

Original Article

Comparison of the standard Q syphilis antibody rapid diagnostic test to gold standards for yaws detection in childrenYudo Irawan¹, Astuti Giantini², Nevi Yasnova¹¹ Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia² Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia**Abstract**

Introduction: Yaws remains a public health problem in Indonesia, and it is the largest contributor to Yaws cases in Southeast Asia. Yaws is caused by bacterial infection of *Treponema pallidum* subspecies *pertenue*, mainly affecting the skin and bones. An estimated 75% of new cases were found in children under 15. The diagnosis of yaws is based on clinical findings with serological confirmation. Rapid diagnostic tests (RDT) have been developed to diagnose Yaws faster and simpler and can thus be used in areas with limited resources.

Methodology: In this study, sensitivity and specificity of the solid phase immunochromatographic assay of Standard Q Syphilis Antibody (Ab) RDT was performed compared to *Treponema Pallidum* Haemagglutination Assay (TPHA Plasmatec®) and Rapid Plasma Reagin (RPR) in 195 children with yaws age 2-15 years in Halmahera Barat, Maluku.

Results: There were 116 children with clinical symptoms representative of yaws, but only 13 were serologically positive. The scar was the most commonly found lesion, and the most affected regions were the legs. The sensitivity and specificity of RDT compared to TPHA were 93.3% and 99.4%, respectively. The sensitivity and specificity of RDT compared to RPR were 100% and 98.4%, respectively.

Conclusions: Based on the excellent performance of this test, this study suggests that Standard Q Syphilis Ab RDT examination can be used as a screening test. However, unusual clinical findings, like scars in RDT reactive patients, indicated that RPR is still required to confirm the diagnosis of yaws.

Key words: RDT; RPR; standard Q syphilis antibody; TPHA; Yaws.*J Infect Dev Ctries* 2024; 18(11):1734-1738. doi:10.3855/jidc.17753

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Copyright © 2024 Irawan *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Introduction**

Yaws is an infectious disease caused by *Treponema pallidum* subspecies *pertenue*, mainly affecting skin and bones [1,2]. This is a non-venereal endemic treponemal disease and is considered a neglected tropical disease. Transmission occurs through direct skin contact with open wounds or excoriations. The spread of infection occurs mainly in tropical regions with high humidity, low levels of hygiene, limited clothing, and high population density. An estimated 75% of new cases are detected in children aged less than 15 years of age [3].

The clinical symptoms of yaws are categorized into several stages based on the disease's progression. In the primary stage, skin lesions appear after an incubation period of 10-90 days (with a mean of three weeks). The classic symptom at this stage is the appearance of solitary, dense, itchy, red, and infiltrative papules (known as mother yaw or *buba madre*), which later develop into papillomas [4]. The lesion's location indicates where the spirochete penetrates the skin, often occurring in the upper and lower extremities and the

buttocks [5]. Mother yaws may increase in size and merge with satellite lesions to form plaques. These lesions are often ulcerative with a raspberry-like base, becoming a "chancre of yaws" covered in brownish-yellow crusts. These lesions typically heal within 3-6 months but may become latent and reappear in the second stage [6]. Persistent symptoms characteristic of this stage include scarring and central depigmentation with darker margins [7].

The secondary stage can occur two years after the onset of the primary lesion. These lesions can resemble mother yaws but are smaller and often spread throughout the body (daughter yaws). This stage is generally accompanied by systemic symptoms such as fever, malaise, and generalized lymphadenopathy. Daughter yaws can be ulcerative and secrete a glossy exudate, which is highly infectious and often attracts flies. Other forms include papulosquamous plaques (pianides) and hyperkeratotic lesions, the most common clinical features found on the palms of the hands and soles of the feet (crab yaws) [5,8]. During the rainy season, the lesions tend to be reddish and spread,

whereas, in the dry season, the lesions become less exudative [9]. Lesions in the secondary stage may heal spontaneously without scarring within a few weeks or months or may become latent [4]. In the latent phase, serological tests remain reactive despite the absence of clinical symptoms [10].

The tertiary stage is a non-infectious stage that occurs in 10% of cases within 5-10 years after bacterial inoculation. This stage is characterized by tissue damage and persistent bone deformities [9]. The lesions are suppurative gummatous nodes on the skin and subcutaneous tissue (gumma framboise); when ruptured, they form necrotic serpiginous ulcers, which subsequently scar and contract [6,9]. Hyperkeratotic lesions on the palms and soles of the feet manifest as palmoplantar keratoderma. Hypopigmentation may be found on the hands, wrists, and shins of adults [4].

The diagnosis of yaws is based on clinical findings followed by serological confirmation [11,12]. The World Health Organization (WHO) devised a classification system that divides yaws into early (active) and late (inactive) stages for disease detection. This classification is a simple modification of the previous system. Early yaws lesions consist of 1) infectious lesions in the form of papillomas, ulcers, papules, macules, micropapules, nodes, and plaques; and 2) non-infectious lesions in the form of hyperkeratosis, bone lesions, and joint lesions. Advanced lesions may include gummas, ulcers, gangosa, and tibial sabers [1-2,13].

These clinical findings are confirmed by serological examination using the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests and the *Treponema pallidum* hemagglutination assay (TPHA). A definitive diagnosis is made when bacteria are observed using dark-field microscopy. Based on the similarity of the biomolecular structure, it is accepted that no serological test can distinguish syphilis from yaws. The use of rapid diagnostic tests (RDTs) has been developed to facilitate faster and simpler diagnosis of yaws, especially in remote areas that lack adequate laboratory facilities and infrastructure. Consequently, RDTs have been widely used to screen for yaws in conditions where infrastructure is limited [14,15]. Current guidelines by the Ministry of Health of the Republic of Indonesia suggest that patients with only clinical findings should be diagnosed as suspected yaws, whereas those with reactive serology are diagnosed as confirmed yaws [16].

Yaws remains a public health problem in Indonesia, with a target for eradication by 2025 [16]. Currently, Indonesia is the largest contributor to yaws cases in

Southeast Asia. Data from 2009 showed that 8,309 cases were spread across the eastern provinces of Indonesia, namely East Nusa Tenggara (NTT), Southeast Sulawesi, Maluku, Papua, and West Papua [17]. The infected population generally resides in poor communities with tropical, warm, and humid climates. Approximately 75-80% of infected individuals are children under 15 years of age, who are the main reservoir of yaws infection [12].

To eradicate yaws, the primary strategy involves increasing case detection and reporting [18]. The World Health Organization also launched a yaws eradication campaign in 2020. To achieve this goal, RDTs for yaws are needed as part of community surveys. Yaws is serologically indistinguishable from syphilis; hence, developing a syphilis RDT with high sensitivity and specificity will aid in evaluating its use in diagnosing endemic treponemal infections. The development of RDTs can expand access to serological diagnosis, even in remote areas where laboratory facilities are unavailable. Additionally, RDTs provide immediate results [14]. TPHA and RDT antibodies are long-lasting, potentially lifelong, for all treponemal infections. If they are reactive in children in endemic areas without a history of adequate treatment, it may indicate a latent case that requires further evaluation by a specialist. If treated, TPHA titers can decrease but will not become non-reactive. In contrast, RDTs, being qualitative and without titers, will also remain reactive for a long time or even a lifetime [2,6].

This study will perform a diagnostic test of the solid-phase immunochromatographic assay Standard Q Syphilis Antibody (A) for yaws. To date, no study has compared RDTs with the previous RPR and TPHA tests. This study aims to examine the sensitivity and specificity of RDTs compared to RPR and TPHA, which are considered the gold standard tests for confirming the diagnosis of yaws.

Methodology

The study was conducted in West Halmahera Regency, Ternate, North Maluku, from October 2017 to May 2018. Subjects had undergone history taking, physical examination, venous blood collection, and the Standard Q Syphilis Ab RDT. Centrifugation of the blood samples and preparations for their delivery to Jakarta was carried out at the local public health center. Furthermore, the AIMTM RPR TEST (Germaine Laboratories, San Antonio, USA) and TPHA Plasmatec[®] (Lab 21 Healthcare Ltd, Dorset, UK) examination were carried out at the Department of Clinical Pathology Laboratory, Cipto Mangunkusumo

Hospital (RSCM) Jakarta, using whole blood and plasma serum collection.

The inclusion criteria for the subjects were:

- Children aged 1 – 15 years
- Willing to participate in the study by signing a

written informed consent form after being explained the study procedure, represented by the subject's parents/guardians.

The exclusion criteria were:

- Children with fever (temperature > 38 °C)
- Insufficient blood or serum samples

RDT examination was performed using the Standard Q Syphilis Ab kit. RPR examination was carried out using the AIMtm RPR TEST (Germaine Laboratories, San Antonio, USA), TPHA examination was carried out using the Plasmatec® (Lab 21 Healthcare Ltd, Dorset, UK) test kit. Statistical tests were performed using the SPSS version 20.0.

Results

A total of 195 subjects were examined. Among them, 116 children had clinical symptoms of yaws, including 62 males (53.5%) and 54 females (46.5%). Most lesions were found in the leg regions (81.9%), followed by the knees, feet, face/neck, hands/fingers, stomach/back/chest, arms/elbows/wrists, palms, and buttocks/thighs. The most common manifestations were scars, followed by wounds/excoriations,

Figure 1. A, skin-colored papules in primary yaws; B, cigarette paper-like scars; C, multiple ulceropapules on the trunks; D, primary ulcer with satellite papules; E, crusted papilloma.



Table 1. Standard Q Syphilis Ab compared with TPHA Plamatec®

		TPHA ¹		Total
		Positive	Negative	
Standard Q Syphilis Ab	Positive	14	1	15
	Negative	1	179	180
	Total	15	180	195

¹Treponema Pallidum Haemagglutination Assay.

Table 2. Standard Q Syphilis Ab compared with RPR.

		RPR ¹		Total
		Positive	Negative	
Standard Q Syphilis Ab	Positive	11	3	14
	Negative	0	181	181
	Total	11	180	195

¹RPR: Rapid Plasma Reagin.

papules/papillomas, hypopigmented/hyperpigmented macules, pustules, ulcers, plaques, and scales.

Among all of the 13 RDTs positive subjects, lesions were mostly found on the legs (92.3%), followed by the face/neck, hands, arms/elbows, knees, palms, and feet. The most common manifestations are scars, followed by papules/papillomas, hypopigmented macules, wounds, pustules, ulcers, and plaques (Figure 1). All subjects with positive RDT were male. There were no asymptomatic subjects in the RDTs positive samples. Of the 195 subjects who participated in this study, 13 had a positive rapid test, and 163 had a negative Standard Q Syphilis Ab rapid test. The comparison between serum and venous blood Standard Q Syphilis Ab results with the TPHA Plasmatec® and RPR are presented in Tables 1 and 2.

Based on Table 1, the sensitivity of Standard Q Syphilis Ab, when compared to TPHA, was 93.3%, with a specificity of 99.4%, a positive predictive value (PPV) of 93.3%, and a negative predictive value (NPV) of 99.4%. The sensitivity of Standard Q Syphilis Ab, when compared to RPR, was 100%, with specificity of 98.4%, PPV of 78.6%, and NPV of 100%. No significant difference in the results of RDT when using serum or venous blood.

Discussion

This study reported 116 children with clinical symptoms of yaws, comprising 62 males (53.5%) and 54 females (46.5%). In line with previous research by Barros *et al.* (2014) and Aruan *et al.* (2013), yaws are more common in boys within the same age group. In this study, the most common site where lesions were found was in the legs (81.9%), similar to previous research by Rachmawati *et al.* (2014). This finding is consistent with the pathogenesis of yaws, where the pathogen invades the host's body through small wounds on the skin, with the lower extremities –susceptible

areas that are frequently traumatized – being the primary predilection site. In addition, the host factor – dominated by children under 15 years of age – contributes to their increased susceptibility to infection, as they are often unable to dress appropriately (frequently not wearing footwear) and tend to play outdoors, leading to frequent skin trauma [19].

In this study, the most common clinical manifestations were scars. Scars were not considered a clinical manifestation of yaws categorized by the WHO but are signs of latent infections. Therefore, conducting a Yaws serological survey is important when a scar is found in children under 15 years of age, especially in endemic areas, including West Halmahera, North Maluku. Of the 13 serologically positive children, scars were also presenting symptoms. However, it is not easy to recognize skin lesions and diagnose yaws based on clinical judgment alone. The ability to recognize yaws skin lesions coupled with serological confirmation is expected to improve the accuracy of diagnosis.

No data from previous studies compared the results of the Standard Q Syphilis Ab RDT examination against RPR and TPHA. Previous research comparing the diagnostic accuracy of other RDTs against RPR and TPHA as the gold standard reported high sensitivity and specificity. A limitation of this study is the small number of samples with positive results, which may affect the overall confidence in the findings. Therefore, larger studies are needed to confirm these results.

Conclusions

Yaws remain a problem in endemic areas in West Halmahera, North Maluku. The clinical manifestations and region of lesion findings were mainly consistent with previous studies. The sensitivity and specificity of Standard Q Syphilis Ab compared to TPHA were 93.3% and 99.4%, respectively. Meanwhile, the sensitivity and specificity of Standard Q Syphilis Ab compared to RPR were 100% and 98.4%, respectively. This study suggests that the Standard Q Syphilis Ab RDT examination can be used as a screening test.

No difference was found in the results of RDT when using serum or venous blood. Scarring marks, a latent yaws infection may not be detected if diagnosed solely based on clinical symptoms. Therefore, RDT is a recommended first step for screening, followed by confirmation with RPR and/or TPHA to establish the diagnosis of yaws before mass drug administration.

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