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Original Article

Conformity of yaws clinical features to combined rapid diagnostic test in children aged 2-15 years in an endemic area

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Abstract

Introduction: The diagnosis of yaws is established by clinical examination and confirmed through a laboratory test. Unrecognized lesions may lead to a missed opportunity for diagnosis and complete eradication of yaws. The use of Dual Path Platform (DPP® RDT) Syphilis Screen and Confirm RDT (Chembio, Medford, New York) has been recommended by the World Health Organization (WHO) for endemic areas with limited laboratory facilities. To date, there have not been any studies assessing the conformity of clinical features based on the WHO guidelines with DPP® RDT.

Methodology: A cross-sectional study was conducted to evaluate the conformity of yaws clinical features based on the WHO guidelines to the DPP® RDT. We recruited children aged 2–15 years old in Alor, Indonesia. All subjects underwent clinical examination and were tested with DPP® RDT. Fisher's exact test was used to analyze the overall agreement between the clinical features and the DPP® RDT results.

Results: A total of 197 study subjects (mean age 9 years) were enrolled. The most frequent skin lesion was a yaws scar (79.7%). Eight subjects (3%) were diagnosed with yaws based on the DPP® RDT examination. The overall agreement between clinical features and DPP® RDT was 26.9% ($p = 0.202$).

Conclusions: The conformity of clinical features in suspected yaws to DPP® RDT is low; thus, clinical features should not be used as a sole initial reference in establishing yaws diagnosis, even in endemic areas.

Key words: diagnosis; endemic; eradication; yaws.

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Introduction

The reports of yaws from endemic countries to the World Health Organization (WHO) are usually solely based on clinical diagnosis. In west African countries such as Ghana, the prevalence of yaws based on clinical diagnosis is between 3% and 10%, but this method of diagnosis is often unreliable.

The prevalence of yaws in Indonesia was 0.31% in 1991; however, Indonesia remains the only contributor of yaws cases in the Southeast Asia region [1,2]. In 2017, 1218 cases of yaws were reported in Indonesia, spread across East Nusa Tenggara (ENT), Maluku, Papua, and West Papua [1,4]. Meanwhile, a higher prevalence of yaws (5.2%) was reported from Southwest Sumba, ENT in 2013 [5,6]. A mass treatment program with azithromycin was administered to the endemic communities to accelerate the eradication of yaws [6].

Yaws eradication in Indonesia had not been achieved until 2020 and the Ministry of Health of the Republic of Indonesia (RI) has set a goal for Indonesia to be yaws-free by 2025, five years earlier than the WHO target of 2030 [3,4].

Yaws primarily affects rural communities, those living in poor economic circumstances and with low standards of hygiene. In Indonesia the endemic areas are located in small pocket regions with limited transportation access and this leads to difficulty in the distribution of serology tests. On the other hand, the atypical lesion associated with yaws clinical features makes it difficult to clinically diagnose and the conventional diagnostic method is often unreliable and not uniformly reported. Nevertheless, the yaws elimination national programme guidelines require initial clinical diagnosis, followed by serological test of all suspected cases to confirm the diagnosis. Thus, Indonesia did not achieve yaws eradication by 2020.

Alor Regency in ENT is one of the endemic areas for yaws. The 2019 Yaws Serological Surveillance (YSS) data from the Alor Regency reported 49 cases after mass treatment with azithromycin in 2017. Based on this data, all new yaws cases and their contacts are treated with azithromycin in 2019 to stop disease transmission. Reassessment has yet to be conducted following the case and contact treatment program by the Alor District Health Office [4]. Assessment of clinical features is done based on the WHO guidelines. In 2012, the WHO guidelines were simplified to facilitate clinical assessment and diagnose more cases; however these guidelines were less comprehensive than the previous version [7]. The 2018 WHO guidelines were used in the current study with some modifications (Table 1) [8-10].

The yaws national guideline programme diagnosis criteria are used to identify suspected and confirmed cases. Yaws suspected cases are limited to all children under 15 years of age who present with clinical features for more than 2 weeks. Yaws confirmed cases are suspected cases who have tested positive with the treponemal-only rapid diagnosis test (RDT) [6]. Atypical clinical features can lead to a missed yaws diagnosis and serological tests are not performed. Moreover, the treponemal-only RDT used in Indonesia is unable to differentiate active and past yaws cases. The WHO has recommended the use of Dual Path Platform (DPP® RDT) Syphilis Screen and Confirm Rapid Diagnostic Test (Chembio, Medford, New York) as a means to confirm the diagnosis of yaws. This tool has the advantage of detecting treponemal and non-treponemal antibodies simultaneously using the Point of Care (POC) method. Despite the recommendation from WHO, the test kit is not available in Indonesia [6].

Diagnosis of yaws is ideally based on clinical diagnosis followed by serological tests. Uneven distribution of RDT in remote areas means that diagnosis is made only using clinical assessment. Atypical clinical features of yaws can lead to inaccurate diagnosis by only relying on WHO clinical guidelines, which often results in incompatibility with serological tests result in the same patient.

To date, there have been no studies assessing the conformity of clinical features based on the WHO guidelines to DPP® RDT. Therefore, this study aimed to evaluate the conformity of yaws clinical features based on the WHO guidelines to the results of DPP® RDT in children living in an endemic area of Alor, Indonesia.

Methodology

The study was conducted from 21-24 September 2020 in the endemic area of Alor Regency, ENT, Indonesia. The regency was selected because it has the highest burden of yaws cases in ENT. The subjects were enrolled consecutively from the elementary school, junior high school, and health centres in Alim Mebung and Kabola Village, Alor regency. The two villages were selected because both contributed to nearly a third of the total new cases in the regency in 2019. All the subjects and their parents who were willing to

Table 1. Classification of yaws based on clinical manifestations according to 2018 WHO guidelines [9].

Lesion types	Examples of lesions	Infectiousness
Early yaws lesions		
Initial lesion	Papilloma	+++
Papillomata	Papillomata	+++
Ulceropapilloma		+++
Ulcer		+++
Macules	Palmar, plantar squamous macules	+
Maculopapules	Maculopapules	++
Papules	Squamous macules	++
Micropapules	Polymorphous	++
Nodules		+
Plaques		+
Hyperkeratosis	Palmar, plantar	-
Bone and joint lesion	Polydactilitis	-
	Osteoperiostitis	-
Late yaws lesions		
Hyperkeratosis	Similar lesions in early and late stages	-
Nodular	Scars	-
Ulcerated nodular	Gangosa	-
Plaques	Osteoperiostitis	-
Bone and joint	Sabre tibia, gondou	-
Juxta-articular nodules		-

- Not infectious; + infectious; ++ very infectious; +++ highly infectious. WHO: World Health Organization.

participate in the study signed an informed consent. Consent for publishing the information and the pictures was also given by all the subjects and parents. We included all children aged 2–15 years, with or without suspected skin lesions of yaws. We excluded subjects who had: 1) any clinical symptoms of COVID-19; 2) a history of diagnosis with lupus, leprosy, congenital syphilis, or the subjects' mother was diagnosed with syphilis during pregnancy; 3) married status or a history of sexual contact; and, 4) history of hemostasis disorders.

Medical history of all the subjects was recorded and a team of trained clinicians performed their physical examination. Subjects were grouped as "suspected yaws" if they had clinical findings of yaws based on the 2018 WHO Guidelines (Table 1) for more than two weeks with or without evidence of close contact (> 20 hours per week) with confirmed yaws case within the previous three months. All the children underwent laboratory testing. Venous blood samples of 3 mL were taken and tested with Chembio Dual Path Platform ® Syphilis Screen and Confirm (Chembio Diagostics Inc., New York, USA). We classified children as "confirmed yaws" if the test was reactive for both treponemal (T1) and non-treponemal (T2) lines and as "not yaws" if the test was reactive only for either T1 or T2 line and if the test was not reactive to both. Children diagnosed with an active yaws infection were treated with azithromycin [11].

All data were analyzed by using Statistical Programme for Social Sciences (SPSS) 20.0. We calculated the positive percent agreement, negative percent agreement, and proportion of overall agreement as a proxy for conformity. The proportion of overall agreement between the clinical features and the results of the DPP® RDT was determined using Chi square or Fisher's exact test. We considered a p value of < 0.05 as significant. This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia (KET-955/UN2.F1/ETIK/PPM.00.02/2020) as a part of the Clinical and Serological Surveillance of Yaws in Children aged 2–15 years old in Alor.

Results

One hundred and ninety seven children participated in this study, with 124 subjects (62.9%) from Alim Mebung village and 73 (37.1%) subjects from Kabola village. There were 114 male (57.9%) and 83 female (42.1%) subjects. The youngest subject was two years old, and the oldest was 15 years old, with a median age of 9 years. Fifteen subjects (7.6%) had family members with similar skin lesions. In addition, there were 82 subjects (41.6%) who had a history of yaws or had previously received yaws treatment.

The observations from the physical examination are presented in Table 2. Out of the 152 subjects with suspected yaws lesions, four subjects (2.6%) had early-stage lesions only, 120 subjects (78.9%) had advanced lesions only, and 28 subjects (18.4%) had both early and advanced lesions. We found a total of 187 lesions (Table 3), with the most common lesion being yaws scars (n = 149, 79.7%). Some clinical features of suspected yaws are shown in Figures 1 and 2. The most common locations of suspected yaws skin lesions in this study were the lower extremities (99.3%), forearms (5.3%), abdomen (3.3%), upper arms (1.3%), back of the hand (1.3%), fingers (1.3%), and instep (0.7%).

The results of the DPP® RDT examination indicated that 8 subjects (3%) tested reactive for both the treponemal and non-treponemal lines, 2 subjects (2%) tested reactive only for the treponemal line, 44 subjects (22.3%) tested reactive only for the non-treponemal line, and 143 subjects (72.6%) tested non-reactive for both lines. The results of the DPP® RDT tests for the subjects with clinical features of suspected yaws are shown in Figures 3 and 4.

Table 2. Suspected yaws with early, advanced, or no lesions based on WHO guideline on subjects in Alor, East Nusa Tenggara (N = 197).

Subjects with/without skin lesions suspected of yaws	n (%)
Suspected yaws lesions	152 (77.2)
Non-yaws lesions	25 (12.7)
No skin lesions	20 (10.1)
Total subjects	197

n: number of research subjects; WHO: World Health Organization.

Table 3. Skin lesion findings in suspected yaws cases in Alor Regency, East Nusa Tenggara based on WHO criteria.

Skin lesions based on WHO Criteria	n (%)
Early stage yaws	
Yaws papules	2 (1.1)
Papilloma	6 (3.2)
Ulcers (ulceropapilloma)	20 (10.7)
Yaws macules	9 (4.8)
Late stage yaws	
Yaws scars	149 (79.7)
Total lesions	**149 (79.7)**
Total of all lesions	**187**

N: number of lesions; WHO: World Health Organization.

Figure 1. Yaws scar with hyperpigmented margin and hypopigmented center, known as "cigarette paper" scar (study subject A).

Figure 2. Single ulcer with painless exudative red granulation tissue, with rancid odor and infesting flies (study subject B).

Table 4. Conformity of clinical features in subjects suspected of yaws based on WHO guidelines to DPP® RDT results.

Clinical conclusion	DPP® RDT		Total	*p*
	Confirmed yaws	Not yaws		
Suspected yaws	8	144	152	$p = 0.202$*
Not yaws	0	45	45	
Total	8	189	197	

*Fisher's test; WHO: World Health Organization.

Figure 3. Reactive DPP® RDT result for treponemal and non-treponemal test lines (study subject A).

Figure 4. Non-reactive DPP® RDT results for both treponemal and non-treponemal test lines (study subject B).

The conformity of yaws clinical features to the DPP® RDT results is presented in Table 4. The proportion of overall agreement of yaws clinical features and the DPP® RDT results for both the lines was 26.9% (p = 0.202); the positive percent agreement was 100%, and the negative percent agreement was 23.8%.

Discussion

This study explored the conformity of clinical features with the positive DPP® RDT test in children in an endemic area. We found that there is no evidence that having yaws clinical manifestation is associated with positivity in RDT, suggesting low conformity between the variables. However, it should be noted that both the villages had received mass treatment with coverage of nearly 97% in 2017. This study has possible clinical and policy implications regarding yaws diagnosis in endemic areas.

There were more males than females in our study. The median age of the subjects was nine years, and the age range was 2-15 years. This finding is in accordance with previous reports that yaws is more often found in boys under 15 years of age with a peak incidence among 6-10 years old children [1,3,12]. Studies on yaws in the Solomon Islands and East Timor in 2014 also reported a mean age of nine years [12]. Eighty-two subjects (41.6%) had been diagnosed with yaws or had previously received treatment for yaws. This could be due to the region's case and contact treatment activities in 2019.

Physical examination indicated that 152 subjects (77.2%) had skin lesions indicative of yaws. The most common skin lesion in this study was the yaws scar, an advanced stage lesion of yaws. Scars are believed to occur because of past yaws infection or current (latent stage) infection. This result is in accordance with the 2016 yaws study in Sei Berombang Village and the 2017 study in Halmahera, which also reported yaws scar as the most common type of skin lesion [13,14]. The 2014 yaws study in the Solomon Islands reported that advanced skin lesions (8.2%) were more commonly found compared to early-stage lesions (2.9%). Arisanti *et al*. in their study in Jayapura, also reported the absence of yaws primary lesion finding in the endemic area after mass treatment [15]. Following the government eradication programs, the incidence of yaws in Indonesia has decreased relative to the previous years and the most frequent clinical finding has shifted to advanced stage lesion pattern [12,16,17].

This study reported eight cases of active yaws following the case and contact treatment program, which reflected an ongoing transmission within the area. Small numbers of confirmed yaws found in this study represent the effectiveness of the 2019 case and contact treatment program implemented by the Alor District Health Office in ENT. One hundred forty-four subjects showed clinical features of suspected yaws; however, they tested as non-yaws using the DPP® RDT kit, which could indicate: 1) past treated yaws cases, which reflect a successful previous mass treatment program, and 2) clinical features alone could not be used to establish the diagnosis of yaws, as a great number of clinical features in suspected yaws cases were later found to be non-reactive according to the recommended RDT DPP® kit. The sensitivity and specificity of the DPP® RDT in diagnosing yaws and syphilis cases are 98.2% and 91.1%, respectively. The sensitivity of DPP® RDT can be affected by the Rapid Plasma Reagin (RPR) titer, which means RPR titer of < 1/16 has treponemal line sensitivity of 73.5% and non-treponemal line of 59.1%, whereas RPR titer of > 1/16 has higher treponemal line and non-treponemal line sensitivity of 97.6% and 96.6% respectively. In endemic areas where the mass treatment program has been implemented, the RPR titer generally decreases, reducing the treponemal line and non-treponemal line sensitivity in DPP® RDT [18,19].

In this study, the proportion of overall agreement between yaws clinical features and the DPP® RDT was 26.9% (Fisher's exact test, p = 0.202). This indicated that clinical features are less associated with positivity in DPP® RDT and therefore should not be used on their own to establish the diagnosis of yaws, even in the endemic areas where pre-test probability is high. In addition to that, recent studies showed that the clinical features of yaws have become more atypical, and yaws scars are reportedly the most common lesion found, especially in endemic areas where mass treatment programs had been conducted [13,14,16,17]. This finding is further proven because all eight confirmed yaws cases in this study had advanced-stage lesions such as scars, while only two out of eight had both early and advanced lesions. As yaws reinfection is possible, the finding highlighted the importance of recognizing scars as a clinical manifestation of yaws for subsequent diagnosis, treatment, and ultimately eliminating community transmission. In order to completely eradicate yaws by 2025, we propose that updated information should be shared with all healthcare providers in the endemic areas to prevent missed diagnosis and treatment.

YSS that has been regularly conducted in accordance with the national program for yaws

eradication by the Ministry of Health of the Republic of Indonesia. The use of DPP® RDT in this study is expected to reduce the cost and duration of examination and is suitable for endemic areas lacking trained laboratory analysts and facilities. The yaws atypical clinical features highlighted the need to update the local yaws diagnosis guideline, considering that it has a significant role as an initial step in diagnosing yaws [20].

Conclusions

The conformity between yaws clinical features and the DPP® RDT test is low; therefore, clinical features alone cannot be used as an initial reference for establishing the diagnosis of yaws in endemic areas. A collaborative effort to increase proficiency in clinical assessment and the use of RDT DPP® for case confirmation is expected to significantly overcome ongoing disease transmission in endemic areas leading to the complete eradication of yaws.

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