FACTORS ASSOCIATED WITH CONFIRMED MEASLES CASES AMONG NOTIFIED MEASLES OF CHILDREN IN PERAK 2017-2024

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UNIVERSITI SAINS MALAYSIA

2025

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by

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Research project report submitted in partial fulfilment of the requirement for the degree of Master of Public Health

June 2025

ACKNOWLEDGEMENT

Bismillahirrahmanirrahim,

First and foremost, Alhamdulillah all thanks to Allah SWT, the Almighty, for His blessings, I have completed this research project report with success. I would like to express my deepest and sincere gratitude to my supervisor, Associate Professor Dr Tengku Alina Binti Tengku Ismail, for the continuous support, expert guidance and constructive feedback throughout the course of the project. Her insight and encouragement were instrumental in the successful completion of this research project. I am sincerely thankful to all the lecturers of Department of Community Medicine, Universiti Sains Malaysia, Kelantan for providing academic foundation and resources that are necessary for this research project. Special thanks also go to my co-researchers, Dr Husna Maizura Binti Ahmad Mahir, Deputy Director of Perak State Health Department (Public Health), Dr Abdulloh Bin Mazalan, Assistant Director of Communicable Disease Control, Perak State Health Department and Dr Noor Rizawati Binti Mahpot, Public Health Specialist, Kinta District Health Office for their assistance in data collection and technical input related to relevant data and reports of measles cases of children in Perak.

I would like to extend my gratitude and thanks to my family and close friends for the unwavering support, understanding, and encouragement that gave me the strength to stay focused and committed throughout this journey. Lastly, my sincere thanks to all individuals who contributed directly or indirectly to the success of this research project making this journey a meaningful and enriching experience.

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LIST OF SYMBOLS

α	Alpha
β	Beta
=	Equal to
<	Less than
>	More than
n	Number of subjects
%	Percentage
P	Population's proportion
Δ	Precision of estimation
m	Ratio between two groups
Z	Z-score

LIST OF ABBREVIATIONS

Adj OR	Adjusted Odd Ratio
CDC	Communicable Disease Control
CDCIS	Communicable Disease Control Information System
CI	Confidence Interval
df	Degree of freedom
DHO	District Health Office
IgM	Immunoglobulin M
JEPeM	Jawatankuasa Etika Penyelidikan (Manusia) Universiti Sains Malaysia
MCV	Measles containing vaccine
MCV1	Measles containing vaccine first dose
MCV2	Measles containing vaccine second dose
MMR	Measles-mumps-rubella
MMRV	Measles-mumps-rubella-varicella
MOH	Ministry of Health
mOR	Matched Odd Ratio
MREC	Medical Research and Ethics Committee
NMRR	National Medical Research Registry
OR	Odd Ratio
R0	R naught
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
SIAs	Supplementary immunisation activities

SM2	Sistem Maklumat Siasatan Measles
SPSS	Statistical Package for the Social Sciences
UNCRC	United Nations Convention on the Rights of the Child
VAM	Vaccine associated measles
VIF	Variance inflation factor
WHO	World Health Organization
WPR	Western Pacific Region

LIST OF APPENDICES

FAKTOR YANG DIKAITKAN DENGAN KES DISAHKAN DEMAM CAMPAK DALAM KALANGAN YANG DINOTIFIKASIKAN SEBAGAI DEMAM CAMPAK DALAM KANAK-KANAK DI PERAK 2017–2024

ABSTRAK

Latar Belakang: Demam campak ialah penyakit yang mudah berjangkit dan boleh dicegah melalui vaksinasi. Ia masih menjadi kebimbangan utama kesihatan awam di peringkat global, khususnya dalam kalangan kanak-kanak, meskipun terdapat vaksin yang tersedia. Oleh itu, penting untuk memahami faktor yang berkaitan dengan demam campak dalam kalangan kanak-kanak bagi mengukuhkan lagi strategi pencegahan.

Objektif: Kajian ini bertujuan untuk mengkaji peratusan kes dan faktor yang dikaitkan dengan kes disahkan demam campak dalam kalangan yang dinotifikasikan demam campak dan untuk mengkaji ciri-ciri klinikal kes disahkan demam campak dalam kanak-kanak di Perak dari tahun 2017 hingga 2024.

Metodologi: Kajian keratan rentas ini menggunakan data sekunder yang diperolehi daripada pangkalan data survelan demam campak SM2 dari Jabatan Kesihatan Negeri Perak bagi tahun 2017 hingga 2024. Pensampelan rawak mudah telah digunakan untuk mendapatkan saiz sampel sebanyak 498. Data yang berkaitan dikumpul menggunakan senarai semak proforma dan dianalisis menggunakan analisis deskriptif serta regresi logistik mudah dan berganda.

Keputusan: Sebanyak 498 kes demam campak yang dilaporkan dalam kalangan kanak-kanak telah dimasukkan dalam kajian ini. Peratusan kes campak yang disahkan ialah 15.1% (95% CI: 12.0,18.2), dengan julat tahunan antara 2.9% hingga 29.2% dari tahun 2017 hingga 2024. Dalam kalangan 75 kes disahkan demam campak, ciri klinikal yang paling kerap dilaporkan ialah demam dan ruam makulopapular (98.7%), diikuti oleh batuk (62.7%), koriza (57.3%) dan konjunktivitis (22.7%). Faktor signifikan berkaitan dengan kes disahkan demam campak ialah etnik, status vaksinasi campak, sejarah kontak dengan kes disahkan demam campak, dan kemasukan ke hospital. Kanak-kanak Orang Asli mempunyai kebarangkalian lebih tinggi dijangkiti berbanding etnik lain (OR terlaras 3.37, 95% CI: 1.05,10.88, nilai p-0.042). Kanak-kanak yang menerima vaksin tidak lengkap atau tidak divaksinasi mempunyai kebarangkalian lebih tinggi untuk disahkan demam campak berbanding yang menerima vaksin lengkap (OR terlaras 2.27; 95% CI: 1.09,4.71; nilai p-0.028 dan OR terlaras 3.42; 95% CI: 1.63,7.19; nilai p-0.001). Sejarah kontak dengan kes yang disahkan demam campak berkait kuat (OR terlaras 51.76; 95% CI: 11.25,238.21; nilai $p < 0.001$), begitu juga dengan kemasukan ke hospital (OR terlaras 4.198; 95% CI: 1.51,11.65; nilai p-0.006).

Kesimpulan: Etnik, status vaksinasi demam campak, sejarah kontak dengan kes disahkan demam campak dan kemasukan ke hospital dikenalpasti sebagai faktor signifikan dengan kes disahkan demam campak dalam kalangan kanak-kanak di Perak dari 2017 hingga 2024. Dapatan ini menekankan kepentingan merangka intervensi kesihatan awam yang bersasar untuk meningkatkan keberkesanan langkah pencegahan dan kawalan demam campak, khususnya dalam kalangan kanak-kanak.

KATA KUNCI: disahkan demam campak, notifikasi demam campak, kanak-kanak, Perak

FACTORS ASSOCIATED WITH CONFIRMED MEASLES CASES AMONG NOTIFIED MEASLES OF CHILDREN IN PERAK 2017-2024

ABSTRACT

Background: Measles is a highly contagious and vaccine preventable disease. It remains a significant public health concern globally, particularly among children, despite the availability of the vaccines. Thus, it is crucial to understand the associated factors of measles in children to strengthen the prevention strategies.

Objective: This study aimed to determine the proportion and factors associated with confirmed measles cases among notified measles as well as to describe the clinical presentation of confirmed measles cases of children in Perak from 2017 to 2024.

Methods: A cross-sectional study was conducted using secondary data extracted from the SM2 measles surveillance database of the Perak State Health Department for the years 2017 to 2024. Simple random sampling was applied to obtain the sample size of 498. The relevant data were collected by using proforma checklist. The data were analysed by using descriptive analysis, simple and multiple logistic regression analyses.

Results: A total of 498 notified measles cases of children were included in the study. The proportion of confirmed measles cases among notified measles of children in Perak was 15.1% (CI: 12.0,18.2) and ranged from 2.9% to 29.2% per year throughout the year 2017 to 2024. Among the 75 confirmed measles cases in children, the most frequently reported clinical features were fever and maculopapular rash (98.7%) followed by cough (62.7%), coryza (57.3%) and conjunctivitis (22.7%). The significant factors associated with confirmed measles cases were ethnicity, measles vaccination status, history of contact with confirmed measles case and hospital admission. Orang Asli children had significantly greater odds of confirmed measles than other ethnic groups (Adj OR 3.37, 95% CI: 1.05,10.88, p-value 0.042). Incomplete and no vaccination were associated with higher odds of measles confirmation compared to complete vaccination (Adj OR 2.27, 95% CI: 1.09,4.71, p-value 0.028) and (Adj OR 3.42, 95% CI: 1.63,7.19, p-value 0.001) respectively. Contact with a confirmed measles case showed a strong association with confirmed measles (Adj OR 51.76, 95% CI: 11.25,238.21, p-value < 0.001), as did hospital admission (Adj OR 4.198, 95% CI: 1.51,11.65, p-value 0.006).

Conclusion: Ethnicity, measles vaccination status, history of contact with confirmed measles case, and hospital admission were identified as significant factors associated with confirmed measles cases among notified measles of children in Perak from 2017 to 2024. These findings underscore the importance of formulating targeted public health interventions to enhance the effectiveness of measles prevention and control measures particularly among children.

KEYWORDS: confirmed measles, notified measles, children, Perak

CHAPTER 1

INTRODUCTION

1.1 Background of measles

Measles is an acute and highly contagious viral illness. It is caused by a single-stranded, negative sense ribonucleic acid (RNA) virus with a non-segmented genome and a lipid envelope, belonging to a member of the genus Morbillivirus and the family Paramyxoviridae (Gastanaduy *et al.*, 2021a).

Measles typically presents with a cluster of symptoms such as fever, maculopapular rash, cough, conjunctivitis (red eyes), and coryza (runny nose). Transmission of the measles disease primarily through person-to-person contact and airborne spread of respiratory droplets. The virus is highly infectious and can be spread through coughing, sneezing, or direct contact with nasal or throat secretions of an infected person. The infectious droplets can remain in the air or on a surface for up to two hours even after the person with measles left the area, permitting the virus to spread to susceptible individuals. However, the virus is rapidly inactivated by acidic pH, light, heat, ether and trypsin (Gastanaduy *et al.*, 2021a).

The incubation period of measles is approximately about 10 days from the time of infection to the onset of fever and 14 days to the onset of rash (Moss, 2017). However, the median incubation period of measles was found to be 12.5 days (95% CI: 11.8,13.2) with 5% of measles cases will be having the symptoms before 8.9 days (95% CI: 8.1,9.8), and others 95% by 17.7 days (95% CI: 16.1,19.2) after exposed with the infection (Lessler J *et al.*, 2009).

R naught ($R0$) stands for the basic reproduction number. It is a measure used to describe the contagiousness of an infectious disease. The $R0$ for measles is estimated to be between 12 to 18, one of the highest among the viruses (Guerra *et al.*, 2017). It indicates that a person with measles illness can often infect 12 to 18 other people in a totally susceptible population which means no immunity from previous illness or vaccination.

Measles is not only a highly contagious viral infection but also carries the risk of serious and potentially life-threatening complications eventually lead to death. One of the most concerning complications is immune suppression which makes the affected individuals more susceptible to secondary bacterial and viral infections includes bacteraemia, pneumonia, gastroenteritis and otitis media. In addition to these systemic complications, measles can also result in severe neurological outcomes, such as acute encephalitis, acute disseminated encephalomyelitis (ADEM), and subacute sclerosing panencephalitis (SSPE). These complications of measles significantly contribute to measles related morbidity and mortality particularly among children globally (World Health Organization, 2024b).

1.2 Measles Vaccination Program

Measles continues to be a significant global public health concern, contributing substantially to morbidity and mortality. Vaccination proven to be an effective measure to prevent measles infection, averting more than 60 million deaths in between 2000 to 2023 (World Health Organization, 2024b). Measles, mumps and rubella (MMR) vaccine found to be safe and effective in preventing the infection of measles in the population. According to the Centers for Disease Control and Prevention (CDC), one dose of the MMR vaccine is 93% effective against measles, while two doses provide approximately 97% protection in preventing measles (Centers for Disease Control and Prevention, 2023). However in 2023, there were an estimated 107, 500 measles related deaths globally, mostly among unvaccinated or under vaccinated children under the age of 5 years despite the availability of a safe and cost-effective vaccine (World Health Organization, 2024b). In addition, 83% of children received the first dose of the measles containing vaccine (MCV1) in 2023, a slight reduces from 86% in 2019 indicating most likely due to stagnation of the vaccination effort influenced by health system disruptions during pandemic Covid 19 (World Health Organization, 2024b).

The first measles vaccines were introduced in 1963 in the United States, comprising two types which were an inactivated (killed) vaccine and a live attenuated vaccine (Edmonston B strain). However, later both have been withdrawn in 1967 and 1975 due to safety concerns. The Schwarz strain was then added in 1965 and eventually eliminated as well. In 1968, the Edmonston-Enders strain became the preferred option since it had less adverse effects and was being utilised extensively around the world. Later, the MMR vaccination was first introduced in 1971 when the measles vaccine was incorporated with the mumps and rubella vaccines. Meanwhile, a combination measles, mumps, rubella, and varicella (MMRV) vaccine were approved in 2005 allowing for broader immunisation coverage through a single administration (Gastanaduy *et al.*, 2021a). The organisation such as Gavi, the Vaccine Alliance, and UNICEF have been supporting to widen the vaccination coverage in low and middle income countries through routine immunisation and supplementary immunisation activities (SIAs).

The implementation of the measles vaccination program in Malaysia began at different times across its regions. In Sarawak, measles vaccination was introduced in August 1977, which was administered in two doses at six months and 12 months of age. In 1982, measles vaccination was introduced into National Immunisation Program (NIP), given a single dose at nine months of age. Prior to the introduction of the vaccine in Sarawak, measles epidemics occurred in cycles every two to three years. In between 1961 and 1977, the incidence peaks reached 50 to 60 cases per 10,000 population. It was then significantly declined to 10 cases per 10,000 population by 1979 after the commencement of measles vaccine. Malaysia continued with the single dose measles vaccination schedule at nine months of age from 1982 until 2002. The vaccination contributed to a significant decline in the national measles incidence rate from 65.2 cases per 100,000 population in 1982 to between 1.51 and 5.87 cases per 100,000 population between 1989 and 1998 (Malaysian Paediatric Association, 2023).

However, further evaluation of the program revealed that approximately 20% of children vaccinated at nine months failed to develop adequate antibody responses and there was an increasing number of measles cases were observed in older children. In response to that, the vaccination schedule was revised on July 1, 2002, with the single dose moved to 12 months of age, and the monovalent measles vaccine was replaced by the combined MMR vaccine (Malaysian Paediatric Association, 2023). The change aimed to strengthen the immunity and correspond with global practices in measles control and elimination.

In 2003, Malaysia was committed to the World Health Organization (WHO) office in Manila, Philippines, to achieve measles elimination status by 2012 (World Health Organization Regional Office for the Western Pacific, 2015). Thus in 2004, two doses of measles vaccine were included in NIP with first dose of measles containing vaccine (MCV1) was given to the children at one year old and second dose of measles containing vaccine (MCV2) was given to the seven years old school children. Nevertheless, the data showed a continued rise in the measles cases and outbreaks among children with estimation of 24% and 36% from 2011 to 2015 especially among children less than one year old who were not yet eligible for measles immunisation. Of these cases, 25% to 54% were among children aged nine to 11 months (Ministry of Health Malaysia, 2016).

The World Health Organization (WHO) Position Paper states that for measles endemic countries, the MCV1 should be given between nine and 12 months of age. The MCV2 should be given between one and two years of age (World Health Organization, 2017). In 2014, WHO categorized Malaysia as a measles endemic country, alongside the Philippines and China (Hagan *et al.*, 2018). Based on epidemiological data of measles cases in Malaysia and WHO recommendations, the National Immunisation Policy and Practice Committee has directed the following changes effective from April 1, 2016, for children born on or after July 1, 2015: 1) MCV1 using MMR combination vaccine will be given when the child is nine months old; 2) MCV2 also using the MMR combination vaccine, will be given when the child is 12 months old. For children born before July 1, 2015, the measles immunisation schedule is as follows:1) MCV1 is given at 12 months of age; 2) MCV2 to Standard One school children will continue until 2021; 3) The administration of MCV2 to Standard One school children will be discontinued in 2022 (Ministry of Health Malaysia, 2016). Figure 1.1 summarises the changes of national measles vaccination schedule since 1982 (Kumar *et al.*, 2023).

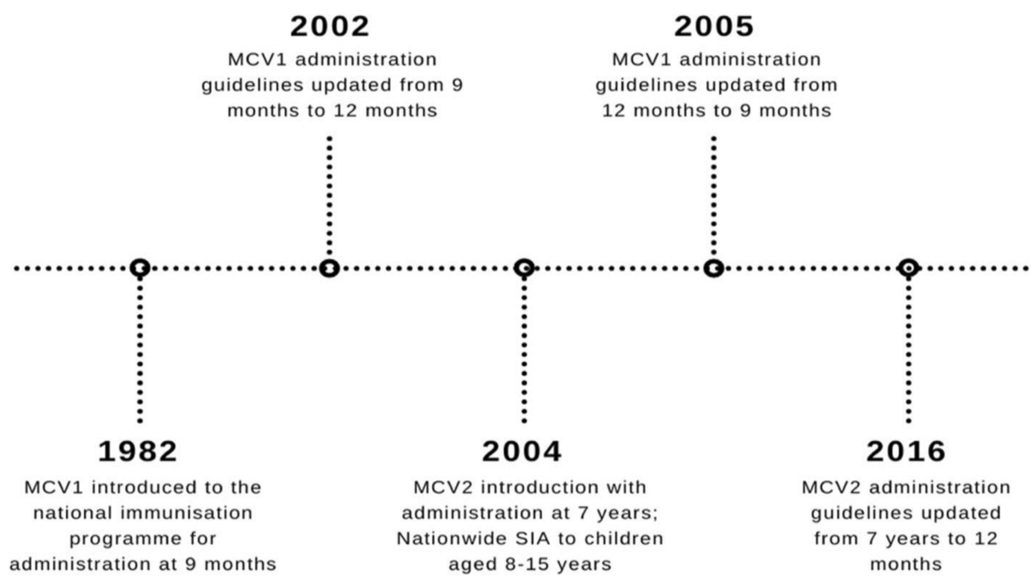

Figure 1.1: Summary of the changes of national measles vaccination schedule since 1982 (Kumar *et al.*, 2023)

1.3 Measles Elimination Program

Elimination of measles is achieved when there is no endemic transmission of the measles virus in a designated geographic area for at least 12 months in the presence of high quality surveillance system. Measles Elimination Program in Malaysia has been initiated by the Ministry of Health, Malaysia in 2004 with the aim to lower the incidence of measles in aligned with the Western Pacific Region (WPR) Plan of Action for Measles Elimination and Field Guidelines for Measles Elimination. Currently, Malaysia is working towards measles and rubella elimination by 2030 (World Health Organization, 2024a). The recommended strategies for elimination were outlined in the WPR Plan of Action for Measles Elimination and the Field Guidelines for Measles Elimination. All the 37 countries, including the territories within the WPR has adopted the strategies as per recommended. The strategies focused on three key components which were 1) ensuring and sustaining at least 95% coverage with two doses of measles containing vaccine (MCV) at national and sub-national levels through routine immunisation programs and Supplementary Immunisation Activities (SIAs) if required; 2) implementing a comprehensive case-based surveillance, which requiring timely and accurate laboratory testing of specimens to confirm or rule out suspected measles cases, and to detect genotype measles virus strains for molecular analysis and 3) strengthening the outbreak preparedness and response systems to enable rapid containment and appropriate management of measles cases (Hagan *et al.*, 2018). Recent developments in Malaysia's measles elimination efforts emphasize on the significant progress in laboratory capacity and disease surveillance. The World Health Organisation (WHO) accredited Malaysia's national and sub-national measles and rubella laboratories in 2023-2024. The accreditation indicating high quality laboratory investigations which is crucial in assessing the effectiveness of the vaccination program as well as understanding the disease burden. In addition, sub-national laboratories also have initiated serological testing and moving towards molecular detection methods to improve the accuracy of the diagnosis and interventions (World Health Organization, 2024a).

1.4 Measles Surveillance System

Disease surveillance system refers to the ongoing, systematic collection, analysis and interpretation of health data related to infectious disease with the goal of monitoring the trends, detecting the outbreaks, guiding the public health actions and directly evaluating the interventions of prevention and control of infectious disease (World Health Organization, 2006). Malaysia implemented the case-based measles surveillance in line with the Measles Elimination Program initiated in 2004, as part of its alignment with the World Health Organization (WHO) Western Pacific Region's goal to eliminate measles (World Health Organization Regional Office for the Western

Pacific, 2015). The surveillance is guided by the "Measles Elimination in Malaysia - Measles Surveillance Manual" (Ministry of Health Malaysia, 2004), which provide the guidelines for the procedures of notification, investigation, laboratory confirmation, and reporting. Figure 1.2 shows the general measles surveillance flow chart in Malaysia.

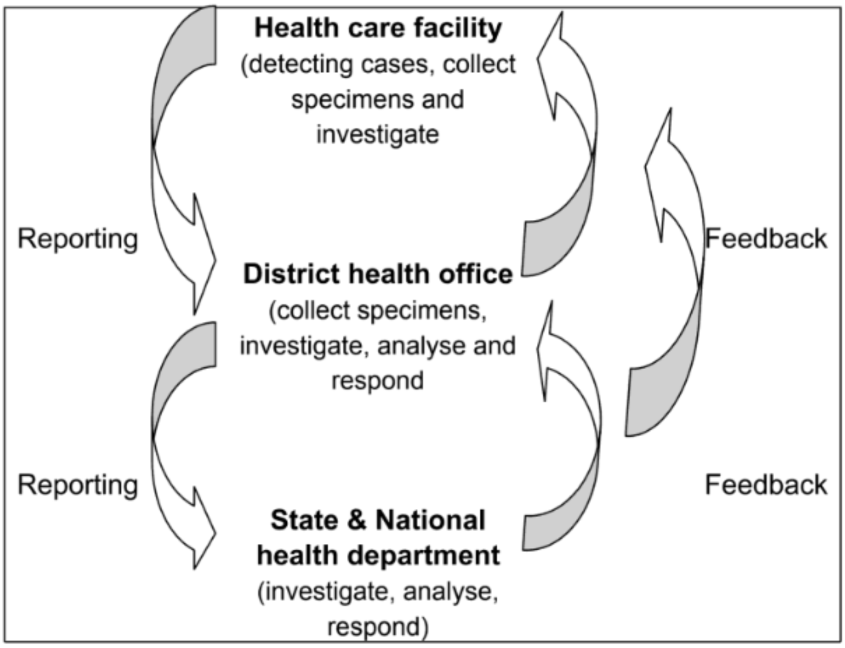

Figure 1.2: General measles surveillance flow chart in Malaysia (Source: Ministry of Health Malaysia, 2004)

According to the Case Definitions for Infectious Diseases in Malaysia 3rd Edition (Ministry of Health Malaysia, 2017), all cases of measles either suspected or confirmed case should be notified within 24 hours of diagnosis to the nearest District Health Office (DHO). Measles is one of the mandatory notifiable disease under the Prevention and Control of Infectious Diseases Act 1988 (Government of Malaysia, 1988). A medical practitioner who fails to notify the measles case within the allocated time may face a compound action for the offence Under Subsection 10(2) of the Prevention and Control of Infectious Diseases Act 1988. The notification can be done through e-Notifikasi system, manual notification form, telephone, mail, fax or e-mail to the nearest DHO.

The e-Notifikasi system is a Malaysia's national online infectious disease notification system that is used to notify all the 33 notifiable communicable diseases integrated centrally under Communicable Disease Control Information System (CDCIS). It was developed and maintained by Ministry of Health Malaysia (MOH) (Qamruddin *et al.*, 2020). The system provides timely and efficient submission of suspected or confirmed measles cases which triggers immediate case investigation. Once a suspected case of measles is notified, it will be investigated by an Assistant Environmental Health Officer to verify the details of the case. Upon verification and registration in the e-Notifikasi system, the case will be automatically transferred to the Sistem Maklumat Siasatan Measles (SM2) for further management and surveillance (Bahagian Kawalan Penyakit Kementerian Kesihatan Malaysia, 2015).

Sistem Maklumat Siasatan Measles (SM2) is an online case registration and investigation network system for measles integrated under CDCIS, developed by the MOH. The system fully utilises basic data from the e-Notifikasi system. It has been implemented nationwide in Malaysia since 2007, in line with the Measles Elimination Program under the WHO Western Pacific Region. Investigation of all measles cases must be conducted within 48 hours from the date the notification is received and updated in SM2. Once verification and investigation of a measles case is completed, together with laboratory results (if any), the case status must be updated in the SM2 within 7 days. Case status can be classified into confirmed measles case and non-measles case. Confirmed measles case can be defined as a case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a laboratory confirmed case (Disease Control Division Ministry of Health Malaysia, 2017). Meanwhile, non-measles can be further classified into clinically compatible with measles, laboratory confirmed rubella and discarded case. A person who shows the signs and symptoms of measles without laboratory confirmation and no clear epidemiological link to a confirmed or epidemiologically linked measles case is referred as clinically compatible with measles. Laboratory confirmed rubella, on the other hand is mean by a person suspected of rubella and has laboratory confirmation for rubella virus infection. As for discarded case is referred as notified measles case that has been investigated and fulfilled the criteria which are negative laboratory confirmation test for measles on an adequate specimen collection and without epidemiologically linked to a laboratory confirmed case, or epidemiological linkage to any other than measles laboratory confirmed case, or meet the clinically compatible measles case definition (World Health Organization, 2022). Once classified, essential public health interventions should be conducted accordingly. The data surveillance in the SM2 directly can be accessed by the State Health Departments as well as Disease Control Division, MOH. The surveillance data also will be shared with the WHO Regional Office for the Western Pacific in Manila on a monthly basis (Bahagian Kawalan Penyakit Kementerian Kesihatan Malaysia, 2015) allowing for regional comparison, molecular epidemiology analysis, and monitoring of virus genotypes.

1.5 Children

According to the legal contexts, the term “children” refers to the individuals who are below the age of 18 years. This definition is consistent with both international and national standards. Based on United Nations Convention on the Rights of the Child (UNCRC), a child is defined as “every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier" (United Nations, 1989). Similarly, under Malaysia's Child Act 2001 (Act 611), a child is legally defined as "a person under the age of eighteen years" (Government of Malaysia, 2006). Therefore, anyone aged less than 1 year old until less than 18 years old is considered as a child. Children are the most vulnerable population when related to illness as they are more exposed to infections and complications due to the immature immune systems. World Health Organisation (WHO) reported that an estimated 107,500 people died due to measles in 2023 and mostly occur in children under the age of five (World Health Organization, 2024b) despite the high vaccination coverage and the availability of vaccine. Thus, it is important to prioritize the children's health to reduce the incidence of measles infection and its complications directly investing in a healthier and more resilient children population in the future.

1.6 Statement of the problem

Measles elimination program in Malaysia has been started since 2004 with the goal to achieve sustainable reduction of measles and to interrupt the transmission of indigenous measles virus in Malaysia. Malaysia aims to eliminate measles by year 2010 (Ministry of Health Malaysia, 2004). However, it has been revised back to be eliminated by the year 2030 in regards with the World Health Organization's (WHO) global strategy outlined in the Measles and Rubella Strategic Framework 2021-2030 (World Health Organization, 2021). The Ministry of Health (MOH), Malaysia reported that the number of measles cases increased remarkably 900% from 195 cases in 2013 to 1934 cases in 2018 over a period of five years with six deaths related to measles, of which none were immunized (WHO 2019). In addition, measles cases among unvaccinated person increased from 125 (69%) in 2013 to 1467 (76%) cases in 2018

(World Health Organization, 2019). Thus, the target for elimination is still far from being achieved.

Measles is a highly contagious and potentially life-threatening vaccine preventable disease particularly among children. It can lead to severe complications such as blindness, encephalitis, severe diarrhoea and dehydration, ear infection, pneumonia and eventually to death (World Health Organization, 2024b). Malnourished and unvaccinated children are more likely to suffer from these consequences particularly due to delay or inadequate access to healthcare facilities. Hence, early detection and rapid execution on prevention and control strategies are crucial to manage the spread effectively.

In Malaysia, according to Ministry of Health Malaysia (MOH), all cases either suspected or confirmed case of measles should be notified within 24 hours to the nearest district health office (Disease Control Division Ministry of Health Malaysia, 2017) as a part of measles surveillance system. Although all the measles cases must be notified, local data on confirmed case of measles remains limited either at the district or state level particularly in children. Lack of data information limits the capacity of the health authorities to determine the real trend and burden of measles infection in children. It is challenging to determine whether the current trend and proportion of confirmed measles cases among children reflects an actual rise of measles cases, incorrect diagnosis or increase clinical suspicion in which subsequently lead to inappropriate use of resources and ineffective disease management strategies.

In addition, there is lack of comprehensive data on clinical presentation of confirmed measles cases among the children. The spectrum of the measles infection may vary across the geographical area and age group even though the classical symptoms of measles such as fever, maculopapular rash, cough, coryza and conjunctivitis are well known. Clinicians may struggle to identify measles from other endemic febrile rash illness such as dengue and malaria in the absence of actual local data of measles in children, particularly in vaccinated children with atypical measles presentation. Therefore, it can delay the clinical suspicion, notification, laboratory testing and subsequently delay the rapid response and initiation of effective public health interventions to eliminate the risk of measles transmission in children.

In the context of Perak, well documented local evidence of confirmed measles cases remains scarce as no other research was done at local level among the children. It is challenging to understand the local changes in the epidemiological behaviour of measles, the patterns of the disease and factors associated with confirmed measles cases of children in Perak. This gap may lead to inaccurate true burden estimation, delayed response to outbreak as early warning signs may be missed, broad and potentially ineffective strategies. Therefore, it presents several challenges for local public health interventions in combating the measles transmission in Perak.

1.7 Rationale of the study

Analysis on the proportion of confirmed measles cases among notified measles in Perak is important to estimate accurately the true burden of the disease at local state level. It will provide information to support health authorities to observe the disease trend, assess the effectiveness of the surveillance system and plan on targeted and focus interventions. This will reduce the risk of overestimation or underestimation of measles prevalence which could result in misallocation of vital public health resources and delayed rapid response to measles outbreak in children.

Other than that, lack of documentation of clinical presentation of measles among children in Perak can delay the early detection of the case. Clinical presentations may be varied depending upon the child's health status, nutritional status as well as their immunity system. This study will provide the local evidence of typically presented measles in children, thus reducing the probability of clinicians missing the diagnosis, and preventing the subsequent delay in treatment, isolation and increase the risk of measles transmission among the children in the community.

In addition, it is essential to understanding the risk factors such as sociodemographic background, measles vaccination status, history of exposure and hospital admission among the children to support the evidence-based strategies for prevention and control of measles infection in children. It then enables the health authorities to precisely target the high-risk group of children, create more effective health education and promotion programs and improve immunisation outreach to address the underlying gaps.

Besides, the findings of this study may serve as the foundation for future research of confirmed measles cases among children. It may help to build the further investigations on measles transmission dynamic, the effectiveness of the vaccine, the response on health system and post elimination surveillance strategies in the future. This study directly strengthens the evidence-based data at the local state level and supports research sustainability as well as the long-term public health improvements.

The findings and the efforts undertaken in this study are expected to assist the health authorities particularly at the State of Perak to reduce measles related morbidity and mortality and directly to achieve the goal of measles elimination by 2030, in alignment with WHO's targets.

1.8 Research Questions

1. What is the proportion of confirmed measles cases among notified measles of children in Perak from 2017 to 2024?
2. What are the clinical presentations of confirmed measles cases of children in Perak from 2017 to 2024?
3. What are the factors associated with confirmed measles cases among notified measles of children in Perak from 2017 to 2024?

1.9 Objectives

This study was guided by the following general and specific objectives.

1.9.1 General Objective

To study the proportion and associated factors of confirmed measles cases of children in Perak from 2017 to 2024.

1.9.2 Specific Objectives

1. To determine the proportion of confirmed measles cases among notified measles of children in Perak from 2017 to 2024.
2. To describe the clinical presentation of confirmed measles cases of children in Perak from 2017 to 2024.
3. To determine the factors associated with confirmed measles cases among notified measles of children in Perak from 2017 to 2024.

1.10 Research Hypothesis

There are significant associations between sociodemographic characteristics, measles vaccination status, history of exposure and hospital admission with confirmed measles of children in Perak from 2017 to 2024.

CHAPTER 2

LITERATURE REVIEW

A comprehensive literature reviews for this study were conducted by using several databases includes PubMed, Google Scholar, Scopus, Web of Science (WoS), Science Direct and Elsevier. These platforms were selected due to the wide coverage of journals and evidence-based research articles. The publication date was set within the year of 2000 to 2024 to ensure the recent studies relevant to measles in children. A systematic search strategy was applied by using Boolean operators such as “AND”, “OR”, and “NOT”. The search keywords used includes “confirmed measles case”, “notified measles case”, “associated factors”, and “children” to capture a targeted range of studies that related to measles in children.

2.1 Confirmed measles cases among notified measles

The proportion of confirmed measles cases among notified measles varies across the country and region depending upon the surveillance activity, case definitions and the effectiveness of measles vaccination program. A study conducted at Southern Nations, Nationalities, and Peoples' Region (SNNPR) of Ethiopia, between 2007 to 2014 found that about 31.3% from notified measles cases tested to be positive for measles IgM antibodies (Getahun *et al.*, 2017). In Greece and Angola, the proportions of confirmed measles cases among notified measles in children were almost similar with 26.6% among children under 16 years old age in Greece and 25.9% in children aged less than 19 years old in Angola (Gianniki *et al.*, 2021; Ramirez *et al.*, 2023). However, the proportion of measles cases is quite lower in Senegal between 2004 to 2013 accounted for 20.3% in children aged less than 15 years old (Dia *et al.*, 2015).

The criteria for confirmed measles cases vary slightly across these countries. In Ethiopia, case confirmation requires a serological testing through detection of measles specific immunoglobulin M (IgM) antibodies, provided the case has not received any dose of MCV 30 days prior to the date of testing. Angola defines a confirmed case based on a positive result for measles specific IgM antibodies similarly with Senegal. In Greece, a confirmed measles case is referred based on clinical criteria along with either a positive measles IgM antibody test or isolation of the measles virus.

Local studies in Malaysia observed notable differences between the states. In Melaka, the proportion of confirmed measles cases among notified cases in children was 37.9%, significantly higher than in Perak accounted only 7.9 % (Qamruddin *et al.*, 2020; Zaini *et al.*, 2023). Although both studies represent same cohort of cases from January 2015 until December 2019, the age ranges differed in which Melaka included children up to 18 years, whereas the Perak study was limited to those under 14 years. Therefore, the lower proportion reported in Perak could be explained by the narrower age range which excluded more than 14 years old case compared with the study conducted at Melaka.

2.2 Clinical presentations of measles

Measles in children appear to show clinically consistently across different geographic locations, even though there is slight variability in the frequency of symptoms. A study in Yemen observed all measles cases among children aged less than five years experienced fever and skin rash, with 93% also presenting with cough, conjunctivitis, and runny nose, only 25% showed lymph node enlargement (Nassar *et al.*, 2021). Similarly, a study conducted in the Jerusalem district among children under 18 years reported high frequencies of typical measles symptoms, with 98.9% of cases presenting with fever, 96.6% with maculopapular rash, 92.7% with coryza, 91.3% with cough, and 88.7% with conjunctivitis (Stein-Zamir *et al.*, 2023). In North Sumatera, Indonesia, all suspected measles cases aged from one year old to 14 years old identified during an outbreak presented with fever and maculopapular rash, while 80% reported cough, 65% coryza, and 25% conjunctivitis (Sitepu *et al.*, 2020). Meanwhile local study in Perak, Malaysia, also highlighted that all 30 confirmed measles cases had fever and maculopapular rash, with 56.7% having at least one of the three symptoms of cough, coryza, or conjunctivitis. In addition, measles cases that met the full clinical case definition had 6.72 times higher odds of being confirmed measles (Qamruddin *et al.*, 2020). These findings support the clinical presentation of classical measles symptoms in diagnosing confirmed cases, particularly among children, and highlighted the importance of adhering to clinical case definitions in surveillance systems.

2.3 Factors associated with measles

There are some factors that have been reported to be significantly associated with measles. These factors can be divided into several categories. Sociodemographic factor plays a significant role associated with measles which includes age, sex, ethnicity and urbanicity. Measles vaccination status is another important factor, further classified into complete, incomplete or not vaccinated. Another factor is mother's formal education which is distinguished by whether the mother has received formal education or not. Meanwhile, factors related to exposure history includes history of contact with confirmed measles case and history of travelling to other country. Lastly, hospital admission factor is also found to be significantly associated with measles.

2.3.1 Age

A community wide outbreak study of measles in Jerusalem District reported that measles cases in children mostly found in the age group of one to five years (44%) followed by six to 17 years (32.1%) and infant under one year (23.9%) with median age was 3.5 years (Stein-Zamir *et al.*, 2023). The findings similarly reported in Pakistan in which age specific positivity rates in those aged nine years and below shows high laboratory confirmed case of measles (Shakoor *et al.*, 2017). Other than that, during the measles outbreak in Kalimantan, Indonesia, 16 out of 23 children between six months and 11 years were also reported to have contracted with measles, with a median age of 41 months (Hartoyo *et al.*, 2017). The attack rate (AR) of measles outbreak was found to be highest in those aged one to four years (50%) compare to other age group in North Sumatera, Indonesia (Sitepu *et al.*, 2020). In Afghanistan, it was reported that the highest proportion of measles infections occurred among infants aged less than nine months (45.5%) followed by children older than 18 months (39.8%) and 10 to 18 months (14.7%) (Tahoun *et al.*, 2025). In Malaysia, a cross sectional study conducted in Melaka found that the most affected age group was one to seven years old (40.8%) with age of eight to 18 years old was significantly associated with laboratory confirmed measles among children in Melaka (OR=0.40, 95% CI: 0.21,0.76, $p = 0.005$) (Zaini *et al.*, 2023). In Petaling, children aged one to less than seven years old showed a high incidence of measles outbreaks (50.8%), followed by seven years old and above (24.2%) (Abd Rahman *et al.*, 2020). Children particularly in the younger age group are more prone to be infected with measles due to low level of measles immunity (Hazlina *et al.*, 2016). Furthermore, measles is highly transmitted among children in the setting such as schools and daycare centers where close contact facilitates the spread of the measles virus in such crowded environment (Zaini *et al.*, 2023)

2.3.2 Sex

Gender differences have been reported to be associated with measles incidence. A meta-analysis study of seven high income countries reported the incidence rate of measles was higher in male across various age groups with 1.07 (95% CI: 1.02,1.11) in infants, 1.10 (95% CI: 1.07,1.14) in children aged one to four years, 1.03 (95% CI: 1.00,1.05) in those aged five to nine years, 1.05 (95% CI: 0.99,1.11) in children aged 10 to 14 years and 1.08 (95% CI: 0.95,1.23) as increasing age of 15 to 44 years. However, the incidence rate of measles in male was lower compared to female in older aged group of 45 to 64 years with 0.82 (95% CI: 0.74,0.92) (Green *et al.*, 2022). Another study in Yemen similarly found that the attack rate was higher in male compared to female (94 vs 68/100,000) (Nassar *et al.*, 2021) as well as in North Sumatera, Indonesia with the attack rate was higher in males (24.3%) compared to females (8.1%) (Sitepu *et al.*, 2020). The increased measles incidence observed in males compared to females may be attributed to sex based immunological differences, where females generally exhibiting stronger immune responses to certain infections and vaccines that boost the protection against measles infection (Klein and Flanagan, 2016).

However, in Greece, there is no significant difference in measles prevalence between male and female children under 16 years old, even though more than half (55.7%) of the reported cases were males (Gianniki *et al.*, 2021). The finding was consistent with a study conducted in Afghanistan during the measles outbreak in 2021, which also reported that sex was not significantly associated with confirmed measles cases (Tahoun *et al.*, 2025). In contrast, a study of measles outbreaks in the Republic of Congo between 2019 and 2022 reported that females were found to be more slightly exposed as compared to males (aOR: 1.25, 95% CI: 1.01,1.6, $p = 0.04$) (Mavoungou *et al.*, 2024). The study does not explore the specific reasons for this gender disparity. It is possible that biological, social, or environmental factors such as differences in immune response or access to vaccination may contribute this result.

2.3.3 Ethnicity

Ethnic disparities are associated with an increased risk of measles infection. A study published in *The Lancet* highlighted that children from Black and Black British backgrounds had the highest rate of measles cases in the UK, with 112.2 cases per 100,000 population, significantly higher compared to other ethnic groups (Jary *et al.*, 2025). The findings in a study at Ecuador reported indigenous populations accounted for 68.2% of confirmed measles cases, with an odds ratio (OR) of 7.28 (95% CI: 5.25,10.09) compared to Mestizo populations (Le *et al.*, 2017). The incidence of measles varies among ethnic groups, with higher rates observed in Indigenous populations. This disparity is influenced by factors such as vaccination coverage, healthcare accessibility, cultural practices, and socioeconomic conditions. (Humble *et al.*, 2023; Lee *et al.*, 2023).

In Malaysia, ethnicity is significantly associated with measles infection. A cross-sectional study conducted at Pahang reported indigenous people have 4.90 times higher odds (95% CI: 1.74,13.78, $p = 0.003$) of contracting with confirmed measles as compared with Chinese and Indian ethnicity (Mat Daud *et al.*, 2022). Even though a few local studies showed that the measles infection was high among Malays with (89.5%) in children aged three months to nine years (Abd Rahman *et al.*, 2020) and about 93.8% in children less than 18 years old, there was no association between ethnicity and laboratory confirmed measles was documented (95% CI: 0.22, 1.18, $p = 0.114$) (Zaini *et al.*, 2023).

2.3.4 Urbanicity

A five-year review on case-based surveillance in Nigeria found those residing in an urban area had high risk of getting measles infection (aOR: 1.55, 95% CI:1.02,2.34) compare to those residing at rural area (Aworabhi-Oki *et al.*, 2020). Similarly in Nigeria, investigation of a measles outbreak in an urban slum within Kaduna Metropolis involved 159 cases and two deaths (Babalola *et al.*, 2019). In the urban area of Mumbai, India, a measles outbreak resulted in 358 reported cases and four deaths, with an attack rate of 11.3% and a case fatality rate of 1.1%, both of which were highest among boys aged zero to 24 months (Yadav *et al.*, 2024). Meanwhile, a study conducted in Malaysia also found that urbanization was significantly associated with measles infection with urban residents had higher risk of getting measles compared to rural residents (aOR, 1.56; 95% CI: 1.16,2.10) (Daud *et al.*, 2024). The high incidence of measles may be attributed to overcrowded living conditions and increased urbanisation driven by population migration. However, a study conducted in the Republic of Congo between 2019 and 2021 reported that the risk of acquiring measles was significantly higher among those residing in rural areas ($p < 0.0001$), suggesting a different pattern of risk compared to other settings (Mavoungou *et al.*, 2024).

2.3.5 Measles Vaccination

Being unvaccinated is another important factor that is associated with measles infection. In Yemen, unvaccinated children (aOR=17.2, 95% CI: 2.9,100.7, $p < 0.05$) was significantly associated of being a measles case compared to vaccinated children (Nassar *et al.*, 2021). Consistent with this, another study identified a significant association between being unvaccinated and contracting measles (aOR=2.31, 95% CI: 1.22,4.27) in North Sumatera, Indonesia (Sitepu *et al.*, 2020). In Ethiopia, research likewise revealed that unvaccinated individuals had a 2.6 fold higher risk of measles infection compared to vaccinated individual (OR=2.63; 95% CI: 1.99,3.48) (Eshetu *et al.*, 2024). Local study in Pahang reported that a person who received incomplete vaccination has 3.38 times higher odds (95% CI: 2.28,5.01, p < 0.001) of contracting measles compared with a person who received complete vaccination (Mat Daud *et al.*, 2022). In addition, the odds of being confirmed measles were 1.72 times greater for those who had either never received the measles containing vaccine (MCV), or were not yet eligible, or had an unclear vaccination status than in those who had received the vaccine (Qamruddin *et al.*, 2020). According to (Zaini *et al.*, 2023), children who had not gotten any MMR vaccination had a 19 fold higher risk of developing laboratory confirmed measles compared to those who had received at least one dose (95% CI: 8.82,42.6, p < 0.001). It was proven that history of administrating two or more measles vaccine doses decreases the odds of contracting measles by 61% compared with those having incomplete vaccination or unvaccinated (Eshetu *et al.*, 2024).

2.3.6 Mother's formal education

Mother's education status significantly impacts the likelihood of children infected with measles. Children in Sokoto State who had mothers without formal education had a considerably higher risk of contracting measles than children whose mothers had completed primary, secondary, or post-secondary school (OR: 2.9; 95% CI: 1.4,5.9) (Ibrahim and Jiya Gana, 2016). The findings were correspond with a study in Ethiopia which documented that measles case from illiterate mothers was 1.4 times higher to have measles infections (OR 1.38; 95% CI: 1.004,1.907) (Eshetu *et al.*,