SPATIAL DISTRIBUTION AND MULTILEVEL ANALYSIS OF DETERMINANTS OF MEASLES IN MALAYSIA, 2018-2022

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By

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DECLARATION

I declare that this thesis was done by myself and follows manuscript-based thesis writing as an alternative format approved by the School of Medical Sciences, Universiti Sains Malaysia. This work has not been submitted for any other degree or professional qualification. I ensured that all references to the works of others have been appropriately credited within this thesis.

Dr Mohd Rujhan Hadfi bin Mat Daud

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LIST OF SYMBOLS

α	Alpha
β	Beta
μ	Mu
σ	Sigma
p	Probability
Z	Z-score
n	Number of subjects
Δ	Precision of estimation
°C	Degree Celcius
μg	Microgram
%	Percentage
π	Pi
km^2	Square kilometre
m^3	Cubic metre
=	Equal to
<	Less than
>	More than
$\geq$	More than or equal to

LIST OF ABBREVIATIONS

aIRR	Adjusted incidence rate ratio
aOR	Adjusted odd ratio
AIC	Akaike Information Criterion
AUC	Area under ROC
BAFF	B-cell activating factor
BIC	Bayesian Information Criterion
CAQM	Continuous Air Quality Monitoring
CDCIS	Communicable Disease Control Information System
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DOE	Department of Environment
DOSM	Department of Statistics Malaysia
GLM	Generalized Linear Model
H-H	High-High
H-L	High-Low
ICC	Intraclass correlation coefficient
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IgG-Ab	Immunoglobulin G antibodies
IQR	Interquartile range
IRR	Incidence rate ratio
LISA	Local Indicators of Spatial Autocorrelation

L-H	Low-High
L-L	Low-Low
MCV	Measles containing vaccine
MCV1	First dose of measles-containing vaccine
MCV2	Second dose of measles-containing vaccine
MMR	Measles mumps rubella
MMRV	Measles mumps rubella varicella
MR	Measles rubella
MREC	Medical Research and Ethics Committee
OR	Odd ratio
PM	Particulate matter
PCID	Prevention and Control of Infectious Disease
REML	Restricted maximum likelihood
RM	Ringgit Malaysia
SAS	Statistical Analysis System
SPSS	Statistical packages for the Social Sciences
SSPE	Subacute sclerosing panencephalitis
SIAs	Supplementary immunisation activities
VIF	Variance inflation factor
WHO	World Health Organization

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ABSTRAK

Taburan Ruang dan Analisis Pelbagai Peringkat Penentu Demam Campak di Malaysia, 2018 - 2022

Latar Belakang: Demam campak terus menjadi cabaran kesihatan awam di seluruh dunia, termasuk di Malaysia, walaupun dengan adanya kadar vaksinasi yang tinggi dan strategi kawalan yang menyeluruh. Perubahan berterusan yang berbeza-beza dalam kejadian demam campak di antara daerah menekankan kerumitan dalam mengawal penyakit ini, yang dipengaruhi oleh pelbagai faktor seperti demografi kawasan setempat, faktor persekitaran, dan faktor berkaitan dengan perkhidmatan kesihatan. Kajian menyeluruh ini bertujuan untuk menganalisa taburan geografi demam campak, meneroka penentu penularannya, dan memahami kesan faktor individu dan kontekstual pada kejadiannya di Malaysia dari tahun 2018 hingga 2022.

Metodologi: Kajian ini mengintegrasikan tiga pendekatan analitik yang berbeza menggunakan data dari pangkalan data e-*measles* yang diperolehi dari Bahagian Kawalan Penyakit, Kementerian Kesihatan Malaysia, serta data demografi dan persekitaran tambahan dari Jabatan Perangkaan Malaysia dan juga Jabatan Alam Sekitar Malaysia. Teknik autokorelasi ruang, termasuk Statistik Global Moran's I dan Penunjuk Lokal Kaitan Ruang (LISA), digunakan untuk mengenal pasti pusat kejadian campak dan kesan pengelompokan. Model kesan campuran binomial-negatif digunakan untuk menilai impak akses kepada penjagaan kesihatan, profil demografi setempat, dan faktor persekitaran pada kejadian demam campak. Selanjutnya, analisis regresi logistik berbilang tingkat mengkaji hubungan antara jangkitan campak dengan faktor peringkat

individu seperti umur, jantina, etnik, status kewarganegaraan, sejarah kontak, sejarah perjalanan dan status vaksinasi dan penentu peringkat daerah termasuklah populasi penduduk, median pendapatan isi rumah, status urbanisasi, bilangan klinik kesihatan dan klinik desa, liputan vaksinasi, PM2.5, kelembapan relatif dan suhu.

Hasil: Analisis mengenal pasti pusat kejadian yang signifikan di daerah seperti Bintulu, Marudi, Miri, dan Gua Musang dengan kadar kejadian campak melebihi 500 per sejuta penduduk dalam tahun tertentu. Penurunan secara keseluruhan dalam kejadian boleh diperhatikan dari tahun 2018 hingga 2021, diikuti dengan sedikit peningkatan pada tahun 2022. Analisis autokorelasi ruang mengesahkan terdapat pengelompokan kes demam campak di Malaysia dengan beberapa kawasan, terutamanya di Lembah Klang dikesan sebagai titik panas demam campak. Faktor-faktor signifikan yang mempengaruhi kejadian campak termasuk pendapatan isi rumah median (aIRR 1.02, 95% CI: 1.01, 1.03), bilangan kemudahan kesihatan (aIRR 1.02, 95% CI: 1.01, 1.04) dan suhu (aIRR 0.85, 95% CI: 0.74, 0.99). Kebarangkalian mendapat campak adalah lebih tinggi dalam kalangan mereka yang berusia lebih tua (aOR 1.02, 95% CI 1.02,1.03), etnik orang asli (aOR 6.80, 95% CI 4.88,9.48), bukan warganegara Malaysia (aOR 34.53, 95% CI 8.42,141.51), mereka yang mempunyai sejarah kontak (aOR 2.36, 95% CI 2.07,2.69) dan mereka yang mempunyai sejarah perjalanan ke luar negara (aOR 2.30, 95% CI 1.13,4.70). Peningkatan satu dos vaksin campak dalam individu mengurangkan risiko jangkitan campak sebanyak 24% (aOR 0.76, 95% CI 0.72,0.79). Untuk faktor kontekstual, perbandaran berkait rapat dengan jangkitan campak (aOR 1.56, 95% CI 1.16,2.10) dan semakin banyak klinik kesihatan dan klinik desa di dalam satu daerah, semakin rendah risiko jangkitan campak (aOR 0.98, 95% CI 0.97,0.99) setelah diselaraskan untuk kesan kelompok daerah.

Kesimpulan: Terdapat ancaman berterusan penularan campak di Malaysia yang menghalang pencapaian sasaran eliminasi. Oleh itu, pengurusan berkesan penyakit ini memerlukan pendekatan yang komprehensif yang memerlukan gabungan survelan epidemiologi yang terperinci, intervensi sosio-ekonomi, dan strategi penjagaan kesihatan yang diperibadikan

ABSTRACT

Spatial Distribution and Multilevel Analysis of Determinants of Measles in Malaysia, 2018-2022

Background: Measles remains a significant public health challenge worldwide, including in Malaysia, despite high vaccination rates and comprehensive control strategies. The persistent fluctuations in measles incidence across districts highlight the complexity of controlling this disease, which is influenced by a multitude of demographic, environmental, and healthcare-related factors. This study aims to analyse the spatial distribution of measles, explore the determinants of its transmission, and understand the impact of individual and contextual factors on its incidence in Malaysia from 2018 to 2022.

Methods: This study integrates three distinct analytical approaches using data sourced from the Disease Control Division of the Ministry of Health Malaysia, the e-measles database, and additional demographic and environmental data from the Department of Statistics Malaysia and the Department of Environment Malaysia. Spatial autocorrelation techniques, including Global Moran's I and Local Indicators of Spatial Association (LISA), were used to identify measles hotspots and clustering effects. A negative-binomial mixed-effect model was employed to assess the impact of healthcare access, demographics profile, and environmental factors on measles incidence. Furthermore, multilevel logistic regression analysis examined the relationship between measles infection and both individual-level factors such as age, gender, ethnicity, travel history, nationality status, contact history, travel history and vaccination status and district-level determinants including population density, median household income, urbanisation, number of healthcare facility, vaccination coverage, PM2.5, relative humidity and temperature.

Results: The analysis identified significant districts like Bintulu, Marudi, Miri, and Gua Musang with measles incidence rates exceeding 500 per million population in specific years. A general decline in incidence from 2018 to 2021, followed by a slight increase in 2022, was observed. Spatial autocorrelation analysis confirmed the presence of clustering of measles cases in Malaysia with persistent hotspots in certain regions, particularly in Klang Valley. Significant factors influencing measles incidence included median household income (aIRR 1.02, 95% CI: 1.01, 1.03), number of healthcare facilities (aIRR 1.02, 95% CI: 1.01, 1.04) and temperature (aIRR 0.85, 95% CI: 0.74, 0.99). The odds of getting measles are higher among older age (aOR 1.02, 95% CI 1.02,1.03), indigenous ethnic (aOR 6.80, 95% CI 4.88,9.48), non-Malaysian (aOR 34.53, 95% CI 8.42,141.51), those with contact history (aOR 2.36, 95% CI 2.07,2.69) and those with travel history (aOR 2.30, 95% CI 1.13,4.70). An increase in one dose of measles vaccine in an individual reduces the risk of measles infection by 24% (aOR 0.76, 95% CI 0.72,0.79). For contextual factors, urbanisation was significantly associated with measles infection (aOR 1.56, 95% CI 1.16,2.10) and the more health and rural clinics in a district an individual resides in, the lower the risk of measles infection (aOR 0.98, 95% CI 0.97,0.99) adjusted for the clustering effect of the district.

Conclusions: There is presence of continuous threat of measles transmission in Malaysia that may hinders the achievement of the elimination target. Thus, effective management of the disease require a comprehensive approach that combines detailed

epidemiological surveillance, socio-economic interventions, and personalised healthcare strategies.

CHAPTER 1

INTRODUCTION

1.1 Background

Measles is a vaccine-preventable disease. The disease is characterised by fever, cough, runny nose, conjunctivitis and pathognomonic Koplik spots on buccal mucosa followed by erythematous maculopapular rashes. Measles is caused by a single-stranded RNA virus from the genus Morbillivirus of the Paramyxoviridae family (Girmay & Dadi, 2019). The virus has a diameter of approximately 100 to 200 nanometres. The measles virus has the ability to be transmitted via respiratory droplets over short distances and via small particles of aerosols or airborne (Misin *et al.*, 2020). Generally, the virus can remain viable on airborne particles or fomites for up to two hours (Kumar & Sabella, 2016). Humans are the sole recognised hosts of the virus, and the viruses are highly infectious. The R naught (R_0), or basic reproduction number of measles, ranges from 12 to 18, in which each infected individual can potentially infect 12 to 18 others in a susceptible population (Guerra *et al.*, 2017). This makes the measles virus one of the most infectious viruses known. The incubation period for measles is about ten to fourteen days, with peak infectiousness occurring from four days before to four days after the appearance of the rash.

1.2 Measles Elimination Program

All member states across the six World Health Organization (WHO) regions have committed to the goal of eliminating measles. As the primary technical agency, WHO leads and supports all nations in coordinating immunisation efforts and surveillance activities to achieve these goals. The measles elimination programme aimed at reducing the number of measles cases and subsequently decreasing the incidence rate of measles. Measles elimination in a country is defined as an interruption in the transmission of the disease where the incidence rate falls below 1 case per million people in a specified geographic area for at least a 12-month period. A country is verified to have achieved measles elimination status when the elimination of measles can be sustained for at least 36 months following the last known endemic case (World Health Organization, 2019a).

The United States became the first country globally to achieve measles elimination status in the year 2000. By the end of 2021, 76 countries, representing 39% of all WHO member states, had also been verified as having eliminated measles. The most recent countries to receive this verification in 2019 were Iran and Sri Lanka. Since then, no additional WHO member states have achieved elimination status. However, several countries, including Albania, Cambodia, Lithuania, Mongolia, Slovakia, the Czech Republic, the United Kingdom, and Uzbekistan, have seen the re-establishment of the diseases in their countries, although these countries had previously been verified as having eliminated measles. Due to the resurgence of the disease, currently, no WHO Region has been able to maintain its measles elimination status (Patel *et al.*, 2020; Dixon *et al.*, 2021; Minta *et al.*, 2022).

Since 2004, Malaysia has been participating in the Measles Elimination Programme, aiming to eliminate measles by 2010 in alignment with the Western Pacific Region's goal. Alongside 36 other member states of the Western Pacific Region, Malaysia has been implementing strategies outlined in the Western Pacific Region Plan of Action for Measles Elimination along with the accompanying Field Guideline for Measles Elimination. The three strategies for the elimination goal of measles include achieving and maintaining 95% or more of vaccination coverage with two doses of measles-containing vaccine (MCV) that can be done through routine immunisation services in national immunisation programs or supplementary immunisation activities (SIAs) whenever necessary. The second strategy is to conduct high-quality case-based measles surveillance, including appropriate and accurate specimen testing for confirmation of measles infection and detection of measles virus for genotyping and molecular analysis. The third strategy is to establish and maintain measles outbreak preparedness in the member state countries to ensure rapid response to outbreaks and appropriate case management (Hagan *et al.*, 2018).

Measles vaccination has been in Malaysia's national immunisation schedule since 1982 in accordance with a recommendation by WHO for countries aiming for elimination. In 2006, Malaysia enhanced its measles surveillance capabilities with the introduction of two online systems, *e-notifikasi* and e-measles. *E-notifikasi* is a digital system that enables online notification by healthcare personnel in healthcare facilities, while e-measles is a system that is developed to standardise case investigation and case-based reporting at district, state, and national levels. Despite the implementation of the strategies, Malaysia had failed to achieve measles elimination status as planned in 2010. Allocation of adequate resources and increasing community awareness of measles vaccination through advocacy activities were crucial complementary strategies (Ab Manan, Suli & A Shukor, 2020). These efforts aim to improve current prevention and control measures and help achieve the goal of eliminating measles.

1.3 Burden of measles in Malaysia

Measles remains in Malaysia despite the availability of effective vaccination and the country's commitment to eliminate the disease. Although the measles incidence rate in Malaysia shows a gradual reduction to 15 per million population in 2020, the incidence rate is still far from the elimination target of less than 1 case per million population (World Health Organization, 2020). Historically, Malaysia has experienced periodic outbreaks at various locations, and in recent years, it has seen a fluctuation in the number of measles cases, often linked to gaps in immunisation coverage or delays in vaccine administration. The demographic most affected includes unvaccinated children and communities with lower vaccine uptake, primarily due to logistical challenges in delivering vaccines to remote areas, such as what happened in Kuala Koh, Gua Musang in 2019, in which 110 confirmed cases of measles were detected and 11 fatalities occurred (Ministry of Health Malaysia, 2019). These outbreaks not only lead to increased morbidity and, in some cases, mortality but also place a significant strain on the healthcare system, diverting resources from other essential health services. The healthcare system in Malaysia also faces hurdles such as vaccine hesitancy that is partly fuelled by historical controversies and misinformation, such as unfounded fears linking the measles-mumps-rubella (MMR) vaccine to autism, which have periodically led to pocket of unvaccinated children complicating efforts to achieve herd immunity (Hussein *et al.*, 2022). These issues complicate the efforts to reach the WHO's target for measles elimination, which has been repeatedly deferred in Malaysia.

1.4 Statement of Problem

Implementation of the Measles Elimination Program in Malaysia is expected to reduce the incidence rate of measles. Nevertheless, despite achieving a high vaccination rate, with at least 96% of the population receiving the first dose and second doses of the measles-containing vaccine (MCV1 and MCV2), measles clusters have shown an upward trend, rising from 110 in 2013 to 133 in 2018. According to a report by the Ministry of Health Malaysia (2019), the incidence rate of measles has escalated from 6.1 per million population in 2013 to 52.1 per million population in 2017. A five-year trend analysis of measles cases in Pahang state from 2016 to 2020 shows a fluctuating trend, with a peak incidence rate occurring in 2019. This local trend is in contrast with the national trend, which has been showing a steady decline since 2018 (Mat Daud *et al.*, 2022).

Additionally, the incidence rate of measles in Malaysia varies significantly and is found to be non-uniform across districts. For instance, Hulu Langat district reported an incidence rate of 225.6 per million in 2018, which dropped to 41.6 per million in 2019. Meanwhile, the Larut, Matang, and Selama districts recorded a 24.5 per million incidence rate in 2019, while the Kuantan district had a rate of 101.9 per million in the same year (Ab Manan, Suli & A Shukor, 2020; Qamruddin, Qamruddin & Malik, 2020; Mat Daud *et al.*, 2022). Certain districts may also be more similar to each other such as Kuala Lumpur and Petaling Jaya than those in different districts such as Gua Musang. The pattern of distribution of measles infection based on the incidence rates seems to differ in different areas in Malaysia. Currently, there is a need for more work on the spatial distribution and clustering effect of measles cases in Malaysia despite measles being one of the diseases currently in the elimination phase in Malaysia.

1.5 Rationale

The persistence of measles in Malaysia, despite extensive efforts to eliminate the disease through prevention and control measures such as high vaccination coverage and surveillance strategies, highlights a critical gap in our understanding of the disease's transmission dynamics and the efficacy of control measures. The continuous resurgence of measles, as evidenced by fluctuating incidence rates and periodic outbreaks in various districts, signals potential issues in the implementation and effectiveness of the Measles Elimination Program. This situation has necessitated repeated revisions of the elimination targets, with the latest target now set for 2025, highlighting the need for a sustained and additional adaptive response to combat this enduring public health challenge.

Therefore, a study on the spatial patterns and clustering of measles incidence in Malaysia is both timely and essential. This research would not only portray the current distribution of disease but also map the hotspots of measles outbreaks and identify areas with effective public health measures. Additionally, this study explores the contextual factors at district level, including the demographics, health care services and environmental factors, alongside individual determinants affecting measles transmission. The use of generalized linear mixed effect model can account for both fixed effects such as individual-level determinants and random effects such as district-level variabilities which provides a more accurate analysis of the factors influencing measles transmission. The findings will enhance our understanding of measles in Malaysia and may provide valuable insights to help policymakers refine and optimise strategies and programs to combat measles at the district, state, and national levels.

1.6 Research Questions

1. What are the incidence rates of measles by district in Malaysia?
2. Where is the spatial clustering of measles cases between 2018 and 2022 in Malaysia?
3. Are there any associations between demographic profiles, healthcare-related factors and environmental factors with measles incidence in Malaysia?
4. Is there any association between individual-level and district-level factors associated with measles cases in Malaysia?

1.7 Objectives

1.7.1 General Objective

To study the distribution and determinants of measles cases in Malaysia from 2018 to 2022.

1.7.2 Specific Objectives

1. To determine the incidence rates of measles cases in Malaysia based on district from 2018 to 2022.
2. To determine the hotspots of measles cases in Malaysia from 2018 to 2022.
3. To determine the relationship between measles incidences with demographic profiles, healthcare-related factors and environmental factors.

4. To determine the relationship between the individual-level and district-level factors and the odds getting measles in Malaysia from 2018 to 2022.

1.8 Research Hypotheses

1. There are hotspots of measles cases in Malaysia from 2018 to 2022.
2. There are relationships between measles incidence and demographic profiles, healthcare-related factors and environmental factors.
3. The individual-level and district-level factors are associated with the odds of getting measles in Malaysia.

CHAPTER 2

LITERATURE REVIEW

The literature search was conducted using multiple search engines and online databases available on the web, including PubMed, Scopus, Science Direct, Springer Link, and Google Scholar. Several searching strategies were applied, including the use of Boolean operators "AND," "OR", and "NOT." The keywords applied during the searches are measles, spatial, multilevel, factors associated, and risk factors.

2.1 Measles

The measles virus is highly infectious. Its incubation period starts when the virus begins to multiply after being inhaled by a susceptible person from an infected individual. Initially, it targets the epithelial cells in the upper respiratory tract to initiate its replication. Another potential site of entry to the susceptible host is through the conjunctiva, which is abundant in dendritic cells and lymphocytes. The replication of the measles virus continues as it spreads through the local lymphatic system, leading to viremia and the spread to various organs such as the lymph nodes, skin, gastrointestinal tract, liver, and kidney. The target cells of the measles virus are endothelial cells, epithelial cells, dendritic cells, monocytes, lymphocytes and macrophages. The clinical signs and symptoms manifested by individuals infected with the measles virus are the results of the immune response of the host at the sites of viral replication (Laksono *et al.*, 2016; Moss, 2017).

The classical course of measles infection starts with a prodromal phase that lasts for two to four days. This prodromal phase often presents with symptoms similar to those of a common cold. It is characterised by increasing fever that can be up to 40 ^{O}C, malaise, anorexia, and the classic triad of cough, coryza or runny nose and conjunctivitis in which the eyes appear watery and red. In certain cases, the prodromal symptoms can be up to seven days (Hamborsky, Andrew Kroger & Charles Wolfe, 2015; Leung *et al.*, 2018). The period of highest infectivity in measles occurs during the prodromal phase. The pathognomonic feature of measles infection is Koplik's spot. It appears on the buccal mucosa opposite to the molars of an infected individual. The Koplik's spots are described as one to three millimetres of punctate blue-white spots on a bright red background resembling grains of sand or rice. However, Koplik's spots only manifest in 60 to 70 per cent of cases. Koplik's spots appear around one to two days before the onset of the rash and last for 12 to 72 hours. The spots often are not appreciable at the time of clinic visits or evaluations by healthcare workers, as they usually start to resolve when the rashes appear (Kumar & Sabella, 2016; Leung *et al.*, 2018).

Typically, rashes of measles emerge three to four days after the onset of fever. These rashes appear as blanching, erythema, macules, and papules with cranial to caudal progression. The rashes appear on the face and move to the hairline areas, to the sides of the neck and behind the ears. As the rash progresses, it spreads downward to the trunk and extremities, becoming more prominent. These rashes may cause itchiness in the affected individuals; however, the rashes rarely affect the palms of the hands and soles of the feet. Additionally, the lesions may also manifest as petechiae or ecchymoses (Bentley, Rouse & Pinfield, 2014; Moss, 2017; Leung *et al.*, 2018). The rashes typically persist for three to seven days. Clinical signs of improvement can be seen in the infected individual within 48 hours after the onset of rashes. There will be a resolution of symptoms, and the rashes will fade gradually according to the directional pattern of their appearance. Brownish discolouration, especially among Caucasian descent, and fine desquamation sometimes occur as the rash fades (Moss, 2017; Leung *et al.*, 2018).

Although most of the cases of measles are self-limiting and resolved spontaneously, the virus can cause neurologic complications. A rare but severe complication can occur when the measles virus spreads to the central nervous system, resulting in subacute sclerosing panencephalitis (SSPE). This condition can develop several years up to a decade after the initial episode of measles infection. SSPE typically starts with a slight change of behaviour, followed by seizures, ataxia and can ultimately be fatal (Laksono *et al.*, 2016).

2.2 Measles Vaccination Program

The first measles vaccine was licensed in 1963 following the isolation of the Edmonston-B strain of the measles virus in the United States in 1954. This strain was propagated using chick embryo cell cultures. By the late 1950s, initial vaccine formulations were deemed effective but were also noted for their high reactogenicity, often inducing rashes in recipients. Subsequent research focused on reducing these adverse effects through further attenuation of the virus. This process led to the development of less reactogenic strains, such as the Schwarz measles virus strain and Enders' measles virus strain. These strains have been adopted globally in recent years. They are currently utilised in various vaccine formulations, including monovalent measles vaccines and combination vaccines such as measles-rubella (MR), measles-mumps-rubella (MMR), and measles-mumps-rubella-varicella (MMRV) (Goodson & Seward, 2015). Prior to the introduction of the measles vaccine in 1963, measles epidemics occurred every two to three years, affecting over 90% of individuals during their childhood. In the era preceding vaccination, it is estimated that measles had infected more than 30 million individuals annually and resulted in more than 2 million deaths each year (States & August, 2013; Goodson & Seward, 2015). Since the widespread availability of the measles vaccine, there has been a significant shift in the incidence of the disease, with a global reduction of more than 88% in measles cases observed (Dixon *et al.*, 2021).

Currently, measles vaccines are administered as live attenuated vaccines, delivered either subcutaneously or intramuscularly. The standard dosage of MCV is 0.5 ml. Depending on the recipient's age, these vaccines are typically administered in the anterolateral thigh or the upper arm. For younger children, the preferred site of injection is the anterolateral thigh. The vaccines are authorised for use as early as six months of age; however, their efficacy is generally lower when administered at this early age compared to later in childhood. This reduced effectiveness can be attributed to the immaturity of the infant's immune system and the presence of maternal antibodies, which can interfere with the development of seroconversion (World Health Organization, 2019b). The optimal timing for administering the first dose of measles-containing vaccine (MCV1) is recommended at nine months of age in countries experiencing ongoing measles transmission, particularly where high rates of transmission occur among infants under one year old. In these settings, timely administration of MCV1 is critical to ensure adequate protection during this susceptible period of infancy. The second dose of measles-containing vaccine (MCV2) is advised to be administered at the age of 15 to 18 months, maintaining a minimum interval of at least four weeks following MCV1. MCV2 is necessary to protect children who may not have developed protective immunity following the first dose. In countries with later occurrences of infection or in countries with low measles transmission rates, such as those countries with measles elimination status, the MCV1 can be administered at 12 months old or later. Delaying the vaccination in such contexts exploits the higher seroconversion rates observed at older ages (World Health Organization, 2019b). The measles strains in MCV induce both humoral and cellular immune responses similar to those caused by wild-type measles virus infection, although antibody concentrations are usually lower compared to immune responses from wild-type measles virus. The effectiveness of MCV can reach up to 99% if given for two doses at appropriate intervals (Leung *et al.*, 2018).

Most countries have included the measles vaccine in the national immunisation schedule. Globally, measles vaccination coverage had increased from 72% in 2000 to 84% in 2010. However, progress stagnated in the decade following 2010, with a marginal rise to 86% by 2019. The coverage subsequently declined to 81% in 2021 amid the Coronavirus Disease 2019 (COVID-19) pandemic. As of the latest data, 91 or 47% out of 194 WHO member states had achieved MCV1 coverage exceeding 90% within their national populations (Minta *et al.*, 2022). Meanwhile, the estimated MCV2 coverage increased fourfold in 20 years, from 17% in 2000 to 72% in 2020, though it slightly reduced to 71% in 2021. Despite these gains, MCV2 coverage is still far from the target goal of 95%.

The national immunisation programme in Malaysia started as early as in the 1950s. Malaysia has incorporated measles vaccination in the national immunisation program since 1982. Initially, the measles vaccine is given at the age of nine months old as a single dose. The timing of measles vaccination and the dose of vaccine had been changed in 2002 from nine months old to twelve months old, and MCV2 was introduced in the national immunisation program to increase protection against measles infection among children. MCV2 was initially given at the age of 7 years old. The most recent adjustments to the measles vaccination schedule in Malaysia were implemented in 2016, aligning with World Health Organization recommendations on countries ongoing measles elimination phase to revert the initial vaccination age to 9 months and scheduling the MCV2 at least four weeks later (World Health Organization, 2019b). Following the recommendations, the age for MCV1 and MCV2 in Malaysia was shifted from the age of 12 months and seven years old to the age of 9 months and 12 months old, respectively (Qamruddin, Qamruddin & Malik, 2020). Despite the adjustments to the vaccination schedule, Malaysia continues to experience periodic measles outbreaks, predominantly among unvaccinated populations. Consequently, the incidence rates of measles in Malaysia remain significantly above the targets set for elimination.

2.3 Measles Surveillance System

One of the three main strategies to eliminate measles based on the Western Pacific Regional Plan of Action for Measles Elimination and Measles Elimination Field Guide is to develop and maintain effective surveillance in each country in the region. This strategy emphasises high-quality case-based measles surveillance, including active surveillance of suspected measles cases with timely investigation (World Health Organization Regional Office for the Western Pacific, 2018). Surveillance is the ongoing systematic collection, analysis and interpretation of health-related data essential to the planning, implementation and evaluation of public health practices closely integrated with the timely dissemination of information and act upon that information (Groseclose & Buckeridge, 2017). A measles surveillance system enables the establishment of the burden of measles in a country through the disease incidence, morbidity and mortality related to the disease. This system is essential for directing the implementation and evaluation of strategies for measles prevention and control. In countries that have already achieved elimination or countries that have low measles incidence, surveillance data provide evidence that the absence of reported cases reflects the true absence of the disease rather than inadequate detection and reporting. For countries actively working towards elimination, these surveillance data are crucial for assessing progress towards achieving disease control and elimination goals. Case-based measles surveillance involves the detailed collection of information on each individual measles case through comprehensive and timely field investigations. As of 2020, all 194 countries globally conducted measles surveillance, but only 32% were verified by WHO for having high-quality, case-based surveillance systems based on the surveillance indicators (Orenstein *et al.*, 2018; Dixon *et al.*, 2021). In the WHO Western Pacific Region, all 37 countries, including Malaysia, have implemented and operated case-based measles surveillance systems. These systems are designed to monitor and analyse measles epidemiology in detail, in collaboration with WHO and other state members (World Health Organization Regional Office for the Western Pacific, 2018).

In Malaysia, measles surveillance is conducted according to a case classification system that categorises cases as either suspected or confirmed measles cases. A suspected case of measles refers to any individual diagnosed by a clinician based on clinical symptoms indicative of measles. A confirmed case is a case that is validated through laboratory means, which includes the detection of measles-specific IgM antibodies, identification of the measles virus using culture or molecular techniques, or by fulfilling the clinical case definition and having an epidemiological link to a laboratory-confirmed case (Ministry of Health Malaysia, 2017). Medical practitioners in Malaysia are legally required to report any suspected measles cases to the nearest district health office within 24 hours, as mandated by the Prevention and Control of Infectious Disease (PCID) Act of 1988, commonly referred to as Act 342. According to the act, the notification of infectious diseases needs to be done without delay using the form prescribed by regulations made under this act. Measles is classified as a disease that is mandatorily notifiable in Malaysia. Failure to report a notifiable disease can result in legal consequences under sections 24 and 25 of Act 342, with penalties including fines up to RM1000, imprisonment for up to 5 years, or both (Ministry of Health Malaysia, 1988).

In addition to the mandatory notification through the prescribed form as stipulated by the PCID Act of 1988, an online notification must also be done using the *e-notifikasi* system. This system was developed by the Communicable Disease Control Information System (CDCIS) and is managed by the Disease Control Division of the Ministry of Health Malaysia. Introduced in 2006, *e-notifikasi* is utilised by healthcare personnel in healthcare facilities across both the public and private sectors to report all notifiable diseases in Malaysia. E-measles is another system developed by the Ministry of Health Malaysia, which has been operational since 2007 in conjunction with the existing *e-notifikasi* system. These online systems are crucial for the case-based measles surveillance process in Malaysia. Initially, all notifiable disease cases, including suspected measles cases, are notified through *e-notifikasi* by healthcare personnel in healthcare facilities. These suspected measles cases are then transferred in real-time from *e-notifikasi* to the e-measles system for further investigations. Following the transfer, investigations are conducted within 48 hours by medical and health officers or assistant environmental health officers from the district health office. These investigations are comprehensive, covering sociodemographic data, disease history, vaccination and medical histories, travel details, and laboratory findings related to measles. The collected data are entered into the e-measles system by the investigators. The analysis of this surveillance data enables the Ministry of Health Malaysia to determine optimal disease control measures, forecast potential outbreaks, and implement preventative strategies accordingly. Additionally, the e-measles system facilitates the monitoring of measles prevention and control measures' efficacy at both district and state levels (Liyanatul Najwa *et al.*, 2016; Ab Manan, Suli & A Shukor, 2020; Qamruddin, Qamruddin & Malik, 2020; Mat Daud *et al.*, 2022).

2.4 Incidence rate of measles

The incidence of measles has demonstrated variability across different countries. There was an 88% decline in the global incidence rate, falling from 145 per million population in the year 2000 to 18 cases per million population in 2016. However, the period from 2017 to 2019 witnessed a notable resurgence, with incidence rates escalating to 120 cases per million population in 2019. Subsequently, a decline was observed, with rates decreasing to 21 cases per million in 2020 and further reduce to less than 17 cases per million in 2021. The reduction in measles incidence observed in 2020 and 2021 globally may be attributed to several factors. These include increased immunity levels following the resurgence between 2017 and 2019, decreased transmission rates due to COVID-19 mitigation measures, potential underperformance of surveillance systems, or a combination of these factors (Minta *et al.*, 2022). In the

Western Pacific Region, a resurgence of measles had occurred from year 2013 to year 2016, resulting in an increase in incidence rate up to 30.1 per million population in 2016 after the lowest incidence of 5.9 per million population had been achieved in 2012. The resurgence was attributed to increase in seasonal endemic transmission in China and the occurrence of large-scale outbreaks in endemic countries, including Malaysia and Philippines (Hagan *et al.*, 2018).

To date, limited published studies are available documenting the incidence rate of measles throughout Malaysia. The trend of measles in Malaysia follows regional and global trends in which gradual reduction is seen from the early 1990s with an incidence rate of 652 per million population and reached the lowest of 5.1 per million population in 2013 before spiking up again to 52.1 per million population in 2017 and reduced back to 32.3 per million population in 2019 (Hagan *et al.*, 2018; Mat Daud *et al.*, 2022). Local studies conducted in Malaysia have demonstrated that the incidence rates of measles across various states and districts significantly diverge from the national incidence rates. In 2019, few local studies at the district level revealed a broad spectrum of incidence rates, ranging from as low as 24 cases per million population to as high as 101.9 cases per million population. This variability indicates substantial regional differences in measles transmission within the country (Ab Manan, Suli & A Shukor, 2020; Qamruddin, Qamruddin & Malik, 2020; Mat Daud *et al.*, 2022). The target incidence rate for the elimination of measles is less than one measles case per one million population, and the incidence rate must be sustained for at least 36 months for a country to be declared as a measles-eliminated country (Jean Baptiste *et al.*, 2021).

2.5 Spatial distribution of measles

Spatial analysis refers to statistical analysis based on patterns and underlying processes. Spatial analysis is a geographical analysis that elucidates patterns of personal characteristics and spatial appearance in terms of geostatistics and geometrics. Spatial analysis is also known as location analysis (Paramasivam & Venkatramanan, 2019). The analysis is the emerging research technique that is used to represent the pattern of both communicable and non-communicable diseases. The analysis requires a geographic information system (GIS) and a computer-based system to integrate and analyse geographical reference data to visualise the distribution of the disease and health outcome. This data analysis technique has supplied better data visualisation on both spatial and temporal correlations. The analysis also provides more dynamic information on the disease, determines the clustering effect of the diseases, and allows the detection of persistent and uncommon patterns of diseases (Byun, Lee & Hwang, 2021).

Spatial autocorrelation is a spatial analysis technique used to measure and analyse the degree to which similar values in a dataset are clustered or dispersed across a geographical area. Spatial autocorrelation in infectious disease research is crucial because it helps to identify patterns of disease spread that are not random but rather influenced by geographical and spatial factors. By examining the correlation of disease incidence between neighbouring locations, researchers can detect clusters or hotspots of high infection rates, which might suggest underlying common environmental conditions or interactions among populations that facilitate the spread of disease (Zhang *et al.*, 2019; Lin & Wen, 2022). This information is essential for public health planning and interventions, as it allows for targeted actions in areas at higher risk and helps in understanding the mechanisms of disease transmission. Overall, spatial autocorrelation provides insights into the spatial dynamics of infectious diseases, supporting more effective disease control and prevention strategies.

Globally, measles shows a significant clustering pattern of distribution (Z-score 6.649, Moran's I 0.02, *p*-value <0.001). Hot spot analysis of measles by year indicates that there were hotspots in Asia in 2009, and the hot spots moved and became more concentrated in Africa from 2010 to 2013. The United States remain as cold spots globally (Jiang *et al.*, 2017). China is a country approaching elimination status in the western Pacific region with a reduction of incidence rate from 20.4 per million in 2013 to 2.8 per million in 2018. Several studies on the spatial distribution of measles have been done in this country (Quanwei, 2016; Tang *et al.*, 2017; Chao *et al.*, 2019; Shen *et al.*, 2021). According to a study in China, there was a high clustering area of measles detected in the western part of China. There was also spatial clustering of measles cases from 2009 to 2012 with Moran's I coefficient value of 0.31. These studies provide evidence for the development of a strategy for measles prevention and control in China (Shen *et al.*, 2021).

2.6 Analysis of correlated data

Regression analysis is a fundamental statistical method used to examine relationships between explanatory and response variables. Traditional regression analysis assumes that all observations are independent of each other, making it ideal for data where this assumption holds true. However, data with hierarchical structure are commonly found in health services, population and public health, and epidemiologic research (Austin & Merlo, 2017). Multilevel analysis, also known as hierarchical linear modelling, is a statistical technique that accounts for data structures where observations are nested within higher-level groups. This method is particularly relevant in fields such as education, where students are nested within classes, and in healthcare, where patients are treated in different hospitals (Austin, 2017). Multilevel analysis has been used for various epidemiological research, including measles and other infectious diseases such as COVID-19, dengue, leptospirosis, malaria, and tuberculosis (Cook *et al.*, 2017; Geremew, Gezie & Abejie, 2019; Saputri, Dewi & Murti, 2019; Ye & Lyu, 2020; Ordoñez-Sierra *et al.*, 2021).

Multilevel modelling allows researchers to correctly model the variability at each level of the hierarchy, providing more accurate estimates and inferences than traditional single-level models. This allows for the analysis of grouped data and accounts for both within-group and between-group variability. It also handles the issue of dependence among observations within the same group, which violates the assumptions of conventional regression analyses (Austin, 2017). In recent advancements, multilevel analysis has expanded to include models that can handle complex nested structures and longitudinal data, incorporating fixed and random effects to account for both time-invariant and time-varying covariates. For instance, Bell et al. (2019) demonstrated how multilevel models could be used to assess the impact of policy changes over time within different regions. This adaptability makes multilevel analysis an essential tool in policy evaluation, allowing for the analysis of interactions between policies and the contexts within which they are implemented. Furthermore, the application of multilevel analysis has been enriched by the development of software tools that simplify the execution of these complex models. Programs like R, Statistical Analysis System (SAS), and Statistical Package for the Social Sciences (SPSS) have incorporated comprehensive multilevel modelling functions, which are continuously updated to include the latest statistical techniques. This has significantly lowered the barrier to entry for researchers wanting to apply these models in their work, leading to broader adoption and more sophisticated analyses across various disciplines (Hox, Moerbeek & van de Schoot, 2017).

2.7 Demographics Profile

Living in either urban or rural areas is an important determinant of measles infection. Analysis of five-year case-based surveillance data in Nigeria revealed that living in urban areas is a predictive factor for measles cases (aOR 1.55, 95% CI: 1.02,2.34) (Aworabhi-Oki *et al.*, 2020). A similar finding was observed in China, where individuals living in urban districts have a higher risk of contracting measles than those who live in counties. A higher percentage of measles cases were in urban areas (43%) compared to suburban (25.1%) and rural areas (31.9%) in China (Wagner *et al.*, 2016). Urban areas, characterised by their dense populations, overcrowding and influx of immigrants, can facilitate the transmission of measles infections. However, an epidemiological study in Iraq found that there is no significant association between measles infection and residing in either urban or rural areas (p-value = 0.083). The study was done in Najaf province, which is covered by a city area with a 1.4 million population mostly residing in the city, and only less than 30 % of the province area was considered rural area in Najaf (Jawad *et al.*, 2021).

Population density is an important risk factor for measles. A study in Italy showed that areas with higher population densities experienced significantly more measles cases than less populated areas (IRR 1.70, 95% CI 1.36,2.12, *p*-value < 0.001) (Andrianou *et al.*, 2019). Similarly, population density is positively associated with measles incidence in China and Ethiopia (Desta *et al.*, 2018; Qin *et al.*, 2019). The risk of measles transmission and outbreaks is particularly high in refugee camps in Ethiopia, where a dense population facilitates the spread of the disease (Ali & Maalin, 2021). In Cameroon, Yaoundé and Douala city, more people at risk of measles infection due to their higher population density (Parpia *et al.*, 2020). These studies collectively support the hypothesis that higher population density allows increased contact, which drives the spread of measles (Sulistyawati & Sumiana, 2018).

There is an association between median household income and measles incidence. Studies have shown that those with lower median household income has higher risk of measles infection. Areas with higher median incomes have lower incidence rates of measles, as economic stability enables timely and complete vaccinations, reducing susceptibility to the disease. (de Glanville *et al.*, 2019; Scarbrough *et al.*, 2019). However, a study in Italy discovered a positive association between median household income and measles incidence. Those living in regions with lower deprivation indexes and higher household income levels reported greater incidence of measles cases which is explained due to different levels of antibodies across different regions with different deprivation index in Italy (Andrianou *et al.*, 2019).

2.8 Healthcare-related factors

Vaccination coverage is an important factor in determining the risk of measles. WHO recommends 95% coverage of measles vaccination will generate and maintain the herd immunity required to block measles transmission in the community (Plans-Rubió, 2019). A study in Iraq using a linear mixed effects model found a significant and positive association between MMR vaccination coverage and the incidence of measles.

An increase in the percentage of vaccination coverage will lower the incidence rate of measles by 0.82 cases per 100,000 (95% CI: 0.64-0.99, p-value <0.001) after controlling for the governate, which is the administrative state of Iraq (Comfort *et al.*, 2022). However, a study in the United States found that measles annual incidence rate was not significantly associated with the percentage of vaccinated case (Dimala *et al.*, 2021). This observation is attributed to the fact that the research was carried out in a post-elimination era, during which a majority of the population had been vaccinated, and the incidence rates were very low.

Healthcare access should be considered an important determinant of disease. The number of clinics in an area is one of the determinants of healthcare accessibility (Tzenios, 2019). In Malaysia, healthcare services are delivered primarily by the government health sector. A systematic review found that reduced accessibility to healthcare services not only increases the burden of infectious diseases but also leads to a decrease in disease reporting. This underreporting further complicates the allocation of resources and delays responses to outbreaks, as health policy and interventions rely heavily on accurate disease data, which is scant due to the low reporting rates from inaccessible areas. Improvements in these areas could be achieved by expanding the number of healthcare facilities and fostering partnerships between the public and private sectors (Hierink *et al.*, 2021).

2.9 Environmental factors

Relative humidity affects the occurrence and transmission of viruses, such as measles. The relative humidity is a measure of the water vapour content of the air. Research conducted in Guangzhou, China, has shown that there is an inverse