

Short Report: Challenges in Recognition and Diagnosis of Yaws in Children in Papua New Guinea

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Abstract. A global resurgence of yaws in developing countries highlights the need for reliable diagnostic criteria for this neglected infection. We conducted a clinical and serologic survey of 233 children less than 15 years of age who had clinically suspected yaws. A total of 138 (59%) cases were confirmed serologically, and 10 of 12 primary stage cases showed positive results for *Treponema pallidum* by a polymerase chain reaction assay that has not yet been validated for identification of yaws. A high proportion of cases (46%) were in the secondary stage; 92% of them had osteoarticular involvement, and only 24% had a Venereal Disease Research Laboratory titer greater than 1:32.

The etiologic agent of yaws, *Treponema pallidum* subsp. *pertenue*, causes a multistage infection transmitted by non-sexual contact with the exudates from active lesions.^{1,2} Although a multinational mass eradication campaign in the 1950s greatly reduced its global incidence,^{3–5} a resurgence of yaws has occurred during the past decade in western and central Africa, southeast Asia, and the Pacific Islands. This resurgence emphasizes the need for reliable diagnostic criteria.^{6–9} Unless diagnosed and treated at an early stage, yaws can become a chronic, relapsing disease and can enter into a late stage characterized by severely deforming bone lesions.

The differential diagnosis of yaws is extensive. The clinical diagnosis may be difficult even for experienced clinicians because yaws produces lesions in the skin, bone, and cartilage, which can resemble several other diseases in the tropics.^{1,2} It has been reported that the disease may show a milder form or an atypical form, with less florid skin lesions.⁷ Moreover, laboratory diagnosis of yaws is based on serologic analysis, which may not be suitable in syphilis-endemic areas because of cross-reactivity. The aim of this study was to describe the clinical signs and symptoms of patients with yaws in Papua New Guinea and determine the accuracy of the commonly used diagnostic procedures.

This study was a descriptive cross-sectional study involving patients who came to Lihir Medical Center (Lihir Island, Papua New Guinea) during January–September 2009. Patients with clinical suspicion of yaws and positive results for the Venereal Disease Research Laboratory (VDRL) test and the *Treponema pallidum* hemagglutination test were eligible.

The study group was limited to children less than 15 years of age whose mothers had negative treponemal test results at antenatal screening to reduce the likelihood of syphilis-related positive results. We repeated the VDRL test after one week for all patients with an initial negative result and a disease duration less than two weeks to reduce the probability of initial false-negative results. A diagnosis of primary yaws was established by clinicians on the basis of chronic (> 2 weeks), painless, atraumatic ulcers with raised margins. Criteria for the diagnosis of secondary yaws included one of the following: 1) multiple hyperkeratotic papules, 2) polyarthralgia, and

3) bone pain and swelling affecting the fingers or toes, forearms, and tibia or fibula, irrespective of accompanying radio-logic abnormalities.

For testing by using a *T. pallidum* PCR specific for the 47-kD membrane lipoprotein gene, not yet validated for yaws, a dry swab specimen was obtained from 12 exudates of primary ulcers and from skin scrapings from three secondary lesions randomly chosen. Histopathologic examination of biopsy specimens, including a margin of normal tissue, was also performed for four cases.

Because yaws is known to cluster in close communities and its prevalence can vary greatly between villages, we estimated the incidence rate derived from hospital-detected cases among the whole population for each of the 27 villages served by our hospital. We defined a high incidence as a rate greater than 1.5%.

In the 12-month study period, 233 patients with clinically suspected yaws were evaluated and 138 patients received a diagnosis of yaws on the basis of a correlation of clinical findings, epidemiologic history, and positive serologic results. The remaining 95 patients evaluated had a negative VDRL test result, including 61 (64.2%) patients with a skin ulcer and 34 (35.8%) patients with bone or joint pains. Patient demographic characteristics, clinical signs and symptoms, laboratory results, and outcome are shown in Table 1. Eighty one (58.7%) persons displayed active primary cutaneous yaws lesions; most exhibited either solitary lesions or a scanty number of papillomata, most commonly on the legs and ankles (85.2%), but also on the buttocks, arms, hands, and face.

Of the 138 patients evaluated, 63 (45.7%) exhibited signs of secondary stage yaws, including 58 (92%) with osteoarticular involvement (Figure 1). In some cases, the initial primary lesion persisted into the secondary stage (6 [9.5%] of 63); in some other cases healed primary lesions were noted. Arthralgias were the most common presentation of secondary stage yaws (48 [76.2%] of 63) and usually affected multiple large joints including the knees, ankles, elbows, and wrists. Marked pain in the long bones of extremities with or without visible bone or soft-tissue swelling or deformity on examination was present in 10 (15.9%) of secondary stage cases.

The association between the stage of infection and patient demographic features and laboratory results is shown in Table 2. There was a positive association between a high initial titer and primary stage disease; 36 (48.0%) of 75 persons with primary yaws compared with 15 (23.7%) of 63 persons with secondary yaws ($P = 0.004$) had a VDRL test titer > 1:32.

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TABLE 1

Demographic data, clinical presentation, laboratory results, and outcome after treatment of 138 patients with yaws, Papua New Guinea*

Characteristic	Global (n = 138)
Mean (SD) age, years	9.6 (4.4)
Male sex, no. (%)	81 (58.7)
VDRL test titer, no. (%)	
1:16	54 (39.1)
1:32	33 (23.9)
1:64	42 (30.4)
1:128	9 (6.5)
Primary lesion, no. (%)	81 (58.7)
Face	2/81 (2.5)
Upper limb	10/81 (12.3)
Lower limb	69/81 (85.2)
Secondary stage, no. (%)	63 (45.7)
Skin lesions	18/63 (28.6)
Arthralgias	48/63 (76.2)
Bone swelling or pain	10/63 (15.9)†
Family history, no. (%)	36 (26.1)

*VDRL = Venereal Disease Research Laboratory.

†Includes seven cases of radiologically confirmed yaws osteoperiostitis among three patients who had dactylitis.

Among the secondary cases, 48 (76.2%) of 63 patients lived in a high prevalence village and only 42 (56.0%) of 75 patients had primary stage disease ($P = 0.014$).

The PCR results were positive for 10 (83.3%) of 12 children with primary ulcers, and 3 of 3 patients with secondary skin lesions had PCR-negative results. The latter negative results could be ultimately related to the scarce numbers of bacteria present in secondary stage lesions, which are mainly an inflammatory infiltrate.¹⁰ The five patients with negative PCR results had positive serologic results and typical clinical signs and symptoms.

Microscopic study of biopsy specimens of four skin samples at the margin of primary ulcerative lesions showed parakeratosis containing neutrophils with epidermal erosion and an inflammatory cell infiltrate in the dermis comprising of lymphocytes. Furthermore, immunoperoxidase staining was positive for *Treponema* sp. and showed scattered spirochetes within the epidermis (Figure 2).

Yaws is endemic to areas of Papua New Guinea, but because this disease is not fatal and occurs primarily in remote areas among isolated communities, it does not receive adequate attention. The clinical and serologic survey we conducted highlights three issues. First, clinical diagnosis of yaws is not easy to determine and support for laboratory techniques is necessary. Second, yaws in Papua New Guinea may have changed its pattern of presentation by showing an increased number of secondary stage osteoarticular forms. Third, molecular biological techniques should be explored as an alternative to dark-field microscopy for direct diagnosis of ulcers of yaws.

In our experience, only 60% of the cases with a clinical suspicion of yaws were confirmed by serologic tests. The diagnosis of yaws is complicated because its clinical manifestations are diverse or may be totally unspecific. Primary yaws is commonly confused with anaerobic fusobacteria-related ulcer, cutaneous leishmaniasis, mycobacterial disease, *C. diphtheriae*, or *A. haemolyticum* skin infection. Similar secondary cutaneous manifestations might be caused by infected bites, psoriasis, excoriated chronic scabies or verrucae. Secondary stage bone lesions need to be differentiated from bacterial osteomyeli-

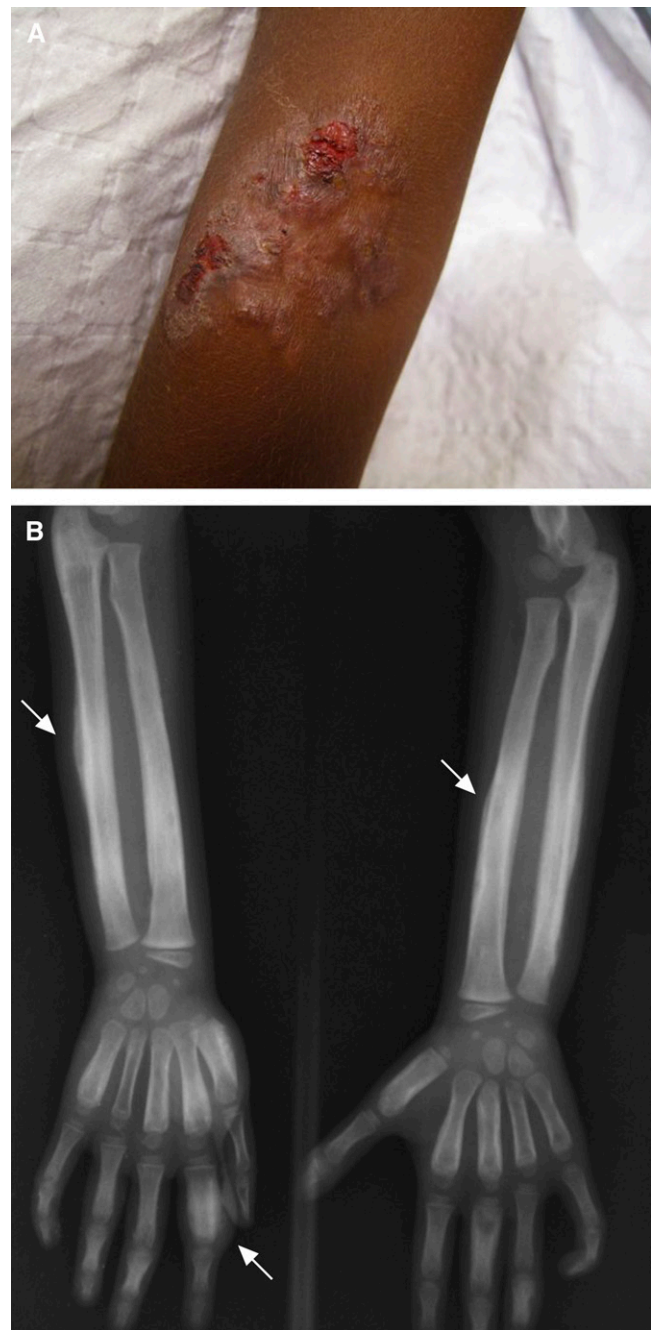


FIGURE 1. Secondary skin lesion (crustopapillomatous) on the left arm of a patient with yaws (A) and radiograph of her forearms and hands (B), Papua New Guinea. Arrows show dactylitis with thickening of the cortex and increase in width of the phalanx and bilateral periosteal reaction of the ulna and radius with widespread onion layering deposition of periosteal bone.

tis, tuberculosis, and sickle cell disease. Arthralgias are also a common but nonspecific symptom of patients.^{1,2}

We believe that clinical findings alone, even for experienced clinicians, are not reliable in reaching a diagnosis of yaws. Conversely, serologic tests commonly used may not enable confident diagnosis of yaws from other treponemal infections. For persons greater than 15 years of age who are known to be sexually active, syphilis infection cannot be strictly excluded. Therefore, a proper diagnosis of yaws requires interpretation

TABLE 2

Association between stage of infection and demographic data, laboratory results, and outcome after treatment of patients with yaws, Papua New Guinea*

Characteristic	Primary stage (n = 75)	Secondary stage (n = 63)	OR (95% CI)	P
Mean (SD) age, years	10.0 (3.4)	9.3 (5.5)	0.72 (0.78–2.22)	0.34
Male sex, no. (%)	48 (64.0)	33 (52.4)	0.61 (0.31–1.23)	0.17
VDRL test titer > 1:32, no. (%)	36 (48.0)	15 (23.8)	0.34 (0.16–0.70)	0.004
High prevalence village, no. (%)	42 (56.0)	48 (76.2)	2.51 (1.20–5.26)	0.014
Family history, no. (%)	12 (16.0)	24 (38.1)	3.23 (1.45–7.19)	0.01

*OR, odds ratio, using primary stage cases as baseline; CI = confidence interval; VDRL = Venereal Disease Research Laboratory. A P value < 0.05 was considered statistically significant.

of clinical findings with reference to laboratory results and the epidemiologic history of the patient.

Manifestations of secondary yaws, particularly bone and joint involvement, are now more frequent and often subtle. In a community survey in the Democratic Republic of Congo, 80% of patients had lesions suggestive of secondary yaws.⁶ On Lihir Island, 46% of case-patients had the secondary stage of yaws, and this feature was more pronounced in those villages with a high endemicity (ratio 2.5).

A factor that could have contributed to the change on clinical presentation is the widespread use of oral antibiotics. Low bioavailability of penicillin and its derivatives given as oral dosages likely prevented eradication of the causative bacteria from bone.¹¹ Also, these drugs could have had a specific effect on skin lesions.

Although there are no detailed data available for yaws in Papua New Guinea, VDRL test results seem to be similar to those for syphilis in which VDRL test results decrease over time.¹² In this study the longer-term infections in secondary stage were more commonly associated with a VDRL test titer < 1:32. A negative correlation between VDRL test titer and

duration of syphilis was reported by McMillan and Young, in which test results were positive in 100% of patients in an early stage of syphilis, but decreased to 85% in patients in a latent stage.¹³

A PCR used in laboratory diagnosis of early syphilis that is specific for the 47-kD membrane lipoprotein gene showed positive results for most of the tested patients with primary ulcers.¹⁴ To our knowledge, this PCR method has not been previously used with clinical specimens from patients with yaws. However, the 47-kD protein is involved in cell wall synthesis and would be expected to be conserved in related treponemes.

Treponema pallidum has historically been detected in clinical specimens by using dark-field microscopy, a method that has high specificity. However, if bacterial load is low or viability of the treponemes is reduced, the sensitivity of this method may be severely decreased.¹⁵ In this context, potential use of the *T. pallidum* PCR specific for the 47-kD gene as a direct and fast test for diagnosis of primary yaws should be explored. However, its additional value for diagnosis of secondary yaws might be limited.

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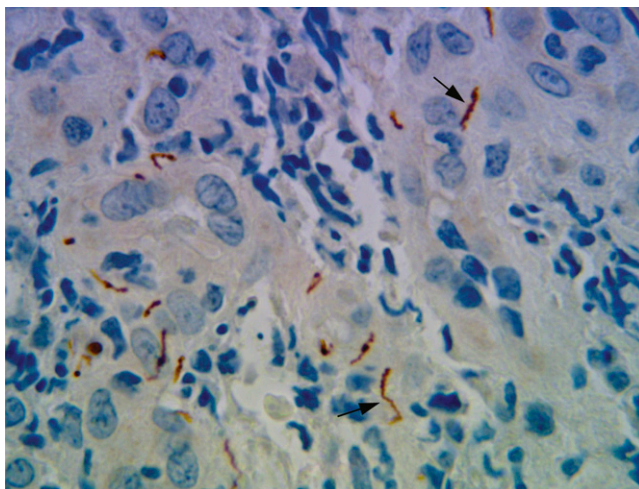


FIGURE 2. Immunoperoxidase staining of a skin biopsy specimen from a patient with yaws, showing scattered spirochetes within the epidermal lesion, Papua New Guinea. Arrows show the spiral-shaped body of *Treponema pallidum* that confers the bacteria a corkscrew-like motility. Photograph courtesy of Sullivan Nicolaides Pathology/Dr. Kevin Whitehead.

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