PREVALENCE AND FACTORS ASSOCIATED WITH SEROLOGICALLY CONFIRMED YAWS INFECTION AMONG ORANG ASLI POPULATION IN HULU TERENGGANU, MALAYSIA

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by

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LIST OF SYMBOLS

AOR	adjusted odds ratio
AUC	Area Under Curve
CI	confidence interval
IQR	interquartile range
OR	odds ratio
p	p-value
ROC	Receiver Operating Characteristic
b	regression coefficient
n	sample size
SD	standard deviation

LIST OF ABBREVIATIONS

DOTS	Directly Observed Treatment Short-course
DPP	Dual Path Platform
ELISA	Enzyme-Linked Immunosorbent Assay
HREC	Human Research and Ethics Committee
JAKOA	Jabatan Kemajuan Orang Asli
JKNT	Jabatan Kesihatan Negeri Terengganu
MDR	Multi-Drug Resistant
NTDs	Neglected Tropical Diseases
PCR	Polymerase Chain Reaction
RPR	Rapid Plasma Reagin
SDG	Sustainable Development Goal
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TPHA	Treponema pallidum hemagglutination
UNICEF	United Nations Children's Fund
UPENT	Unit Pembangunan Ekonomi Negeri Terengganu
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF APPENDICES

PREVALENS DAN FAKTOR-FAKTOR YANG BERKAITAN DENGAN JANGKITAN YAWS YANG DISAHKAN SECARA SEROLOGI DALAM KALANGAN POPULASI ORANG ASLI DI HULU TERENGGANU, MALAYSIA

ABSTRAK

Latar belakang: Yaws, yang disebabkan oleh bakteria *Treponema pallidum* subspesies *pertenue*, merupakan kebimbangan kesihatan awam utama di kawasan tropika, mempengaruhi terutamanya kanak-kanak dan komuniti terpinggir seperti Orang Asli di Hulu Terengganu, Malaysia. Penyakit tropika terabai yang muncul semula ini menimbulkan cabaran kepada usaha penghapusan global yang disokong oleh Pertubuhan Kesihatan Sedunia (WHO), menunjukkan keperluan penting untuk data epidemiologi tempatan diwujudkan bagi memastikan strategi eliminasi penyakit ini dapat diperkukuhkan.

Objektif: Menilai prevalens dan mengenal pasti faktor-faktor yang berkaitan dengan jangkitan yaws yang disahkan secara serologi dalam kalangan populasi Orang Asli di Hulu Terengganu, Malaysia.

Metodologi: Kajian keratan rentas yang dijalankan menggunakan data sekunder daripada 249 individu Orang Asli dari Pangkalan Data Surveilans Berdasarkan Peristiwa (Event Based Surveillance Database) Jabatan Kesihatan Negeri Terengganu. Pensampelan mudah digunakan bagi pengambilan sampel yang menepati kriteria kajian. Data kategori diterangkan menggunakan frekuensi dan peratusan, sementara min dan sisihan piawai digunakan untuk data berangka. Data-data dianalisis dengan

menggunakan Regresi Logistik Berganda (Multiple Logistic Regression) untuk menilai perkaitan antara faktor- faktor dengan kejadian jangkitan yaws.

Keputusan: Kajian ini mengenal pasti prevalens jangkitan yaws pada 17.3%, (95% CI : 0.128, 0.225) atau 17,300 per 100,000 populasi pada tahun 2020. Umur adalah faktor tunggal didapati signifikan bagi jangkitan yaws, dengan nisbah ods teraras (Adjusted OR) sebanyak 0.977 (95% CI: 0.959, 0.995; p=0.012) yang mana menunjukkan risiko jangkitan yang menurun dengan peningkatan umur. Tiada hubungan signifikan ditemui untuk jantina, status perkahwinan, tahap pendidikan, dan status pekerjaan dengan jangkitan yaws.

Perbincangan dan Kesimpulan: Prevalens yaws yang tinggi dalam kalangan Orang Asli di Hulu Terengganu menekankan keperluan untuk intervensi kesihatan awam yang berfokus, peningkatan surveilans, dan usaha penyelidikan, terutamanya dalam kalangan Orang Asli dan terpinggir. Penemuan kajian ini dapat digunakan untuk menyokong keperluan pelaksanaan program pencegahan dan rawatan yang bersasar bagi menangani yaws dalam kalangan populasi berisiko di Malaysia.

Kata kunci: Yaws, Orang Asli, penyakit tropika terabai, prevalens, faktor risiko, Malaysia.

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ABSTRACT

Background: Yaws, caused by *Treponema pallidum subspecies pertenue*, is a major public health concern in tropical regions, affecting primarily children and marginalized communities, such as the Orang Asli in Hulu Terengganu, Malaysia. This reemerging neglected tropical disease poses a challenge to the global elimination efforts endorsed by the World Health Organization (WHO), highlighting the need for local epidemiological data to guide eradication strategies, thereby informing targeted interventions aligned with WHO's elimination goals.

Objectives: To assess the prevalence and identify associated factors of serologically confirmed yaws infections among the Orang Asli population in Hulu Terengganu, Malaysia.

Methodology: Using secondary data from the Terengganu State Health Department's Event Based Surveillance Database, a cross-sectional analysis was performed on 249 Orang Asli persons. The relationships between yaws infection and characteristics like age, gender, marital status, and comorbidities were investigated using Multiple Logistic Regression.

Result: The study found that the prevalence of yaws infection in Hulu Terengganu, Malaysia is 17.3%, (95% CI: 0.128, 0.225) or 17,300 per 100,000 population in 2020. Age was the only significant predictor of yaws infection, with an adjusted odds ratio (AOR) of 0.977 (95% CI: 0.959, 0.995; p=0.012) per additional year, demonstrating

that the risk of infection is decreasing with increment of age. No significant associations were found for gender, marital status, education level, and employment status with yaws infection.

Discussion and Conclusion: The high prevalence of yaws infection among Orang Asli in Hulu Terengganu highlights the need for focused public health interventions, enhanced surveillance, and research efforts, particularly within indigenous and marginalized communities. The study's findings support the need for implementation of targeted prevention and treatment programs towards the risky population in Malaysia.

Keywords: Yaws, Orang Asli, neglected tropical disease, prevalence, associated factors, Malaysia.

CHAPTER 1

INTRODUCTION

1.1 Background

Throughout human civilization, numerous diseases have been discovered, diagnosed, and treated over the centuries. However, there are still a multitude of antique illnesses that persist to this day, which include yaws. It is a symbolic of a persistent health challenge that has troubled humanity for generations, but not being combated properly. Currently, yaws is one of the neglected tropical diseases that had been highlighted by WHO to be eliminated in 2030 (WHO, 2021). Neglected Tropical Diseases (NTDs) represent a group of debilitating and often disfiguring infections that disproportionately affect marginalized communities in low-income regions of the world (Koffi et al., 2020). Among those abandoned diseases, yaws stands as an exemplar of the ongoing global battle against the existing health disparities, as it thrives where access to healthcare and preventive measures is limited. Hence, yaws is not just a disease but also represents as a reminder of the inequities in health that persist despite our modern advances in healthcare (Popejoy, 2011). This can be seen clearly as yaws had become a reemergence disease in the impoverished, marginalized, and underserved group of people such as rural population in Africa, indigenous people in Philippines and even Orang Asli in Malaysia, which underscores a critical gap in our public health priorities (Alwi et al., 2021; Boock et al., 2017; B. Dofitas et al., 2023).

Historically, yaws can be considered as an antique disease as it has been a companion of humanity for millennia, with evidence of yaws-like infections identified in human remains dating back 1.6 million years ago (Charlotte A. Roberts, 2007). However, there was lack of detailed information about the historical situation of yaws until 1950s as it marked by significant eradication effort by World Health Organization (WHO). As mentioned by Asiedu et al. (2014), a global campaign was led by WHO and the United Nations Children's Fund

(UNICEF) to eradicate yaws using benzathine penicillin injection between 1952 and 1964. There is a remarkable decline in its prevalence following this global campaign against yaws as the worldwide prevalence of yaws reduced by 95%, proving the power of concerted public health efforts (Dyson et al., 2019). However, Agana-Nsiire et al. (2014) pointed out that the resurgence of yaws had started, as the emergence of the disease can be seen in neglected communities in many countries across the world despite the initial successful case reduction that mentioned before. This neglected communities are away from the spotlight of global priorities leading to current neglected situation of the disease (Asiedu et al., 2014).

Nowadays, yaws is still endemic in warm, humid regions of Africa, Asia, Latin America, and the Pacific Islands, with nearly 200,000 new cases occur annually as estimated by WHO (Kazadi et al., 2014). At least 15 countries still had been confirmed as endemic for yaws where countries like Ghana, Papua New Guinea, and the Solomon Islands have reported a significant number of cases in recent years (Giacani et al., 2019; Marks, Vahi, et al., 2015). In 2023, WHO (2024) points out that 16 countries are considered as currently endemic for yaws, while 82 countries, areas and territories are considered previously endemic, with current status unknown, as shown in Figure 1.1.

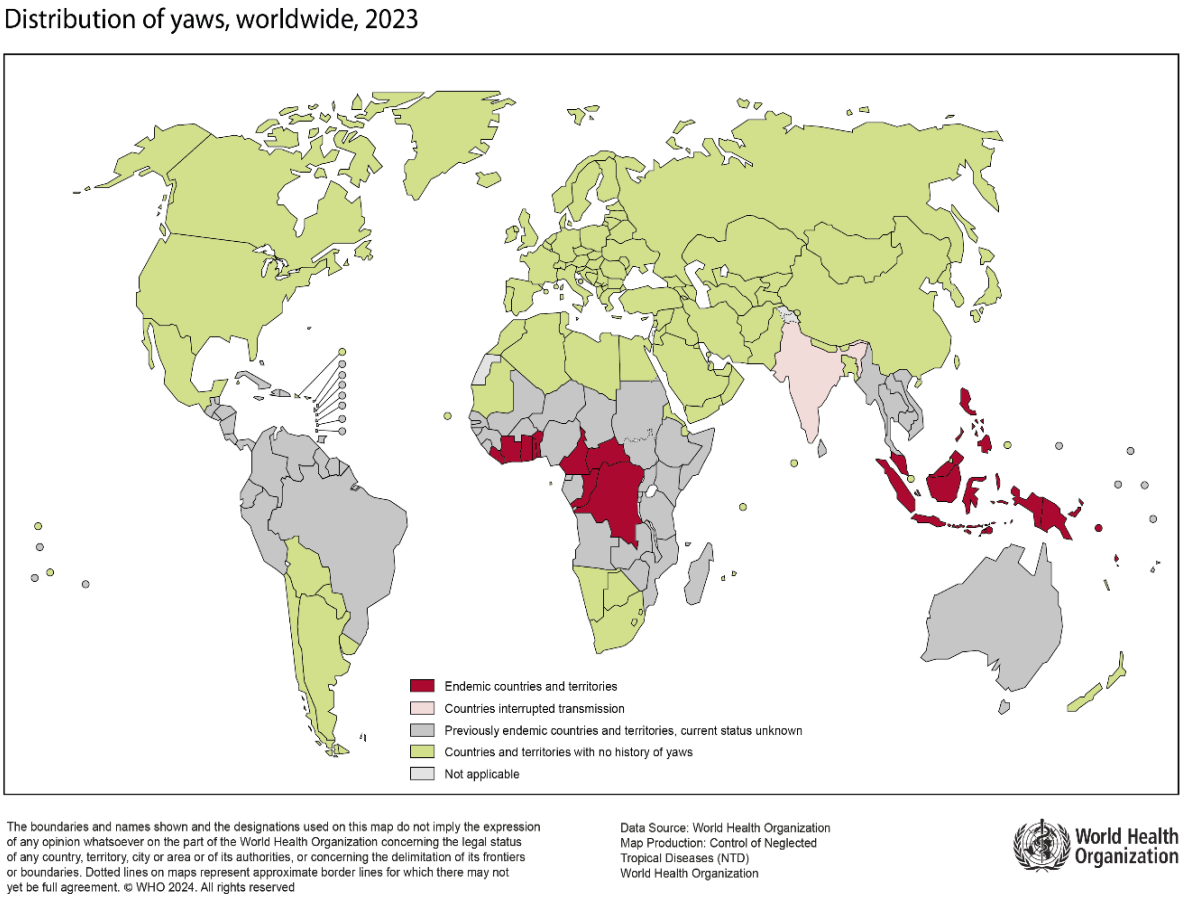

Figure 1.1 Distribution of yaws worldwide, 2023

(Source: The Global Health Observatory, 2024)

In 2012, WHO held a consultation of yaws experts in Morges, Switzerland and recommended mass treatment using single-dose oral azithromycin (30 mg/kg body weight) to eradicate the disease by 2020, in which the new treatment strategy has been referred to as the Morges Strategy. However, the target had been extended as WHO has launched a renewed plan to globally eradicate yaws by 2030 (Fongwen et al., 2022).

In Malaysia context, yaws also cannot be considered as a mere historical artifact but also a modern-day challenge. It has been an endemic, rural disease in Malaysia. However, due to its rarity, the disease is often neglected, goes unrecognized and misdiagnosed. Since yaws is not a notifiable disease in this country, the numbers of reported cases have tended to vary with the nature, extent of health services and the reporting system of various places in

Malaysia. The earliest recorded campaign against yaws in Malaysia was carried out in 1920 in four states: Negeri Sembilan, Pahang, Perak, and Selangor (Ministry of Health Malaysia, 2024). Between 1958 to 1982, the reported annual incidence of yaws in Malaysia fell from 140.85 to 0.12 per 100,000 population, as mentioned by Lo (1985). Since then, no proper publication of yaws cases can be found, but a few clusters of suspected yaws had been reported among Orang Asli from 2006 onwards (Ministry of Health Malaysia, 2024).

As happened in most of marginalized group across the world, the Orang Asli in Malaysia who is traditionally semi-nomadic hunter-gatherers, is also vulnerable to this yaws infection due to their geographical isolation, lower education, socioeconomic status, and limited healthcare access (Ithnin et al., 2021; King et al., 2009; Okine et al., 2020). The August 2020 yaws cluster that happen in Hulu Terengganu, is the evidence of the disease reemergence in this country among this special population that needs to be highlighted and managed effectively.

1.2 Event Based Surveilance Report and Yaws

It started with an incidental finding of bizarre skin lesions on a 13-year-old Orang Asli girl in Hulu Terengganu, that spotted by a community clinic nurse when she accompanied her father for a regular tuberculosis follow-up and DOTS (Directly Observed Treatment Short-course) in August 2020.

She was then referred to the doctor, who initially suspected a form of TB skin presentation due to her father's TB status. As for that, she was referred to a dermatologist for further management of suspected TB skin.

At the dermatology clinic, a senior dermatologist consultant suspected the rare and neglected yaws disease based on the clinical characteristics of the lesions. The patient did not report associated symptoms such as fever, itchiness, or pain and mentioned that the lesions had been present for four months without seeking medical attention. On physical examination, the patient was alert and conscious with a temperature of 37°C. Multiple yellow-crusted hyperkeratotic plaques were observed on her face, involving her forehead, cheek, upper lip, and chin (Figure 1.2). The plaques were non-tender but exuded a yellow discharge. Her other vital signs and systemic examinations were unremarkable.

Figure 1.2 Multiple yellow-crusted hyperkeratotic plaques on the patient's face, involving the forehead area, the upper lip and chin area

(Source: Dermatology Clinic Hospital Sultanah Nur Zahirah, 2024)

Serological tests for *Treponema*, including the *Treponema pallidum* hemagglutination (TPHA) test and rapid plasma reagent (RPR) test, returned positive results with a titre of 1:256. Based on clinical and serological findings, she was diagnosed with yaws. The patient received a single dose of 1.2 million units (MU) of intramuscular Benzathine Penicillin G and was advised on proper personal hygiene.

Active case detection was done following the detection of the first case and mass drug administration was implemented to the whole community as a control measure of the cluster occurrence. The event was reported and filed into Event Based Surveillance Database in Terengganu Health State Department Surveillance unit office and will be analysed in this study.

1.3 Problem Statements

There is an emerging trend in the reporting of yaws cases among Orang Asli in Malaysia, including Orang Asli in Terengganu, emphasizing the urgency of addressing this issue (Ministry of Health Malaysia, 2024). Hence, the focus should be given to manage the risk imparted by this neglected disease towards the Orang Asli community.

This is further emphasized by the fact that yaws is a rapidly transmissible disease that predominantly affects the rural and marginalized populations, as mentioned by Fitzpatrick et al. (2014), making the Orang Asli community in Malaysia particularly susceptible to infection and its debilitating consequences.

As recommended by the World Health Organization's (WHO), more localized data is needed to ensure progress for yaws elimination. The data should cover various aspects such as endemicity mapping, prevalence rates, and the identification of risk factors (WHO, 2021). However, it is an obvious challenge in Malaysia itself as yaws is not a notifiable disease in this country at the moment, which results in a lack of data and publications. This lack of information is a significant obstacle to the effective progress of yaws elimination efforts.

1.4 Rationale of the study

More data and publications will be very helpful to understand the epidemiological distribution of yaws infection, which will assist policymakers in establishing yaws endemicity mapping in this country. This is important to help them in developing focal and targeted interventions that will in turn enhance faster elimination of this disease.

In addition to that, insight into the factors associated with the disease is also critical for policymakers to plan effective strategies that can prevent further transmission of the infection. This knowledge gap about the disease prevalence, characteristics and associated factors

highlights the necessity for focused research and study to facilitate the elimination of yaws in this country.

Hence, this study aims to establish the prevalence of yaws cases in Hulu Terengganu, Malaysia, while also exploring into the factors that play a role in serologically confirmed yaws infections among the Orang Asli in Hulu Terengganu, Malaysia. This effort is critical towards establishment of endemicity mapping and formulation of strategies to combat the disease.

1.5 Significance of the study

Examining the reemergence of the historic disease yaws in Hulu Terengganu, Malaysia through this study will contribute valuably to the World Health Organization's endeavors to eliminate yaws by the year 2030. This effort necessitates a detailed understanding of local epidemiological patterns of the disease (WHO, 2021). Marks, Vahi, et al. (2015) stated that the major obstacle to interrupt yaws transmission is the lack of detailed research and data on the current locations of case occurrences. The significance of such research is amplified by the rarity of the disease and the historical neglect that has occurred, emphasizing the need for focused surveillance and intervention strategies tailored to affected populations (Asiedu et al., 2014; WHO, 2018).

For the Department of Orang Asli Development (JAKOA) in Malaysia, the findings of this study are particularly significant. By identifying the key factors driving yaws transmission among the Orang Asli, JAKOA can develop more awareness and effective health intervention programs tailored to the unique needs of these communities.

This study aligns with Sustainable Development Goal 3 (SDG 3), which aims to ensure healthy lives and promote well-being for all at all ages. Specifically, SDG Target 3.3 seeks to end the epidemics of neglected tropical diseases (NTDs) by 2030 (United Nations, 2015; WHO, 2020). By addressing the reemergence of yaws, this research supports the global health

agenda to reduce the burden of NTDs, contributing to the broader goals of reducing morbidity and mortality associated with these diseases (WHO, 2021).

1.6 Research Questions

i. What is the prevalence of serologically confirmed yaws infection among Orang Asli in Hulu Terengganu, Malaysia?

ii. What are the associated factors that contribute to serologically confirmed yaws infection among Orang Asli in Hulu Terengganu, Malaysia?

1.7 Objectives

1.7.1 General Objective

To study the prevalence of serologically confirmed yaws infection and its associated factors among Orang Asli in Hulu Terengganu, Malaysia

1.7.2 Specific Objectives

i. To determine the prevalence of serologically confirmed yaws infection among Orang Asli in Hulu Terengganu, Malaysia

ii. To describe socio-demographic characteristics of serologically confirmed yaws infection among Orang Asli in Hulu Terengganu, Malaysia

iii. To determine the associated factors of serologically confirmed yaws infection among Orang Asli in Hulu Terengganu, Malaysia

1.8 Research Hypotheses

There are significant factors (sociodemographics/comorbidities) associated with serologically confirmed yaws infection among Orang Asli in Hulu Terengganu, Malaysia.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The literature review was conducted by using multiple search engines available freely in the web, such as PubMed and Google Scholar. Besides that, the university subscribed database also being utilised as a medium to look for literature. The literature search not filtered to recent publications only as there is limited publication regarding the topic especially with regards to Malaysia or Asia. Numerous searching strategies were applied, such as a combination of terms with the use of Boolean operators (AND, OR, NOT). List of keywords applies during the searches such as yaws, Associated factors, Orang Asli, Indigenous, Aborigines, Malaysia, Global, Incidence and Prevalence. Table 2.1 and 2.2 show the key references that were found in this literature search.

Table 2.1 Key references for objective 1

Author	Study Location	Data (Year)	Findings
Mitja *et al.*(2015)	Global (Sytematic Review)	1990-2014	Prevalence of active disease ranged from **0·31% to 14·54%** in yaws-endemic areas.
Guerrier *et al.* (2011)	Wallis and Futuna (Western Pacific Region)	2010	Percentage of yaws infection is from **10%** only. n= 27/264
Mitja *et al.*(2015)	Cameroon (Africa Region)	2012	Prevalence of active disease is **9.02%**. n= 97/1072
Milena dos santos(2010)	Timor-Leste (Asia Region)	2007	Prevalence of active disease is **0.39 %**. n= 6/1535
Dofitas *et al.*(2023)	Philipines (Southeast Asia)	2022	Prevalence of active yaws detected is **7.8%** among indigenous people in Philipines

Chan *et al.*(2022)	Sabah (Malaysia)	2015	Seroprevalence estimates for yaws Rp17 was **4.91%**.

Table 2.2 Key references for objective 2 and 3

Variables	Author	Study Location	Data (Year)	Findings
Age	Milena dos santos (2010)	Timor Leste	2007	All yaws cases (100%) was found from children age group (<15 years old) n=6/1535
	Mitja *et al.* (2013)	Wallis and Futuna (Western Pacific Region)	2010	Yaws predominantly affects children; 75% of new cases are in individuals younger than 15 years and children (aged 2–15 years) are the main reservoir of infection
	Dzotsi *et al.* (2017)	Ghana	2013	The proportion of yaws case among above 15-year-old group is 0.4
	Marks *et al.* (2015)	Solomon island	2013	About 65% of confirmed cases are among below 15 years old population
	Okine *et al.* (2020)	Ghana	2017	The proportion of yaws case in under 15-year-old group is 0.5 (n=186)
Gender	Dofitas *et al.* (2023)	Philipines	2010	There were about 60% of yaws cases among indigenous people in Luzon and Visayas island are male gender.
	Milena dos santos (2010)	Timor Leste	2007	Males were more commonly affected than females (male 42.3%, n= 362/855 and female 34.0%, n= 231/680

	Okine *et al.* (2020)	Ghana	2019	Yaws cases were two times more likely to be males (cOR = 2.70, 95% CI: 1.38–5.26).
	Md Alwi *et al.* (2021)	Kelantan	2021	Boys are reportedly more prone to infection because they are physically active and more likely to acquire abrasions in the lower limbs
	Dzotsi *et al.* (2017)	Ghana	2013	Males were most affected with 71.7% while females represented 28.3% of detected cases.
Sub-Ethnicity	Okine *et al.* (2020)	Ghana	2019	The Ga/ Adangme (cOR = 4.80, 95% CI: 1.23–18.63) ethnic groups had increased odds of yaws infection compared to the other ethnic groups
	Anuar *et al.* (2014)	Malaysia	2013	Infections like Trichuriasis and ascariasis are significantly higher rates were observed among Senois, especially those aged 15 years and below
	Dofitas *et al.* (2023)	Philipines	2010	54.3% of yaws cases were detected among Aetas while there was no cases detected among Dumagat or Remontados indigenous people
	Anuar *et al.* (2014)	Malaysia	2013	Most of the Senoi tribes still pursue nomadic lifestyles and live by hunting and gathering fruits, which make them separated from proper medical and health services
Education Status	Dzotsi *et al.* (2017)	Ghana	2013	The proportion of primary education level who detected to have yaws cases is 0.31 (n=122) meanwhile, 15.22% of detected yaws cases had never been to school while only 7.61% of control group had never been to school.

Comorbidities	Aguado *et al.* (2011)	Papua New Guinea	2009	5.1% Individuals with other infections or comorbidities may have weakened immune systems, increasing their susceptibility to yaws infection. n =138
	Berbudi *et al.* (2020)	Indonesia	2020	People with diabetes will become immunocompromise and have an increased risk of infections, including bacterial, viral, and fungal infections
	Huson *et al.*, 2015	Africa	2014	The immunocompromised state caused by HIV infection makes individuals more susceptible to various infections, including bacterial, viral, fungal, and opportunistic infections
Employment Status	Dzotsi *et al.* (2017)	Ghana	2013	The proportion of employed cases is 0.33 (n=112). 82.61% of detected yaws cases are those who did not have job. n=38/46
Personal Hygiene	Mitja *et al.* (2015)	Global (Sytematic Review)	1990-2014	The main risk factor for these groups which bring 11% of prevalence, is the scarcity of access to health care and poor personal hygiene.
	Chan *et al.* (2022)	Sabah (Malaysia)	2015	One of the significant associations in decreasing prevalence of the disease is the use of bathrooms compared to not.
	Okine *et al.* (2020)	Ghana	2019	Good hand washing practices was less frequent among cases compared to community controls. A greater proportion of cases compared to controls (cOR = 4.98, 95% CI: 2.42–10.27) reported that they did not wash their hands regularly when required

Health Seeking Behaviour	Muslimah ithnin (2021)	Negeri Sembilan, Malaysia	2018-2019	Some members in the Orang asli community still are afraid of using modern medical treatments, as they prefers medicinal plant roots from the nearby forest based on the knowledge they attained from the older generations, even though the health care facilities are available nearby their settlement
Sanitation and clean water supply	Marks *et al.* (2015)	Solomon island	2013	Lack of water and the absence of hand washing facilities and latrines contribute to 33.2% while those who did have the water facilities were 23.4%
	Fitzpatrick *et al.* (2018)	Global (Sytematic review)	1945-2016	Based on the reviews of the literatures, improved water supply have been attributed to the recession of yaws in Sri Lanka
Overcrowding	Marks *et al.* (2015)	Solomon island	2013	The household with more than 5 residents (18.9%) have unadjusted OR of 1.22 compared to household with less crowd less than 5 residents (16.0%).
	Okine *et al.* (2020)	Ghana	2019	Compared to community controls, cases had a three-fold increased odds of sharing a sleeping room with more than four persons (cOR =3.31, 95% CI: 1.71–6.41) or sharing a house with 5–8persons (cOR = 4.65, 95% CI: 1.68–12.86) or more than eight persons (cOR = 6.78, 95% CI: 2.24–20.50)
	Dzotsi *et al.* (2017)	Ghana	2013	Overcrowding was significantly associated with yaws infection [Adjusted OR (MH); 2.8; 95% CI; 1.3-5.95.0; p-value; 0.014]

2.2 Overview of Yaws

Yaws is a chronic bacterial infection caused by *Treponema pallidum subspecies pertenue*, a close relative of the infamous bacterium responsible for syphilis. The disease primarily affects the skin, bones, and cartilage and predominantly affects children under the age of 15, as up to 75% of the cases were those among this group (Giacani and Lukehart, 2014; WHO, 2018). Genetic studies have revealed minimal genomic differences between *T. pallidum* subspecies causing yaws and syphilis, emphasizing the importance of epidemiological and clinical distinctions in diagnosing and managing these diseases (Čejková et al., 2012; Marks, Lebari, et al., 2015).

The clinical manifestation of yaws is characterized by distinct stages which are primary, secondary, latent, and tertiary with incubation period range from 9 to 90 days. The primary yaws begin with an initial skin lesion, or "mother yaw," that emerges at the site of the bacterial entry, which is usually on the legs or feet. As weeks to months pass, secondary lesions may emerge across the body, spreading from the initial site of infection which become the secondary stage of the disease. Without intervention, a person may enter a latent phase with no visible outward symptoms. However, the disease still simmers beneath the surface which makes it capable of resurfacing after years to inflict the tertiary stage that cause disfiguring of the bones and joints (Mitjà et al., 2015).

Yaws primarily spreads through skin-to-skin contact during childhood, with infectious lesions typically resolving before sexual maturity, reducing the likelihood of sexual transmission (Giacani and Lukehart, 2014). However, clinically active and latent yaws cases serve as reservoirs for sustaining transmission, highlighting the importance of targeted treatment and contact tracing to interrupt the spread of the disease (Cooper et al., 2022; Dyson et al., 2019).

The pathogenesis of yaws involves the progression of primary, secondary, and tertiary lesions that predominantly affect the skin, bones, and cartilage, with potential complications such as central nervous system and cardiovascular infections (Šmajs et al., 2012). The disease can manifest as skin ulcers, and factors young age and male gender have been associated with yaws infection (Okine et al., 2020).

In term of diagnosis, WHO define that the diagnosis of confirmed yaws is based on positive result of Dual Path Platform (DPP), which is not available in most countries including Malaysia (Ministry of Health Malaysia, 2024; WHO, 2021). However, Polymerase Chain Reaction (PCR) test also can be done as an alternative for DPP in confirming yaws infection, but practically not been used regularly due to its high cost and availability. Hence, yaws diagnosis often lean on a combination of clinical signs and serological tests, such as the Rapid Plasma Reagin (RPR) test, which detects an immune response to the infection, and the *Treponemal*-specific tests like *Treponema pallidum* haemagglutination (TPHA) that confirm the presence of the bacteria, as practised in this country. Thus, the accepted diagnosis of confirmed yaws in Malaysia is a clinically suspected yaws individual with positive serological tests (RPR and TPHA) as stated in draft Guideline Yaws Eradication Program for Malaysia (Ministry of Health Malaysia, 2024). Nevertheless, treatment is a game-changer for this neglected disease, as a single dose of Benzathine Penicillin G or oral Azithromycin has been proven to be an effective cure to halt the transmission and prevent the unwanted complications such as deformities and disability (Marks, Lebari, et al., 2015).

2.3 Prevalence of yaws infection

2.3.1 Global Prevalence

Yaws continues to be a substantial public health issue in many regions of the world. A comprehensive worldwide survey conducted in 15 countries with documented endemicity revealed a wide range of prevalence rates, ranging from 0% to 38% (Handley et al., 2022). This variety highlights the diverse nature of the disease burden in various regions. Moreover, a comprehensive analysis of data from 1990 to 2014 revealed that the occurrence of active yaws disease varied between 0.31% and 14.54% in regions where the disease is prevalent (Mitjà, Marks, et al., 2015). These statistics indicate a continuous existence of yaws, which is influenced by factors such as the availability of healthcare, the accuracy of reporting, and the effectiveness of public health initiatives.

Recent reports by the World Health Organization (WHO) support these findings, indicating that yaws is endemic in 13 countries, with the majority of cases occurring in West and Central Africa, Southeast Asia, and the Western Pacific (WHO, 2018). Furthermore, the latest data on Global Health Observatory shows that yaws is still endemic in 16 countries while and a lot more are considered previously endemic with current status unknown (WHO, 2024).

2.3.2 Regional Prevalence

When examining specific regions, the prevalence of yaws continues to reveal notable patterns. In the Western Pacific, studies reported a prevalence rate of approximately 10% (dos Santos et al., 2010). Similarly, in Africa, the prevalence was documented at 9.02% (Guerrier et al., 2011). In Asia, the reported prevalence was relatively lower at 0.39% (Marks, Vahi, et al., 2015). These statistics reflect regional endemicity and emphasize that yaws remains a significant public health issue across diverse geographical landscapes.

2.3.3 Prevalence Among Specific Populations and Risk Groups

Certain populations and risk groups are particularly vulnerable to yaws. In Southeast Asia, a study focusing on indigenous populations in the Philippines found a yaws prevalence of 7.8% (B. Dofitas et al., 2023). This higher prevalence among specific groups highlights the necessity for targeted public health interventions. In Malaysia, recent studies on yaws are scarce. However, a seroprevalence study among the rural population in Sabah used serological multiplex beads to monitor various diseases simultaneously, revealing a yaws seroprevalence of 4.91% (Chan et al., 2022). These findings indicate that yaws may still be present in rural and isolated communities, necessitating further investigation and focused public health efforts.

2.3.4 Limitations and Challenges in Determining Prevalence

Determining the prevalence of yaws presents several limitations and challenges that hinder accurate assessment and effective disease control. These challenges range from diagnostic difficulties to socio-cultural barriers, and each plays a significant role in complicating the epidemiological understanding of yaws.

2.3.4(a) Diagnostic challenges

One of the primary challenges in determining yaws prevalence is the difficulty in accurate diagnosis. Yaws, caused by *Treponema pallidum pertenue*, presents symptoms similar to other skin infections and conditions, making clinical diagnosis challenging. In addition, serological tests, such as the Rapid Plasma Reagin (RPR) test and the *Treponema Pallidum* Particle Agglutination (TPPA) test, are commonly used, but they do not distinguish between yaws and other *treponemal* infections, such as syphilis (Mitjà et al., 2013). This diagnostic ambiguity complicates prevalence estimation as misdiagnosis or over-diagnosis can occur.

2.3.4(b) Lack of surveillance system

Effective surveillance systems are essential for accurate prevalence data. However, in many yaws-endemic regions, surveillance systems are either weak or non-existent. According to Fitzpatrick et al. (2018), the absence of robust health information systems results in underreporting and inconsistent data collection. This limitation is exacerbated by the remoteness of affected areas, where healthcare infrastructure is often inadequate, further impeding regular surveillance and reporting.

2.3.4(c) Socio-cultural behaviour

Socio-cultural barriers significantly impact the determination of yaws prevalence. In many communities, there is a reliance on traditional healers and remedies, which delays individuals from seeking formal medical care (Matungwa et al., 2022). This reliance can lead to underreporting of cases as infections are managed outside the formal healthcare system. Additionally, stigma associated with yaws may discourage individuals from reporting symptoms or seeking treatment, as noted by Mitja et al. (2011).

2.3.4(d) Geographic and environmental factors

The geographic and environmental characteristics of yaws-endemic regions pose significant challenges to prevalence determination. Many of these regions are remote, with limited access to healthcare facilities. This remoteness hampers the ability of health workers to conduct regular screenings and follow-up visits, leading to gaps in data collection (Marks, Vahi, et al., 2015; Mitjà, Marks, et al., 2015). Moreover, the tropical climate and terrain can make transportation and communication difficult, further complicating surveillance efforts.

2.3.4(e) Financial and resource constraints

Financial and resource constraints are substantial barriers to accurate prevalence determination. Limited funding for yaws control programs results in inadequate resources for comprehensive surveys and research (Fitzpatrick et al., 2018). This constraint affects the availability of diagnostic tools, trained healthcare personnel, and logistical support necessary for large-scale epidemiological studies.

2.4 Risk factors of yaws infection

Various studies had embarked on exploring the potential underlying factors contributing to the transmission and prevalence of yaws infection. This disease predominantly thrives in tropical environments where sanitation and access to clean water are compromised. Researches highlight a diverse range of factors, such as environmental conditions, socio-economic status, and co-existing health issues, which may influence an individual's susceptibility to infection.

2.4.1 Sociodemographic factors

2.4.1(a) Age

Age is a critical determinant in the epidemiology of yaws, with the disease predominantly affecting the pediatric population globally. dos Santos et al. (2010) highlighted that in Timor Leste, all reported yaws cases were found in children under the age of 15, accounting for 100% of the cases. This underscores the heightened vulnerability of the pediatric group, who are the primary sufferers and reservoirs of yaws. Similarly, Guerrier et al. (2011) and Mitjà et al. (2013) reported that in Wallis and Futuna, located in the Western Pacific Region, yaws predominantly affects children, with 75% of new cases occurring in individuals younger than 15 years, identifying children aged 2–15 years as the main reservoir of infection.

Regionally, the pattern persists across different continents. In Ghana, Dzotsi et al. (2017) found that the proportion of yaws cases among individuals above 15 years old was only 0.4%, further emphasizing the concentration of the disease within the younger population. Marks, Vahi, et al. (2015) reported similar findings in the Solomon Islands, where about 65% of confirmed yaws cases were among those below 15 years old. In a more recent study, Okine et al. (2020) reaffirmed this trend in Ghana, noting that the proportion of yaws cases in the under-15 age group was 0.5% (n=186). These findings collectively highlight the critical need

for age-targeted public health interventions and educational programs to effectively manage and reduce the incidence of yaws among children, who are at the epicenter of this disease's spread.

2.4.1(b) Gender

Gender differences play a significant role in the epidemiology of yaws, with males often being more frequently affected than females. This trend has been observed globally and can be attributed to various cultural, behavioral, and environmental factors. In Philippines, B. Dofitas et al. (2023) reported that about 60% of yaws cases among indigenous people in Luzon and Visayas islands were male. Similarly, dos Santos et al. (2010) found in Timor Leste that males were more commonly affected than females, with males comprising 42.3% of the cases (n=362/855) compared to females at 34.0% (n=231/680). These findings suggest that males are at a higher risk, possibly due to more frequent engagement in outdoor activities that increase the likelihood of skin abrasions and subsequent infection.

In Africa, similar patterns are observed. Okine et al. (2020) noted that in Ghana, yaws cases were two times more likely to occur in males (cOR = 2.70, 95% CI: 1.38–5.26). This increased susceptibility among males was also reported by Dzotsi et al. (2017), who found that males accounted for 71.7% of yaws cases, while females represented only 28.3%. In Malaysia, Alwi et al. (2021) mentioned that boys in Kelantan were reportedly more prone to infection due to their physical activity levels, which make them more likely to acquire abrasions on the lower limbs, a common site for yaws lesions. These consistent findings across different regions underscore the importance of considering gender-specific factors when designing public health interventions and educational programs to effectively reduce the incidence of yaws.

2.4.1(c) Indigenous and marginalized group

Yaws primarily affects marginalized populations, including indigenous communities, due to socio-economic and environmental factors. For instance, the Orang Asli in Malaysia, who live in geographically isolated areas with limited healthcare access, are particularly susceptible to yaws (Alwi et al., 2021; Pah Rokiah SyedHussain et al., 2017). This pattern is mirrored in other countries, as yaws cases is also detected in indigenous population (B. L. Dofitas et al., 2020).

Moreover, the level of susceptibility is discovered even deeper between the sub-ethnicity of the indigenous population themselves. For example, the Aetas tribe in the Philippines has been identified as having a higher incidence of yaws compared to other ethnic groups (B. Dofitas et al., 2023). Similarly, in Ghana, the Ga and Adangme ethnic groups exhibit higher odds of yaws infection compared to other ethnic groups, with an odds ratio (OR) of 4.80 (Okine et al., 2020).

Nevertheless, this pattern of sub- ethnic susceptibility could potentially be mirrored in certain Orang Asli tribes in Malaysia, as suggested by research that found infections like Trichuriasis and Ascariasis at significantly higher rates among the Senoi tribe compared to the other Orang Asli sub-ethnicity like Negrito and Malay Proto tribes, potentially due to nomadic lifestyles practice and reluctance to embrace modern healthcare (Anuar et al., 2014; Ithnin et al., 2021).

2.4.1(d) Education and Employment status

The correlation between low education levels and the prevalence of yaws is a significant aspect of the disease's epidemiology. In Ghana, a study conducted among residents in the West Akim Municipality revealed that 82.61% of yaws cases were found in individuals from lower education groups (Dzotsi et al., 2017).