
		Spiritual healing	1	10
		Others	0	0
4	Prevention	Antibiotics	7	70
		Washing of wounds	2	20
		Wearing of protective clothes	0	0
		Net beds	1	10
		Avoiding wetlands	0	0

Discussion

Yaws is still endemic in a number of countries worldwide despite a significant reduction in the number of affected individuals following mass treatment campaigns in the middle of the twentieth century. Clinicians need to be aware of the epidemiology and manifestations of yaws, which should be considered in the differential diagnosis of patients with reactive serology from endemic countries. Older individuals may have acquired yaws in countries that are no longer endemic. Routine testing cannot distinguish between syphilis and yaws. Treatment strategies are similar for the two diseases, although a lower dose of penicillin is used in yaws. Given the limitations in distinguishing the two diagnoses clinicians should consider treating for venereal syphilis in patients with reactive serology without a clear history of yaws. In this context it is important that the clinician carefully explains to the patient and their partner that reactive serology alone is not diagnostic of a sexually-transmitted route of infection. Development of near-patient and laboratory tests specific for treponemal sub-species is long overdue. We also need to know if yaws can be transmitted from mother to child in utero and whether it can produce neurological and/or cardiovascular complications. Given the prevalence of macrolide and azalide resistance reported in *Treponema pallidum* ssp. it is important that surveillance of treatment efficacy is maintained in planned yaws mass treatment campaigns.

Conclusion

Yaws presents new challenges such as poor awareness and knowledge among health care workers, unknown epidemiological situation, and attenuated clinical forms of the disease. These challenges, combined with the current competing priorities in the public health arena, require new, innovative, and country-tailored approaches. Increased attention required to address the resurgence of yaws in the affected countries does not necessarily mean increased resources. In view of the many health priorities and the human and financial resources constraints, it rather calls for new and innovative approaches. Today, utilization of existing programs with similar primary target population (*i.e.*, children under 15 years of age) in implementing yaws control activities may provide a cost-effective option. For example, yaws screening and detection could be included in school-based health promotion programs such as a deworming program for soil-transmitted helminthiasis or dental surveys. Cost-effective strategies in identifying cases, in providing treatment, and in tracing all contacts need to be identified at country level in order to take into account logistical constraints, resources available locally, and other health priorities in the affected countries. Many opportunities to revitalize yaws control activities already exist at country level: Maternal and child Health clinics and their related activities, water and sanitation programmes, or school-based programmes are such examples. One way to approach yaws control might be to address it in the broader context of the Primary Health Care (PHC) where lessons learnt from past failures would be used to avoid repeating the same mistakes.

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