

**DISTRIBUTION AND INCIDENCE OF CONFIRMED
MEASLES INFECTION AND ITS RELATIONSHIP
WITH VACCINATION STATUS IN KELANTAN,
2016-2023**

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by

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LIST OF ABBREVIATION

AOR	Adjusted Odd Ratio
AIC	Akaike Information Criterion
AUC	Area under Receiver Operating Characteristic Curve
BIC	Bayesian Information Criterion
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
JEPeM	<i>Jawatankuasa Etika Penyelidikan (Manusia) Universiti Sains Malaysia</i>
MCV	measles containing vaccine
MCV1	measles containing vaccine first dose
MCV2	measles containing vaccine second dose
MMR	measles-mumps-rubella
MREC	Medical Research and Ethics Committee
NMRR	National Medical Research Registry

OR	Odd Ratio
R_0	R naught
ROC	receiver operating characteristic
SIAs	supplementary immunization activities
SM2	<i>Sistem Maklumat Siasatan Measles</i>
WHO	World Health Organization

LIST OF SYMBOLS

α	Alpha
$\&$	And
β	Beta
$=$	Equal to
$<$	Less than
$>$	More than
\geq	More than or equal to
n	Number of subjects
$\%$	Percentage
P	Population's proportion
Δ	Precision of estimation
m	Ratio between two groups

Z

Z-score

TABURAN DAN KEJADIAN KES DEMAM CAMPAK YANG DISAHKAN DAN HUBUNGANNYA DENGAN STATUS VAKSINASI DI KELANTAN, 2016-2023

ABSTRAK

Latar Belakang: Walaupun Malaysia mempunyai program eliminasi campak yang lama serta liputan vaksinasi yang baik, negeri Kelantan tetap mencatatkan beberapa kejadian wabak campak berulang. Hal ini menimbulkan persoalan tentang kecukupan imuniti populasi setempat dan peranan vaksinasi dalam risiko jangkitan campak dalam kalangan penduduk Kelantan.

Objektif: Kajian ini bertujuan untuk menggambarkan taburan jangkitan campak yang disahkan, menilai kadar kejadian jangkitan campak yang disahkan mengikut kadar negeri dan kadar spesifik, dan mengkaji hubungan antara status vaksinasi dan risiko jangkitan campak yang disahkan di Kelantan bagi tempoh 2016 hingga 2023.

Metodologi: Satu kajian keratan rentas menggunakan data pemantauan dari sistem SM2 E-Measles telah dijalankan. Sebanyak 5,495 kes disyaki yang dilaporkan dari Januari 2016 hingga Disember 2023 telah dianalisis. Kadar kejadian dikira menggunakan data populasi pertengahan tahun Jabatan Perangkaan dan dipersembahkan mengikut tahun, daerah, jantina, umur, dan etnik. Regresi logistik berbilang digunakan untuk mengkaji hubungan antara status vaksinasi dan jangkitan campak yang disahkan, diselaraskan mengikut umur, jantina, etnik dan sejarah kontak.

Keputusan: Hanya 398 kes (7.2%) yang disahkan melalui makmal. Kadar kejadian tahunan menurun daripada 21.1 per sejuta (2016) kepada 17.5 (2017), kemudian melonjak ke 69.0 (2019) akibat wabak Orang Asli di Gua Musang, menurun ke sifar pada 2021 sewaktu sekatan COVID-19, dan kembali meningkat ke 28.5 pada 2023, dengan Pasir Puteh menjadi kawasan panas baharu (11.3 per 100,000). Bayi berumur kurang 1 tahun mencatatkan kadar kejadian tertinggi, memuncak pada 127.4 per 100,000 pada 2020. Walaupun Orang Asli merupakan sebahagian kecil daripada keseluruhan kes yang dilaporkan, lebih separuh daripada kes yang disiasat dalam kalangan Orang Asli sebanyak 56.4% disahkan sebagai campak berbanding 6.0% dalam kalangan Melayu dan 2.1% dalam kumpulan etnik lain.. Setelah disesuaikan dengan faktor lain, tidak divaksinasi sepenuhnya (AOR 3.97, 95% CI: 2.69, 5.97) dan tidak divaksinasi langsung (AOR 3.51, 95% CI 2.39, 5.27) kekal sebagai peramal kukuh risiko jangkitan campak yang disahkan berbanding dengan yang lengkap divaksinasi. Sejarah kontak dengan kes positif campak (AOR 14.80, 95%CI: 9.36, 23.40) dan etnik Orang Asli (AOR 15.4, 95%CI: 10.5, 22.6) turut menjadi faktor risiko bebas yang signifikan.

Kesimpulan: Analisis epidemiologi kes campak yang disahkan di Kelantan dari 2016 hingga 2023 menunjukkan bahawa meskipun liputan vaksinasi nasional tinggi, terdapat jurang imuniti yang besar, terutama dalam kalangan individu yang tidak atau kurang divaksinasi, serta komuniti terpinggir seperti Orang Asli. Kajian ini menekankan kepentingan vaksinasi lengkap dalam mengurangkan risiko jangkitan campak yang disahkan, serta keperluan untuk

kempen imunisasi yang disasarkan, pendekatan yang sensitif budaya, dan usaha pemantauan yang dipertingkatkan bagi memastikan penghapusan campak secara berterusan di negeri ini.

KATA KUNCI: demam campak, vaksinasi campak, kadar insidens

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2023**

ABSTRACT

Background: Despite Malaysia's long-standing measles elimination programme and good vaccination coverage, Kelantan has recorded recurrent outbreaks, calling into question the adequacy of local population immunity and the role of vaccination to contracting measles risk in Kelantan population.

Objective: To describe the distribution of confirmed measles infection, to examine the state and specific incidence rate trends of confirmed measles infection, and to describe the relationship between vaccination status and confirmed measles infection in Kelantan from 2016 to 2023.

Methods: A cross-sectional study of surveillance data from the SM2 e-Measles system was undertaken. All 5495 suspected cases notified from January 2016 to December 2023 were analysed. Incidence rates were calculated with Department of Statistics mid-year population denominators and presented by year, district, sex, age and ethnicity. Multivariable logistic regression examined the relationship between vaccination status and confirmed infection, adjusting for age, sex, ethnicity and contact history.

Results: Only 398 notifications (7.2%) were laboratory-confirmed. Annual incidence fell from 21.1 per million (2016) to 17.5 (2017), rose sharply to

69.0 (2019) driven by an Orang Asli outbreak in Gua, declined to zero in 2021 during COVID-19 restrictions, and rebounded to 28.5 in 2023, with Pasir Puteh emerging as a new hotspot (11.3 / 100 000). Infants less than 1 year persistently recorded the highest incidence, peaking at 127.4 / 100 000 in 2020. Although the Orang Asli ethnic constitute only a small proportion of all notifications, more than half of the Orang Asli cases investigated (56.4%) were confirmed measles, compared with 6.0% among Malays and 2.1% in other ethnic groups. After adjustment with each covariate, incomplete vaccination (AOR 3.97, 95% CI: 2.69, 5.97) and unvaccinated (AOR 3.51, 95% CI 2.39, 5.27) remained strong predictors of confirmed measles infection compared to complete vaccination. Contact with a measles positive case (AOR 14.80, 95%CI: 9.36, 23.40) and Orang Asli ethnicity (AOR 15.4, 95%CI: 10.5, 22.6) were the other major independent risk factors.

Conclusions: This epidemiological analysis of confirmed measles cases in Kelantan from 2016 to 2023 highlights that, despite high national vaccination coverage, significant immunity gaps remain, especially among unvaccinated or partially vaccinated individuals and within marginalized communities such as the Orang Asli. The findings highlighted the crucial role of complete vaccination in reducing confirmed measles infection risk and the need for targeted immunization drives, culturally tailored outreach, and enhanced surveillance efforts to prevent future outbreaks and achieve sustained elimination of measles in the state.

KEYWORDS: confirmed measles, incidence rate, measles vaccination

CHAPTER 1

INTRODUCTION

1.1 Measles infection

Measles, an infectious disease caused by Morbillivirus, is a highly contagious viral disease, characterized by a basic reproduction number (R_0) ranging from 12 to 18, making it one of the most transmissible diseases globally (Guerra et al., 2017). It usually presents with fever and skin rashes, and commonly preceded by cough, coryza and conjunctivitis. While it commonly affects children worldwide, adults are also affected and sometimes become the reservoir for measles spread in the community (Pokharel et al., 2024). Measles cases are mostly mild and self-limiting, but a significant number further developed complications such as pneumonia and long-term neurological damage (Iinuma, 2008). Prior to the introduction of measles vaccine in 1963, it is estimated that the global measles cases reached 30 million and caused 2 million deaths each year, primarily in low-income countries (World Health Organization, 2020).

1.1.1 Measles Epidemiology

Between 2000 and 2019, global measles incidence fell by 88%, and measles mortality declined by approximately 62% (from 539,000 to 207,500 deaths), largely due to improved vaccine coverage (Patel et al., 2020). However, the trend reversed in recent years, with global resurgence peaking in 2019 at nearly 870,000 reported cases, the highest since 1996, and over 200,000 deaths

(Minta et al., 2023). The resurgence has been linked to gaps in routine immunization, inadequate delivery of second-dose measles-containing vaccine (MCV2), and disruptions caused by the COVID-19 pandemic (Cutts et al., 2021). Although measles predominantly affects children under five years, recent studies indicate a growing proportion of cases among adolescents and adults, reflecting immunity gaps and missed vaccination opportunities (Mengistu et al., 2023). These global patterns highlight the fragility of measles control and the continued threat it poses as one of the most contagious vaccine-preventable diseases.

The Western Pacific Region (WPR), which includes Malaysia, has made significant strides in measles elimination but continues to face challenges. Between 2013 and 2016, reported measles incidence declined substantially, but widespread outbreaks occurred in 2018-2019, particularly in the Philippines, Vietnam, and China (Takashima et al., 2024). Regional incidence peaked again in 2019, reflecting accumulated immunity gaps despite high reported coverage for the first measles vaccine dose (MCV1). The COVID-19 pandemic temporarily reduced reported measles cases in the WPR, mainly due to public health restrictions, but it also disrupted routine immunization services, creating a backlog of susceptible children (Minta et al., 2023). Recent evidence indicates that several countries in the region are experiencing renewed outbreaks post-pandemic, underscoring the difficulty of sustaining elimination (Takashima et al., 2024).

1.1.2 Global Measles Elimination Programme

As a vaccine-preventable disease, substantial efforts have been directed towards its elimination through the World Health Organization's Measles Elimination Programme, which aims to eradicate measles by sustaining high vaccination coverage, strengthen disease surveillance systems and enhance outbreak preparedness (WHO, 2012). The widespread implementation of childhood vaccination against measles has led to a dramatic reduction in disease rates worldwide (WHO, 2025). It is estimated that measles vaccination averted more than 60 million deaths globally between 2000 and 2023 (Centres for Disease Control and Prevention, 2025a). The United States declared measles eliminated in 2000, signifying the absence of continuous disease transmission within the country for more than 12 months. The Region of the Americas achieved a historic milestone in 2002 by becoming the first WHO region to eliminate endemic measles transmission (CDC, 2024b). Although global measles trend initially shown positive signs, with the annual reported measles incidence decreasing 88% from 2000-2016 and estimated annual measles deaths dipped 62% to 207,500 from 539,000 (Patel et al., 2020), recent reviews and reports revealed more worrying trends. In 2019, the world experienced a dramatic increase in measles cases, with approximately 869,770 cases reported, which represented a 556% increase from the historic low of 132,490 cases in 2016. The global death toll from measles also rose sharply, with an estimated 207,500 fatalities, marking a 50% increase since 2016 (WHO, 2020). The primary driver of this surge was identified as a failure to vaccinate children adequately with two doses of measles-containing vaccines (MCV1 and

MCV2) (Sarkar et al., 2019). This situation worsened with the occurrence of COVID19 pandemic, in which despite reported measles cases decreased during this period, significant disruptions to routine immunization services were reported (Kumar et al., 2023). Despite global and regional initiatives, measles incidence has been on the rise, and it remains one of the leading causes of vaccine preventable deaths (Frenkel, 2021).

1.1.3 Measles Elimination Programme in Malaysia

In Malaysia, Measles Elimination Programme was introduced in 2004, with the goal of reducing measles mortality and morbidity and stopping indigenous measles transmission in the country (Ministry of Health, 2004). These objectives are achieved by increasing vaccination coverage, enhancing surveillance system and case management, and strengthening measles outbreak preparedness and response. As one of the member countries in World Health Organization's Western Pacific Region (WPR), Malaysia has reaffirmed the commitment to eliminate measles by year 2012 (Takashima et al., 2024). One of the strategies to enhance the measles surveillance system in Malaysia is the utilisation of online notification systems, namely *E-notifikasi* and *Sistem Maklumat Siasatan Measles* (SM2 E-measles) system (Mat Daud et al., 2022). All suspected measles cases will be notified through these systems to ensure timely and prompt measles case investigation and management. After investigation, these notified cases will be classified as confirmed measles or non-measles discarded cases. A high discard rate suggests that the surveillance system is sensitive enough to capture a wide range of suspected

cases, which are then accurately confirmed or discarded through laboratory testing (Wang et al., 2007).

Malaysia introduced the measles vaccine into its national schedule in 1982, in line with the World Health Organization's Expanded Programme on Immunization. Initially, a single dose of a measles-containing vaccine (MCV) was given at 9 months of age under the routine immunization schedule (Hazlina et al., 2016). This early start was aimed at protecting infants in a country where measles was endemic and often contracted at a young age. Throughout the 1980s and 1990s, the measles immunization program steadily expanded its reach as part of maternal-child health services, offered free of charge in all government clinics and hospitals. By the turn of the 21st century, Malaysia had achieved high coverage for the first measles dose, generally exceeding 90% of infants nationwide (Wong et al., 2020). In the period of 2002-2004, following WHO recommendations, the Ministry of Health transitioned from a one-dose to a two-dose regimen. In practice, a measles-mumps-rubella (MMR) vaccine was added as a second dose. By 2004, the routine schedule included MCV1 at 12 months and MCV2 at school entry (around 7 years) (Hazlina et al., 2016). In 2016, in response to ongoing outbreaks and in line with updated guidance, Malaysia revised its measles vaccination schedule again, where the age of administration was shifted earlier: MCV1 at 9 months, and MCV2 at 12 months of age.

Initially, measles elimination in Malaysia has achieved notable success in reduction of measles cases with incidence decreasing from 22.3 cases to

2.27 cases per 100,000 individuals from 2004 to 2006 (Saraswathy et al., 2009), supported by high vaccination coverage of around 95% in 2009 (Qamruddin et al., 2020). However, despite good historical vaccination coverage, reported measles cases in Malaysia peaked to 873,373 in 2019, the highest level since the implementation of National Measles Elimination Programme largely due to several outbreaks occurring in multiple states, including the state of Kelantan (WHO, 2024a). The resurgence also prompted a revision of the elimination timeline - the target for measles elimination was postponed to 2025, replacing the missed 2010 goal. Incidence rate fluctuated throughout the years, plummeted during the COVID19 pandemic, and peaked again post-Covid 19 era, with a recorded incidence rate of 52.7 cases per 1 million population in 2023, higher than the pre-pandemic period. In terms of vaccination coverage, in Malaysia, MCV1 and MCV2 vaccine coverage dipped in to 95% and 84% in 2020 and 2021 respectively but subsequently recovered to 107.51% in 2023 (WHO, 2024). These high vaccination rates however did not achieve the intended impact as measles incidence in Malaysia is estimated to reach more than 100 cases per 1 million population in 2024, the highest level since the introduction of Measles Elimination Program in 2004 (WHO, 2024b).

1.1.4 Emerging issues in measles elimination

While global measles vaccination programmes have achieved remarkable success, elimination efforts face increasing threats. Vaccine hesitancy, fuelled by misinformation, mistrust, and in some contexts, religious concerns, has emerged as a major obstacle, reducing parental confidence in

immunization and contributing to declining coverage in certain populations (de Figueiredo et al., 2020; Othman et al., 2024). Social media has amplified conspiracy narratives and anti-vaccine content, narrowing the reach of accurate health information and deepening resistance to immunization (Rodrigues et al., 2023). Beyond hesitancy, inequities in vaccine access and delivery remain problematic. Administrative data often mask hidden immunity gaps, with effective vaccine coverage falling below the herd immunity threshold even in countries reporting high uptake (Kumar et al., 2023). Serosurveys and outbreak investigations repeatedly reveal that zero-dose and incompletely immunized groups, particularly those in marginalized or remote settings, continue to sustain measles transmission (Ariyaratnam and Crowcroft, 2021; Lessler et al., 2016).

In addition, incomplete or delayed vaccination schedules undermine vaccine effectiveness, leaving communities vulnerable to outbreaks despite vaccine availability (Trevisan et al., 2021a). These vulnerabilities were amplified by the COVID-19 pandemic, which disrupted routine immunization services worldwide, leading to an estimated 21 million children missing their first measles vaccine dose in 2022 and triggering resurgent outbreaks across multiple regions (Minta et al., 2023). In the Western Pacific Region, including Malaysia, post-pandemic surges underscore how fragile elimination gains can be when systemic gaps align with social and cultural barriers (Takashima et al., 2024). In Kelantan, such barriers are particularly visible, as recurring outbreaks have coincided with parental vaccine refusal linked not only to misinformation

but also to religious concerns over vaccine permissibility, which remain influential in shaping health-seeking behaviour (Othman et al., 2024). As a result, measles incidence in the state has continued to rise despite historically strong vaccination coverage, highlighting how these emerging challenges persist and demand closer examination.

1.2 Statement of Problem

Despite high vaccination coverage, measles incidence in Malaysia continues to be on the rise and estimated to be the highest among Western Pacific Region member countries in 2024 (WHO, 2024). Multiple studies have shown that overall vaccination rates can provide a misleading picture of measles incidence due to local and regional disparities (Packham et al., 2024) and that there is complex interplay of socio-cultural and local demographic factors contributing to the transmission of measles (Cutts et al., 2021). Kelantan, one of the states in Malaysia has observed increasing trend of measles cases and recurrent measles outbreaks post-COVID19 pandemic. Despite up-to-date national incidence data, there is a lack of studies on the state-specific measles incidence which is vital for examining the varying impacts of vaccination policies, demographic factors, and public health responses across different regions (Mathis et al., 2022). Cross sectional studies carried out in the state of Pahang (Mat Daud *et al.*, 2022) and Larut Matang and Selama District, Perak (Qamruddin *et al.*, 2020) reported the measles incidence of 21.15 and 28.82 cases per 1 million population in 2020 and 2019 respectively. There is a notable gap in studies which investigate measles incidence in Kelantan.

Furthermore, previous studies reported measles incidence as overall state-level and district-level incidence without examining the age-specific, gender-specific and ethnic specific incidence (Zaini et al., 2023). This stratified data is essential for identifying high-risk groups and refining targeted

interventions for measles control and prevention (Green et al., 2022). To date, there has been no specific study in Kelantan that examines district-specific, age-specific, gender-specific measles incidence.

Globally, substantial evidence has been established on the effect of non-vaccination or incomplete vaccination to higher risk of contracting measles. However, such studies are limited in Malaysia. A nation-wide cross-sectional study revealed that the number of total measles vaccine dose has a protective effect against measles infection with AOR 0.76 (95%CI: 0.72, 0.79) (Yaacob et al., 2024) while Zaini *et al.* (2023) reported higher crude risk of getting laboratory-confirmed measles among unvaccinated children in Melaka (OR 19.39, 95%CI: 8.82, 42.6). In Kelantan, there are no such studies assessing this relationship yet. Therefore, the magnitude of risk of contracting measles infection due to under-vaccination in this state is still unclear. In most of these studies, the statistical analyses did not adjust for age, gender or ethnicity or history of contact (Qamruddin *et al.*, 2020). A more detailed analysis is required to remove the confounding effects and estimate and quantify the valid relationship between vaccination and measles specific to Kelantan population.

1.3 Rationale

This study will help to examine the current trend of measles infection in Kelantan using the latest data and identify changes in these trends. This will act as baseline data, as well as assist in assessing the progress of measles elimination in Kelantan and enable the Ministry of Health to allocate resources

effectively. By determining group-specific incidence rate this study will highlight certain demographic groups that may require prioritized attention in public health campaigns to curb transmission effectively. These will help the Ministry of Health in devising precise intervention to devise precise public health strategies for measles elimination. Apart from that, the relationship between vaccination status and risk of measles infection will be examined and quantified in depth in this study. This analysis will allow local health authority to prioritise and focus on specific factors that might confound or modify the effect of vaccination on the risk of measles infection in the prevention and control effort. Furthermore, this will give support to the health promotion effort on vaccine effectiveness and can be used to counter misinformation and rising vaccine hesitancy among the communities in Kelantan.

1.4 Research Questions

1. What are the incidence and distribution of confirmed measles infection recorded in SM2 E-Measles System in Kelantan between 2016 and 2023?
2. What are the trends based on incidence and distribution of confirmed measles infection recorded in SM2 E-Measles System in Kelantan between 2016 and 2023?
3. What is the estimated relationship between vaccination status and risk of confirmed measles infection among notified measles cases in Kelantan between 2016 and 2023?

1.5 Objectives

1.5.1 General Objective:

To study the distribution, incidence and risk of confirmed measles cases in Kelantan between 2016 and 2023 using SM2 E-measles data.

1.5.2 Specific objectives:

1.5.2(a) Objective 1

To describe the distribution of cumulative confirmed measles cases in Kelantan from 2016 to 2023.

1.5.2(b) Objective 2

To examine the annual trend of overall incidence of confirmed measles cases recorded in SM2 E-measles System in Kelantan from 2016-2023.

1.5.2(c) Objective 3

To examine the annual trend of district specific, sex-specific, age-specific, and ethnic specific incidence of confirmed measles cases recorded in SM2 E-Measles System in Kelantan from 2016-2023.

1.5.2(d) Objective 4

To estimate the relationship between vaccination status and confirmed measles infection among notified measles cases in SM2 E-measles System in Kelantan population from 2016-2023.

1.6 Research Hypothesis

The study hypothesizes that vaccination status remains significantly associated with the likelihood of confirmed measles infection even after adjusting for potential confounding factors.

1.6.1 Null Hypothesis (H_0):

There is no statistically significant association between measles vaccination status and the likelihood of confirmed measles infection among notified measles cases in Kelantan from 2016 to 2023, after adjusting for age, sex, ethnicity, and history of contact.

1.6.2 Alternative Hypothesis (H_1):

There is a statistically significant association between measles vaccination status and the likelihood of confirmed measles infection among notified measles cases in Kelantan from 2016 to 2023, after adjusting for age, sex, ethnicity, and history of contact; specifically, individuals who are unvaccinated or incompletely vaccinated have higher odds of confirmed measles infection compared to those fully vaccinated.

CHAPTER 2

LITERATURE REVIEW

The literature review in this study was conducted through a systematic exploration of reputable academic and scientific databases, including Scopus, PubMed, Web of Science, Google Scholar, ScienceDirect, and SpringerLink. A combination of search techniques was employed. These included the application of Boolean operators such as "AND," "OR," and "NOT" to refine and expand search results. The selection of search terms included key concepts such as "measles," "incidence rate," "vaccination," "associated factors," and "risk determinants."

2.1 Global Distribution and Incidence of Measles Infection

The global epidemiology of measles varies significantly across age groups, regions, and socioeconomic backgrounds. Studies have demonstrated that measles incidence differs by age and gender. Green *et al.* (2022) analysed data from Europe, Australia, Canada, and Israel from 1997-2016, finding that males under 45 exhibited higher incidence rates, while females aged 45-64 showed a higher incidence than their male counterparts. The pooled incidence rate ratios (IRRs) for measles by age group highlight elevated incidence in younger groups, with IRRs as follows: ages <1 (1.07), 1-4 (1.10), 5-9 (1.03), 10-14 (1.05), and 15-44 (1.08), before decreasing in older age groups (IRR of 0.82 for ages 45-64). Mengistu *et al.* (2023) explored the measles incidence in Eritrea from 2002 to 2020, revealing the highest age-specific positivity rate among

individuals over 30 years, at 69.9 per 100,000 suspected cases. This study indicated that age was a strong predictor of measles positivity, with adults aged 30 years and older showing the highest odds ratios for test positivity (OR 16.7, 95% CI 11.7-24, $p < 0.001$). This finding reinforces the need for focused vaccination efforts in older populations to mitigate adult susceptibility. A historical study by Atkinson et al. (1992) on measles incidence in the United States found that the highest incidence was among children under 12 months, with 46.9 cases per 100,000, and among children aged 1-4 years at 19.6 cases per 100,000. The study also revealed ethnic disparities, as American Indian, Hispanic, and black children under five years had a significantly higher incidence than non-Hispanic white children. During the 1989 -1991 measles epidemic in the U.S., attack rates among non-white children were 4-7 times higher than among white children, reflecting socioeconomic and healthcare-access disparities (Hutchins et al., 2004). In recent years, outbreaks in high-income countries have been concentrated in specific communities with lower vaccination rates. For instance, measles outbreaks in parts of Europe and the U.S. have occurred in certain religious or cultural communities and among recent immigrants or refugees with limited healthcare access (Bell et al., 2020) . In Malaysia, a striking ethnic disparity has been observed between the majority Malay population and certain indigenous groups. Indigenous Orang Asli communities have faced higher measles risk due to lower vaccination coverage (Mat Daud et al., 2022). These findings highlight potential sociodemographic determinants of measles risk that may inform targeted immunization strategies.

Despite notable reductions in global measles incidence over the past two decades, the disease remains a major cause of vaccine-preventable mortality, particularly in low-income countries. From 2000 to 2021, measles vaccination prevented an estimated 56 million deaths worldwide, yet in 2019 alone more than 207,000 measles-related fatalities were recorded, reflecting persistent immunity gaps (Patel et al., 2020; World Health Organization, 2020). Recent resurgence has been observed even in high-income countries with historically strong vaccination programs, as outbreaks in Europe and the United States between 2018 and 2019 were concentrated in under-vaccinated religious and migrant communities, demonstrating how localized lapses can undermine elimination (Phadke et al., 2016; Sarkar et al., 2019). The COVID-19 pandemic further disrupted routine immunization services, leaving millions of children unprotected. Although reported cases temporarily declined in 2020–2021 due to movement restrictions, a sharp rebound followed, with over 40 countries experiencing outbreaks by 2022–2023 (Minta et al., 2023). These developments highlight the fragility of progress toward measles elimination and the importance of resilient surveillance and immunization systems worldwide.

Despite these valuable insights, each of these studies has limitations. For instance, Green *et al.* (2022) did not report ethnicity-specific data, which limits its applicability in regions with diverse populations. Mengistu *et al.* (2023) focused solely on age-specific incidence without gender or ethnicity-specific analysis, while Atkinson *et al.* (1991) relied on older data from a single year in the U.S., which limits its generalizability to present contexts and other regions.

2.2 Measles Incidence in Malaysia

Studies conducted in Malaysia reflect regional variations and fluctuations in measles incidence over the years. According to Saraswathy *et al.* (2009), the national incidence rate of measles in Malaysia decreased significantly from 22.3 cases per 100,000 in 2004 to 2.27 cases in 2006, possibly due to intensified vaccination campaigns. However, more recent studies show fluctuating trends, with Daud *et al.* (2022) reporting incidence rates ranging from 13.51 to 50.97 per million in Pahang state from 2016 to 2020, which might indicate variability in control efforts and vaccine coverage. In Larut, Matang, and Selama District in Perak state, Qamruddin *et al.* (2020) observed a significant rise in suspected measles cases from 2015 to 2019, with confirmed cases peaking at 36.11 per million in 2017. This rise, followed by fluctuating rates in subsequent years, might suggest regional disparities and nuances in vaccination rates and health policies.

Measles' epidemiology in Malaysia reflects both national progress and persistent challenges in achieving elimination. Surveillance reports indicate that annual incidence declined markedly in the mid-2000s, but measles resurged in the late 2010s, with a nationwide peak in 2019 when 873 confirmed cases were reported, equivalent to an incidence of 26.6 per million population, the highest level since the initiation of the Measles Elimination Programme (World Health Organization, 2024a). This national peak mirrored broader global trend, with the WHO Western Pacific Region experiencing large outbreaks in the Philippines, Vietnam, and Malaysia during the same period (Minta *et al.*, 2023).

The subsequent COVID-19 pandemic temporarily suppressed measles transmission due to school closures, mobility restrictions, and widespread use of masks, and Malaysia reported only 128 confirmed cases in 2021 (Pillai, 2023). However, this apparent progress was short-lived. By 2022, incidence rose again to 209 cases nationally, and by 2023 exceeded pre-pandemic levels in several states, with Kelantan, Selangor, and Sabah recording the steepest increases (Pillai, 2023; World Health Organization, 2024a).

Vaccination coverage data help explain these epidemiological fluctuations. While coverage for the first dose of measles-containing vaccine (MCV1) has generally exceeded 90%, the second dose (MCV2) fell to 84% in 2020 and 2021, below the $\geq 95\%$ threshold required to achieve herd immunity (World Health Organization, 2024b). This dip created a sizeable cohort of children vulnerable to infection, which contributed to the resurgence as COVID-19 restrictions eased. The WHO elimination target of < 1 confirmed case per million population has not been consistently met in Malaysia; instead, incidence has exceeded this threshold in multiple years, especially in states with historically lower coverage (Mat Daud et al., 2022; Yaacob et al., 2024). Moreover, recent analyses have shown that even within states with high overall coverage, subpopulations such as migrants and rural communities remain under-immunized, sustaining pockets of susceptibility that can ignite outbreaks (Qamruddin et al., 2020; Zaini et al., 2023). Collectively, these data emphasize that Malaysia's measles epidemiology is increasingly characterized by episodic surges driven by coverage gaps and regional disparities.

A limitation across Malaysian studies is their use of pre-COVID-19 data, which may not account for shifts in healthcare priorities, vaccine accessibility and demographic changes during the pandemic. Additionally, Saraswathy *et al.* (2009) provided national but not state-specific data, while Mat Daud *et al.* (2022) and Qamruddin *et al.* (2020) lacked detailed incidence rate breakdowns by demographic factors like gender or age.

2.3 Relationship between Vaccination and Measles Infection

Vaccination remains the most effective strategy for preventing measles infection. Numerous studies in Malaysia and worldwide demonstrate a strong inverse association between measles vaccination and infection. The measles vaccine (usually given in 2 doses of MMR) induces protective immunity in most recipients - one dose is about 93% effective and two doses about 97-99% effective at preventing measles (Bianchi *et al.*, 2021). A meta-analysis by Dhony *et al.* (2024) found that vaccinated children had a significantly reduced risk of contracting measles, with an adjusted odds ratio (AOR) of 0.30 (95% CI: 0.22, 0.40) compared to unvaccinated children. This finding emphasizes the critical role of vaccination in reducing measles incidence.

Yaacob *et al.* (2024) studied measles risk factors in Malaysia, identifying that non-Malaysian nationality, prior contact with infected individuals, and lack of vaccination significantly increased measles risk, while urbanization and healthcare accessibility also played roles. In Pahang, Daud *et al.* (2022) demonstrated that indigenous status and incomplete vaccination correlated

with significantly higher odds of measles infection, therefore emphasizing the need for culturally tailored vaccination strategies.

Further studies by Zaini *et al.* (2023) in Melaka highlighted that unvaccinated children and adolescent aged 8-18 years faced a higher risk of contracting laboratory-confirmed measles. Meanwhile, Qamruddin *et al.* (2020) noted that individuals in Larut Matang and Selama District who did not receive measles immunization had a markedly higher risk of infection (AOR 1.98), which highlights the vulnerability of unvaccinated populations at the district level.

Causality is further supported by time-trend data: the introduction of routine measles immunization in the 1960s to 1970s led to more than 90% reduction in cases in many countries, and between 2000 and 2022 measles vaccination prevented an estimated 56-57 million deaths globally (Parums, 2024). Conversely, when vaccination was disrupted (as in the COVID-19 pandemic), measles cases surged in the following years.

While the protective effect of measles vaccination is well established, real-world evidence highlights additional nuances in its relationship with infection risk. Breakthrough cases have been reported among fully vaccinated individuals, though these remain rare. For instance, surveillance data from Europe indicated that approximately 3–7% of confirmed measles cases occurred in individuals who had received two doses, consistent with the small proportion who either fail to seroconvert after vaccination or experience waning immunity over decades (Bianchi *et al.*, 2021; Green *et al.*, 2022). A study in Italy demonstrated that antibody levels may decline 10-25 years post-vaccination,

with about 15% of adults showing reduced seroprotection, raising concerns about susceptibility in older cohorts (Bianchi et al., 2021). Nonetheless, two-dose schedules remain overwhelmingly effective; analyses of outbreaks in the UK and Malaysia confirmed that incidence and severity were far lower in fully immunized groups compared to partially or unvaccinated individuals (Qamruddin et al., 2020; Zaini et al., 2023).

Timeliness of vaccination also plays a critical role in determining effectiveness. Infants vaccinated later than the recommended 9–12 months remain vulnerable during a period when maternal antibodies have waned, leading to higher infection rates in under-one population (Yang et al., 2020). Conversely, administering the first dose too early (before 9 months) may reduce immunogenicity, which is why outbreak situations may require supplementary doses at 6 months, followed by the routine schedule (World Health Organization, 2017). This balance underlines the importance of both high coverage and adherence to age-appropriate schedules. Taken together, these evidences demonstrate that while occasional breakthrough cases occur, incomplete or delayed vaccination remains the dominant driver of measles transmission in Malaysia and globally.

Limitations in the literature on vaccination include contextual differences in study populations, with Dhony et al. (2024) focusing on African countries, which may limit applicability to Malaysia. Yaacob et al. (2024) integrated contextual factors like urbanization but did not focus specifically on Kelantan while Zaini *et al.* (2023) studied the population of Melaka state.

Additionally, Zaini *et al.* (2023) reported crude odds ratios without adjusting for confounders such as age, sex, and ethnicity, which are critical factors in understanding measles risk. Most of the studies carried out exploratory factors analysis, through which they find the best-fit model to explain measles risk by including vaccination status as a factor, without analysing in-depth regarding the role of vaccination to risk of contracting measles, and the effect of demographic factors and exposure factors on modifying this risk.

2.4 Confounders in Evaluating Vaccination Status and Measles Risk

The main confounding factors in the literature include age, sex, ethnicity, and exposure history, among others. These variables can influence both vaccination status and risk of measles, thus they need to be adjusted for in epidemiologic analyses.

Firstly, age is a critical confounder because measles vaccination is age-dependent (first dose in infancy, second dose in childhood in most schedules) and susceptibility varies with age. Infants and very young children are often unvaccinated (or only partially vaccinated) simply because they have not reached the eligible age for all doses. Measles cases occurring in infants too young to have received MMR vaccine could exaggerate the association between “unvaccinated” status and disease if age is not accounted for. In Malaysia 2018-2022, the median age of confirmed cases was less than 1 year old, reflecting this phenomenon (Yang *et al.*, 2020). On the other end of the spectrum, older adults might be classified as vaccinated if they received childhood

immunization decades ago, yet some may have waning immunity. Studies show measles antibody levels can decline over time in vaccinated individuals - for example, an Italian study showed that measles vaccine-induced immunity might wane after 10 - 25 years after vaccination in 15% of individuals (Bianchi et al., 2021). These studies suggest the importance of incorporating age as a confounder in analyses of the relationship between vaccination status and measles risk. Failing to adjust for age can overestimate the risk in infants too young to vaccinate and underestimate it in adults whose immunity has diminished over time, thereby obscuring the relationship of vaccination and risk of measles infection.

Sex, in the other hand, is not a strong determinant of measles risk in most settings, but it can still act as a confounder if male and female children have different vaccination rates or healthcare access. In rural India, analyses have shown that girls are less likely than boys to receive measles vaccinations on time. This delay can increase the risk of infection and complications, highlighting the role of gender-based disparities in healthcare access and practices. However, in Malaysia and globally, routine immunization coverage is generally similar for boys and girls. Consistently, studies find no significant difference in measles incidence by sex after accounting for exposure and vaccination (Trevisan et al., 2021b; Voigt et al., 2016; Yaacob et al., 2024). However, a recent study in Europe across seven countries found that males had a consistently higher incidence of clinical measles than females in childhood

(Green et al., 2022). This conflicting evidence requires us to examine this relationship further.

Ethnic background can confound the vaccination-measles association because of cultural and socioeconomic factors that influence vaccine uptake. Based on studies done globally, the risk is driven by differences in vaccination and exposure (CDC, 2024a). For instance, Somali American children in Minnesota had a 33.1% probability of receiving their first MMR dose by 24 months, significantly lower than other groups (Mohammed et al., 2025), while in London, areas with diverse populations have seen MMR coverage drop to as low as 68% (National Health Service England, 2024). These disparities indicate the necessity of accounting for ethnic background as a confounding factor when analysing the association between vaccination and measles risk.

Exposure history, particularly close contact with measles cases, has been identified as a significant confounding factor in evaluating the effectiveness of measles vaccination. Studies have demonstrated that individuals with a history of contact with measles cases have a higher risk of infection, even after accounting for vaccination status. For example, a study in Dhaka observed that nearly half of the measles cases had a reported history of contact with another child exhibiting measles-like symptoms (Akramuzzaman et al., 2002) while a Senegal study found that vaccine efficacy estimates varied when accounting for the intensity of exposure, indicating that contact history can influence perceived vaccine effectiveness (Augusto et al., 2018; Garenne et al., 1993). This shows that exposure history is a crucial factor that needs to be