FACTORS ASSOCIATED WITH CONFIRMED MEASLES AMONG NOTIFIED MEASLES CASES IN PAHANG, 2016 - 2020

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By

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LIST OF ABBREVIATION

AdjOR	Adjusted Odd Ratio
CDCIS	Communicable Disease Control Information System
CI	Confidence Interval
df	degree of freedom
GVAP	Global Vaccine Action Plan
IBM	International Business Machines Corporation
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
MMRV	measles-mumps-rubella
MMRV	measles-mumps-rubella-varicella
mOR	Matched Odd Ratio
MREC	Medical Research and Ethics Committee
NMRR	National Medical Research Registry

OR	Odd Ratio
PCID	Prevention and Control of Infectious Disease Act
R_0	R naught
ROC	receiver operating characteristic
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SIAs	supplementary immunization activities
SM2	*Sistem Maklumat Siasatan Measles*
SPSS	Statistical Package for the Social Sciences
VIF	variance inflation factor
WHO	World Health Organization
WPR	Western Pacific Region

LIST OF SYMBOLS

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

ABSTRAK

FAKTOR YANG BERKAITAN DENGAN KES DISAHKAN DEMAM CAMPAK DALAM KALANGAN KES YANG DINOTIFIKASI SEBAGAI DEMAM CAMPAK DI PAHANG, 2016 - 2020

Latar Belakang: Demam campak adalah penyakit berjangkit cegahan vaksin akut yang telah menjadi keprihatinan utama kesihatan awam. Eliminasi demam campak telah menjadi matlamat untuk semua negara. Malaysia telah memulakan Program Eliminasi Demam Campak sejak tahun 2004 namun kejadian demam campak di Malaysia tidak menunjukkan perkembangan yang ketara.

Objektif: Kajian ini bertujuan untuk mengkaji perkadaran kes disahkan demam campak dalam kalangan kes yang dinotifikasi sebagai demam campak, untuk menghurai tren kejadian demam campak dan untuk menentukan faktor yang berkaitan dengan kes disahkan demam campak dalam kalangan kes yang dinotifikasi sebagai demam campak di Pahang dari tahun 2016 hingga tahun 2020.

Metodologi: Ini adalah kajian keratan rentas menggunakan data sekunder tahun 2016 sehingga tahun 2020 daripada SM2 e-measles oleh Jabatan Kesihatan Negeri Pahang. Kajian ini dijalankan dari November 2020 sehingga April 2021. Data yang berkenaan diekstrak dari SM2 e-measles, iaitu sistem survelan demam campak di Malaysia, dikumpulkan dengan menggunakan proforma dan dianalisa menggunak perisian IBM SPSS versi 27. Data dianalaisis secara deskriptif, regresi logistik mudah dan berganda

Keputusan: Sejumlah 2844 kes dimasukkan ke dalam kajian ini dengan perkadaran kes disahkan demam campak adalah 7.41%. Kadar kejadian demam campak di Pahang pada tahun 2016 sehingga tahun 2020 adalah dari julat 13.51 hingga 50.97 per

1,000,000 populasi dengan tren yang berubah-ubah. Faktor berkaitan kes disahkan demam campak yang dikenalpasti berkepentingan adalah Orang Asli (AdjOR = 4.90), sejarah kontak kepada kes demam campak (AdjOR = 14.03) dan vaksinasi demam campak tidak lengkap (AdjOR = 3.38).

Kesimpulan: Etnik, sejarah kontak kes demam campak, dan status vaksinasi adalah faktor yang berkaitan dengan kes disahkan demam campak di kalangan kes yang dinotifikasi. Liputan vaksinasi Orang Asli perlu dipertingkatkan dan dos lengkap demam campak hendaklah menjadi perhatian utama dalam mengurangkan kejadian demam campak justeru sasaran eliminasi demam campak akan boleh dicapai.

KATA KUNCI: disahkan demam campak, kes dinotifikasi, kejadian, faktor berkaitan

ABSTRACT

FACTORS ASSOCIATED WITH CONFIRMED MEASLES AMONG NOTIFIED MEASLES CASES IN PAHANG, 2016 – 2020

Background: Measles is an acute communicable vaccine preventable disease that has become the major concern of public health. Elimination of measles has been a goal for all countries under the WHO region. Malaysia has started Measles Elimination Program since 2004 however the incidence trend of measles in Malaysia has not make much improvement.

Objective: The study aimed to describe the proportion of confirmed measles among notified measles cases, to describe the trend of incidence rate of measles and to determine the factors associated with confirmed measles among notified measles cases in Pahang from 2016 to 2020.

Methodology: This was a cross-sectional study using secondary data year 2016 until year 2020 from SM2 e-measles from Pahang State Health Department. The study was conducted from November 2020 to April 202l. Relevant data were extracted from SM2 e-measles which is a measles surveillance system in Malaysia. The data were collected using proforma and were analysed using SPSS software version 27. The data were analysed using descriptive analysis, simple and multiple logistic regression.

Result: A total of 2844 notified measles cases were included in this study in which the proportion of confirmed measles cases were 7.41%. The incidence rate of measles infection in Pahang from 2016 until 2020 were ranges from 13.51 to 50.97 per 1,000,000 population with fluctuating trend. The associated factor for confirmed measles that were found to be significant were being indigineous (AdjOR = 4.90), history of contact with measles cases (AdjOR = 14.03) and incomplete vaccination (AdjOR = 3.38).

Conclusions: Ethnicity, history of contact with measles case and vaccination status were the factors associated with confirmed measles among notified measles cases. Aborigine vaccination coverage should be improved, and complete dose of measles vaccination should be a main target in reducing the incidence of measles and thus, target for measles elimination will be achievable.

KEYWORD: confirmed measles, notified cases, incidence, associated factors

CHAPTER 1

INTRODUCTION

1.1 Measles

Measles is an acute communicable viral disease. It is vaccine-preventable and characterized by fever, cough, runny nose, conjunctivitis and pathognomonic enanthem of Koplik spots followed by the characteristic erythematous maculopapular rashes. Measles infection is caused by single stranded RNA virus with a diameter of 100 to 200 nanometres from the genus Morbillivirus of the Paramyxoviridae family (Girmay and Dadi, 2019). Measles virus is transmitted by respiratory droplets over short distances and by small particles aerosols that remain suspended for several hours in the air (Misin *et al.*, 2020). Measles virus is highly infectious. The infectivity rate of measles is among the highest among viruses and it is transmitted from human to human. R naught (R_0), or basic reproduction number of measles range from 12 to 18 in which each person infected with measles, would infect another 12 to 18 persons on average in a susceptible population (Guerra *et al.*, 2017). Measles virus has incubation period of about 10 to 14 days and the host will be the most infectious from four days before the onset of maculopapular rash and the infectiousness persist up to four days after its appearance.

1.1.1 Measles vaccination programme

Prior to the introduction of measles vaccine in 1963 and widespread measles vaccination, major epidemics of measles occurred every two to three years and it was estimated that 2.6 million deaths was due to measles infection each year. However, things have change since then as globally, 84 percent decrease in measles deaths was observed between 2000 and 2016 as the vaccine became more widely available (WHO, 2020). The currently used measles vaccines contain live attenuated measles strains. The measles strains in the vaccine will induce humoral and cellular immune response that protect against wild type measles virus. It can be given alone but more often the measles vaccine were given in combination with other vaccine such as measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine. Measles vaccine can reach up to 99% effectiveness in preventing measles if given for two doses and in timely duration. (Javelle *et al.*, 2019; Leung *et al.*, 2018) Measles vaccination has been included in national immunisation schedule in most countries globally. In 2018, 118 (61%) countries have achieved 90 percent measles containing vaccine first dose (MCV1) immunization coverage which shows vast increment compared to only 86 (45%) countries in the year of 2000. There was increased in number of countries that provides measles containing vaccine second dose (MCV2) from 98 (51%) countries in 2000 to 171 (88%) countries in 2018. However the global coverage of MCV2 is only at 69 percent which is still far from target of 95 percent coverage (Patel *et al.*, 2019).

Measles containing vaccines have been included in Malaysia immunisation schedule for Malaysian citizen since 1982 with the vaccine initially given at the age of nine months old. In 2002, the timing of measles vaccines was shifted from nine months old to twelve months old and MMR was introduced to replace measles vaccines. Subsequently, in 2004, Malaysian Ministry of Health added another dose of MMR at the age of seven years old as part of the measles elimination strategy giving each child opportunity to receive two doses of measles containing vaccine (MCV) for better protection against the disease. In 2016, another changes was made on MCV vaccination schedule to follow WHO recommendation for measles vaccination in which the age for MCV1 and MCV2 was shifted from twelve months and seven years old to nine months old and twelve months old respectively (Qamruddin *et al.*, 2020).

1.1.2 Measles Elimination Programme

Measles vaccine is an efficient and cost-effective measures that had been estimated to prevent 21 million death globally since 2000 (Nandi *et al.*, 2019). Coverage of measles vaccination of more than 90 percent is expected to reduce the transmission of measles in a country. Measles vaccination is part of measles elimination programme. The programme aimed to reduce the number of cases of measles and following initiation of the measles elimination programme, the incidence rate of measles is expected to be reducing in trend. The goal is for the disease to be no longer constantly present in a measles eliminated country. United States was the first country worldwide to be declared eliminated from measles on the year of 2000. 43% of all countries globally has been verified to eliminate measles in 2018. Iran and Sri Lanka was among the latest countries to achieved elimination of measles (Patel, Goodson, *et al.*, 2020).

An analysis of post elimination measles data from 2002 to 2011 in United States reveals that the trend showed an increasing number of cases yearly and requiring continuous monitoring of measles cases (Blumberg et al., 2014). Recent endemic measles transmission was also re-established in few countries including Venezuela, Brazil, Albania, Czechia, Greece, and United Kingdom. No WHO region was reported to achieve and able to maintain measles elimination (Patel, Goodson, *et al.*, 2020)

Elimination of measles has been a goal for all countries under the WHO region. The Global Vaccine Action Plan (GVAP) was developed in May 2012 during the World Health Assembly and one of the objectives of the plan was for five out of six

WHO regions achieved measles elimination by the year of 2020. Elimination of measles can be defined as interrupted measles transmission in a given geographical area for at least a duration of 12 months followed by verification after the condition is sustained for at least 36 months. Following the assembly, many countries strive to achieve elimination of measles and WHO reported that 83 individual countries has been verified as having achieved or maintain elimination of measles (Patel, Goodson, *et al.*, 2020).

Malaysia has started Measles Elimination Programme since 2004 in conjunction with WHO Western Pacific Region target to achieve elimination of measles by 2012. Each 37 countries in Western Pacific Region (WPR), including Malaysia implement the strategies from WPR Plan of Action for Measles Elimination and Field Guidelines for Measles Elimination. The three main strategies in the action plan and guidelines are to achieve and maintain 95% or more coverage with two doses of MCV which was done through routine immunization services and also supplementary immunization activities (SIAs) whenever necessary, to conduct high-quality case-based measles surveillance which includes appropriate time and accurate testing of specimens to confirm or discard suspected cases and detect measles virus for genotyping and molecular analysis, and thirdly to establish and sustain measles outbreak preparedness in order to provide rapid response and appropriate case management (Hagan *et al.*, 2018). Two online systems, *e-notifikasi* and SM2 e-measles, involved in measles notification. *E-notifikasi* is a system for online notification by healthcare facilities while SM2 e-measles is a system developed to standardise the reporting, investigation and findings at district, state and national level for the control and prevention of measles (Qamruddin *et al.*, 2020).

1.2 Statement of Problem

Malaysia had announced in 2004 that Malaysia will be a country that had eliminated measles by the year of 2010 (Baigi and Holmen, 2017). Despite having good coverage of measles containing vaccine which are 96% coverage for MCV1 and 99% coverage for MCV2, the incident rate is increasing from 6.1 per million population in 2013 to 52.1 per million population in 2017. Ministry of Health Malaysia reported that the number of measles cases in Malaysia had increased exponentially from 195 cases in 2013 to 1934 cases in 2018 and number of clusters are increasing from 110 in 2013 to 133 in 2018. The target for measles elimination is far to be achieved and the latest target of measles elimination for Malaysia had been revised to year 2025 (Norfazillah *et al.*, 2020).

1.3 Rationale

Analysis of measles trend will be able to illustrate the disease control. Identification of factors that may contribute to the rise of measles incidence may facilitate further plan to prevent and control of the disease in order to achieve the target of elimination of measles by the year 2025.

1.4 Research Questions

1. What is the proportion of confirmed measles among notified cases in Pahang?
2. What is the trend of measles by year in Pahang?
3. What are the factors associated with measles among notified cases in Pahang?

1.5 Objectives

1.5.1 General Objective

To study the distribution and associated factors of measles cases in Pahang

1.5.2 Specific Objectives

1. To describe the proportion of confirmed measles among notified measles cases in Pahang from 2016 until 2020.
2. To describe the trend of confirmed measles cases in Pahang from 2016 until 2020.
3. To determine the factors associated with confirmed measles among notified measles cases in Pahang.

1.6 Research Hypothesis

Sociodemographic, exposure factors and vaccination status are significantly associated with confirmed measles among notified measles cases in Pahang.

CHAPTER 2

LITERATURE REVIEW

The search of papers in this study was done using an online search engine and database that include Scopus, PubMed, Web ISI, Google Scholar, Science Direct and Springer link. Several searching strategies were applied including the use of Boolean operators, "AND," "OR" and "NOT". The keywords used were measles, vaccination, factors associated and risk factors.

2.1 Measles

Measles virus is highly transmissible virus. Once a person had contact with measles virus, the incubation period began in which the measles virus starts to replicate and spreads within the infected host. Viral replication occurs initially in epithelial cells in the upper respiratory tract. The virus spreads to local lymphatic tissue followed by viremia and disseminate to various organs in the body which includes skin, lymph nodes, gastrointestinal tract, kidney, and liver. In the target organ, measles virus replicates in endothelial and epithelial cells, monocytes, lymphocytes and macrophages (Moss, 2017). The manifestation of sign and symptoms of measles are due to the host immune responses at sites of virus replication.

In a classical course of measles, after a person had contact with measles virus, the prodromal illness starts with symptoms of a common cold. The prodrome last for two to four days and the range of prodromal symptoms can be from one to seven days (Hamborsky, Andrew Kroger & Charles Wolfe, 2015). The prodrome states is characterized by fever, which can be as high as 40 ^{0}C, followed by the onset of cough, coryza or runny nose, and conjunctivitis. A pathognomonic feature of measles is Koplik's spots. It is described as an exanthem on mucous membranes. It appears as punctate blue-white spots on bright red background on buccal mucosa at one to two days before rash till one to two days after rash (Hamborsky, Andrew Kroger & Charles Wolfe, 2015). The prodrome symptoms of measles are resembles those of common respiratory illness (Misin et al., 2020). The rash of measles initially emerges three to four days after the onset of fever with cranial to caudal progression starting from the ears and spread to the face, trunk, and extremities. However, the palm and soles are rarely involved (Moss, 2017; Gans & Maldonado, 2019). In two days after onset of rashes, person with measles will show sign of clinical improvement in which the rashes began to fade, and desquamation can be seen in some area of the skin that are severely involved. The rashes fade according to the order of its appearance and the rash generally last for six to seven days (Gans & Maldonado, 2019).

2.2 Measles Surveillance System

The three strategies implemented in Measles Elimination Programme are to achieve and maintain 95% coverage with two doses of measles containing vaccine (MCV), to establish and maintain measles outbreak preparedness and to conduct high quality case-based measles surveillance (Hagan et al., 2018). Surveillance is ongoing systematic collection, analysis, and interpretation of outcome-specific data for use in planning, implementation, and evaluation of public health practice. For countries which aim for measles elimination, surveillance data of measles are used to monitor progress towards achieving disease control and elimination goals. For countries that had achieved measles elimination and countries with low measles incidence, high quality measles surveillance provides proves that the absence of reported cases is attributable to the absence of disease rather than to inadequate detection and reporting (World Health Organization, 2017).

Measles surveillance in Malaysia is based on case classification system. Case will be classified as either suspected or confirmed case. Suspected case is any person diagnosed measles by a clinician while confirmed case is a case that is laboratory confirmed or case that meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case (Ministry of Health Malaysia, 2017). In Malaysia, all suspected measles cases from government health care facilities or private sector, by law, must be notified to district health office. It is one of the diseases under mandatory notifiable diseases surveillance. Reporting or notifying infectious diseases is mandated by the Prevention and Control of Infectious Disease Act (PCID) 1988. Under the act, manual reporting of the disease must be done using a standard notification form. Notification must also be done electronically via *e-notifikasi* that is developed by electronic Communicable Disease Control Information System (CDCIS) (Qamruddin et al., 2020). Under section 24 and 25 of PCID 1998, compound of RM1000 and imprisonment can be penalized to a person if he is found guilty of the offense of not reporting a mandatory notifiable disease to the nearest district health office.

E-notifikasi is the first online notification system in Malaysia. It was introduced in 2006 and received a major upgrade in 2010. On the other hand, e-measles system is developed by Ministry of Health Malaysia and was implemented starting on 2007. Both systems were necessary in measles surveillance in Malaysia. The cases initially are notified through *e-notifikasi* from any health centres and once case registration was confirmed in the *e-notifikasi*, the data of the case will be transferred automatically to e-measles. Any cases transferred to e-measles will then be investigated in 48 hours from time of notification. The investigation covers all the details from the sociodemographic, medical history, diseases history and immunisation history. All this data is entered by the assistant environmental health officer into the e-measles for surveillance purpose (Qamruddin et al., 2020). The surveillance data from e-measles will be analysed and interpret to provide appropriate control measures of the diseases by Ministry of Health Malaysia and to predict any potential outbreak based on the available data and thus, implement strategies to prevent the occurrence of the outbreak. This system also assists in monitoring investigation done by district or state level.

2.3 Epidemiology of Measles

Proportion of confirmed measles cases among notified measles cases varies between countries worldwide. Studies in India and Nigeria shows that the proportion of confirmed measles cases among the notified and suspected cases varied from 60-80% (Weldegebriel et al., 2011; Bose et al., 2014; Vaidya & Chowdhury, 2016). However, the proportion was found to be lower in Ethiopia with confirmed case was found to be 40.9% (Hassen *et al.*, 2018). However, the study in India, Nigeria and Ethiopia are limited to case reported by the case-based surveillance system data only in which not all cases were reported, sample were not taken for all the cases and not all sample received were tested. In 2013 to 2014, Philippines reported 38% of 67,029 total suspected cases were confirmed measles either by laboratory confirmed or epidemiologically linked cases (Ylade, 2018).

The target for incidence for elimination of measles is less than one measles case per one million population (Jean Baptiste *et al.*, 2021). Globally, there was a decrease in the reported number of measles cases from 4,211,431 in 1980 to 132,325 in 2016 with reduction in incidence of 8% every year from 1980 to 2016. However, the decline has not been uniformed across countries and region (Krishnamoorthy *et al.*, 2019). From the year of 2001 until the year of 2015, the incidence per million population in United States, a country which had eliminated measles, fluctuates with lowest incidence rate at 0.08 (95% CI: 0.05,0.12) and highest incidence rate at 2.06 (95% CI: 1.91,2.22). Though the rate was fluctuating, the incidence per million population was noted to be increasing over a period of time, from 0.28 (95% CI: 0.22,0.35) in 2001 to 0.56 (95% CI: 0.48,0.65) in 2015. The increase of incidence was due to 10 of total of 13 outbreak occurred after the year 2010. In Nigeria, the incidence rate was reducing in trend though it was still high at 24.98 per million population in 2018 compared to 53.73 per million population in 2008. Singapore also reported decrease in measles cases from 885.0 per million population in 1981 to 3.0 per million in 2012 (Ho *et al.*, 2014). However, incidence rate of measles in Malaysia shows gradual increment from 42.9 in 2015 to 59.5 in 2018 and reduced to 32.3 per million population in 2019 (Ministry of Health Malaysia, 2019; WHO Western Pacific Region, 2019). Introduction of measles vaccine in current immunization schedule of most countries were one of the reasons in reduction of incidence rate of measles.

2.4 Risk Factors

2.4.1 Sociodemographic factors

A study on epidemiological trends of measles in Singapore reported that the incident of measles was highest with age group of less than one year old followed by age one to four years old (Ho *et al.*, 2014). An outbreak study of measles in Nigeria found a corresponding findings in which the attack rate of measles outbreak was highest at 13 per 10,000 among child aged zero to five years and the attack rate declined as age increased (Nsubuga *et al.*, 2018). Liu *et al.* (2013) reported that the children aged less than 1 years old in China had higher risk of measles with age-specific incidence rate of 239 per 100,00 population on average per year from 2004 to 2011. China reported that measles is more common in adult age and infant (Zhang et al., 2015; Deng et al., 2019). Being too young was also a risk for measles infection in United Kingdom as they were not eligible for vaccination and early waning of maternal antibodies from mothers of post elimination era exposed them to the infection (Hungerford et al., 2014). However, case-control study on measles infection in Mongolia by Hagan *et al.* (2017) and in Indonesia by Sitepu *et al.* (2019) found that there was no significant differences in age among those in case group and control group.

Measles had been reported differently by gender. More measles cases were found to be among male compared to females (Getahun *et al.*, 2016; Ibrahim *et al.*, 2016; Khan *et al.*, 2014). However, a study by Mersha *et al.* (2017) found that males and female were equally affected and similar findings also found in Iran which the gender distribution for confirmed measles cases was relatively equal between male and female (Karami *et al.*, 2020). A study in Vietnam found that although, male had a higher case than female, it was not significantly different (Nmor *et al.*, 2011).

In term of ethnicity, a study by Balé *et al.* (2011) in Africa found that ethnicity was not associated with the risk of getting measles infection. In Malaysia, Rahman *et al.* (2020) in his study on trend analysis of measles outbreak from 2014 to 2018 in Petaling district found that Malays were commonly affected with proportion of 89.5% compared to other ethnic. This finding is coherent with the fact that Malays were the major ethnic in Malaysia. However, a similar result was found in a study from Singapore although Malays were not the predominant, Malay ethnic were reported to have the highest incidence rate of confirmed measles among the major ethnic group with incidence of 0.4 to 6.32 per 100,000 population (Ho *et al.*, 2014).

Location where a person live is one of the risk factors for measles. Based on a study In China, people living in urban area is found to be at higher risk of contracting measles compared to people from rural area (Liu *et al.*, 2013). However, another study in China found that a person from rural area have 2.28 times higher odds (95% CI: 0.92,5.63, *p*-value = 0.0004) to get measles compared to urban area. In Ethiopia, measles is more common in peri-urban area compared to urban area (Mersha *et al.*, 2017). This could be related to a higher population density in certain area of the country due to migration resettlement or economic activity.

2.4.2 Exposure factors

Contact history with confirmed measles cases was reported to be a significant association with measles infection in a study by Sitepu *et al.* (2019) in Indonesia with AdjOR 1.15 (95% CI: 1.12, 3.70). Similar findings was observed from two studies in Ethiopia in which having a contact history with measles cases increased the risk of measles infection at Sekota Zuria district (AdjOR 3.44, 95% CI: 1.26, 9.38) and at Kabridahar district (AdjOR 3.5, 95% CI: 5.9, 21.4) compared to those with no contact history of contact (Girmay and Dadi, 2019; Sheikaden Ismail *et al.*, 2019).

Other associated exposure factor is history of visiting other country especially countries with outbreak of measles. India, Nigeria, and Yemen are among the top 3 countries with the highest measles outbreak globally (Centers for Disease Control and Prevention, 2021) A study in Singapore found that 51.5% of the cases had a travel history to Philippines and Indonesia which were countries with documented outbreaks of measles (Vemula *et al.*, 2016). In 2013, a surveillance report in Canada found that of all 83 confirmed measles cases reported in Canada, 14.5% were related to travelling to measles-endemic country and 54.2% were epidemiologically linked to these import cases. Similar findings were also observed in China in which travelling outside the prefecture is associated with measles infection (Ma *et al.*, 2020). Travelling is linked with exposure risk particularly when travelling to area with higher transmission of measles.

History of visiting hospital was found to be a risk factor associated with measles infection (Hagan *et al.*, 2017; Ma *et al.*, 2020; Tang *et al.*, 2016). A case-control study in China by Ma *et al.* (2016) reported that history of visiting outpatient department associated with risk for measles infection (OR 9.4, 95% CI 6.6, 13.3). Hospital and health care visits were identified as risk factor as nosocomial infection was found to be the source of infection among cases especially in emergency department in which the settings were close and crowded leading to higher transmission rate (Botelho-Nevers *et al.*, 2012; Tang *et al.*, 2016).

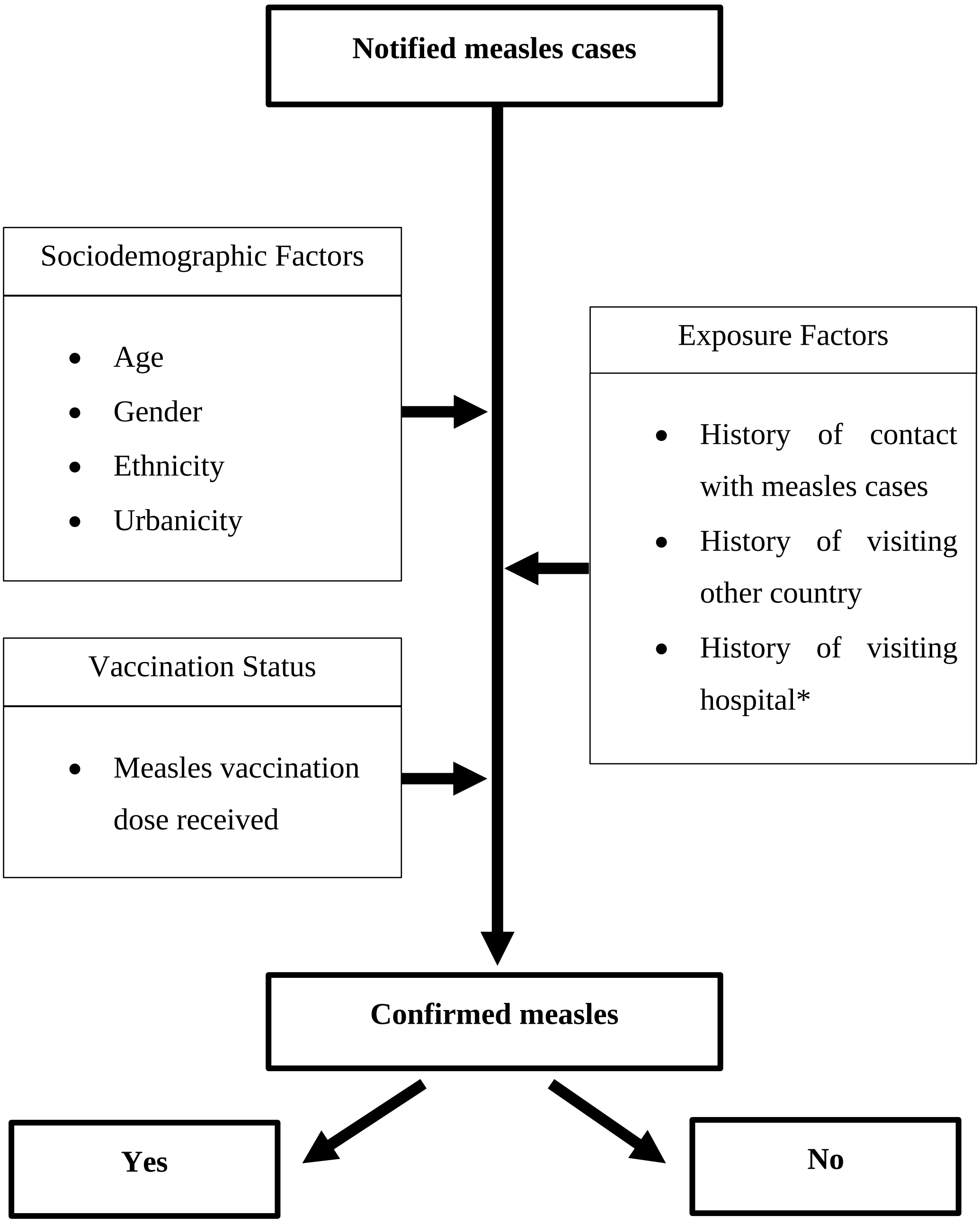
2.4.3 Vaccination status

Vaccination status is one of the associated factors of measles. Measles vaccine gave protection from measles infection of up to 95% effectiveness if given for one dose and up to 99% after a second dose (Javelle *et al.*, 2019). A study by Sitepu *et al.* (2019) in Indonesia found that those who have not received measles vaccine had higher odds of having measles infection (AdjOR 2.31 95% CI: 1.22,4.27) compared to those who had been vaccinated whereas a study by Girmay and Dadi (2019) found that previously vaccinated individuals had 83% less risk compared to those who are not vaccinated. Joseph Babalola *et al.* (2019) states that routine immunization is significantly associated with decline in number of measles cases among vaccinated individuals and people who were not vaccinated were more likely to be infected with measles virus. However, a study on outbreak in United Kingdom found that although a person is vaccinated, incomplete vaccination with only one dose of measles vaccine was a factor associated with measles infection (Hungerford *et al.*, 2014).

2.4.4 Conceptual framework

Based on the literature review, associated factors of confirmed measles among notified measles cases can be divided based on sociodemographic factors, exposure factors and vaccination status. Sociodemographic factors consist of age, gender, ethnicity and urbanicity. The components of exposure factors are history of contact with measles cases, history of visiting other country and history of visiting hospital. Number of measles vaccination dose received is the factor in vaccination status component which is associated with confirmed measles cases.

The outcomes of notified measles cases were divided into confirmed measles cases and non-measles cases.



Note: * Variables not included in the study

Figure 2.1 Conceptual framework of the study

CHAPTER 3

METHODOLOGY

3.1 Study Design

This was a cross sectional study using secondary data from Pahang state SM2 e-measles database from 2016 until 2020.

3.2 Study Area

This study was carried out in Pahang State Health Department. Pahang State Health Department is responsible for data collection of all measles notification in Pahang. Pahang is one of the states in Malaysia and are the third largest states after Sarawak and Sabah with total of 35,965 km^2 land area. The total population of Pahang is 1.68 million (Department of Statistics Malaysia, 2020).

3.3 Study Period

The study was conducted within 6 months from November 2020 till April 2021.

3.4 Reference Population

Pahang Population

3.5 Source Population

All notified measles cases in Pahang

3.6 Sampling Frame

List of notified measles cases in Pahang

3.7 Inclusion Criteria

All data of notified measles cases registered to e-measles database from 2016 until 2020.

3.8 Exclusion Criteria

1. Data of notified measles cases among non-Malaysian citizen

2. Data with at least one variable missing

3.9 Sample Size Calculation

Objective 1:

Sample size was calculated using formula of single proportion:

$$n = \left(\frac{Z}{\Delta}\right)^2 p\ (1 - p)$$

Table 3.1: Calculation of sample size for single proportion

Z	Δ	P	n	n+10%*	Author, Year
1.96	0.05	0.76	280	336	Bose *et al.*, 2014
1.96	0.05	0.41	371	446	Hassen *et al.*, 2018

Objective 2:

The sample size was not calculated as all available data was used to plot graph trend.

Objective 3:

Sample size was calculated with PS Software Version 3.1.6 using comparison of two independent proportion formula.

Table 3.2: Sample size calculation for two independent proportion

Variables / Factors	P_0	P_1	m	n	2n+ 10%*	Literature review
Male gender	0.79	0.70	1	367	807	Elidio *et al.*, 2019
Had history of visit to other country	0.10	0.20	1	199	438	Watanabe *et al.*, 2019
Had history of contact with measles case	0.77	0.60	1	116	255	Girmay and Dadi, 2019
Complete vaccination	0.67	0.50	2	97	213	Al-Arabi Al-Ghamdi *et al.*, 2011

P_0 = Proportion of exposed in non-measles cases based on literature review
P_1 = Estimated proportion of exposed in confirmed measles cases
Power of study = 80%
$\alpha = 0.05$
*10% addition to sample size due to possibility of data entry error, missing and outliers.

Therefore, based on the above calculations, the biggest sample size estimated was 807. Thus, the available data within the time duration was sufficient to be used in answering all the objectives.

3.10 Sampling Method and Subject Recruitment

Data were taken from SM2 e-measles (http://emeasles.moh.gov.my/). For objective 1, 2 and 3, the data of notified measles enrolled in the system from January 2016 till December 2020 was compiled. The total number of available data was 2866. All available data were included in this study, thus no sampling method applied.

3.11 Research Tool and Variables

SM2 e-measles contains all the investigation details of suspected measles cases entered by assistant environmental health officer in district health office. The data extracted from SM2 e-measles were exported to IBM SPSS software version 27. The softcopy template includes all the independent and dependent variables of this study (Appendix A).

3.12 Operational Definition

3.12.1 Notified measles case

Any suspected measles cases that are notified to SM2 e-measles

3.12.2 Confirmed measles case

Any cases that are indicated as laboratory confirmed measles either by:

1. presence of measles-specific IgM antibodies or

2. presence of measles virus in clinical sample using culture techniques or

3. presence of measles virus in clinical samples using molecular techniques

OR

epidemiologically linked measles as listed in SM2 e-measles databases.

3.12.3 Non measles

Any suspected case which confirmed negative by laboratory findings either by:

1. RT-PCR taken within 5 days of onset of rashes is negative or

2. IgM serology taken 4 days or more after onset of rashes is negative or

3. IgM serology taken 4 days or more after onset of rashes is equivocal and second sample of IgM serology taken 10 to 21 days post rash is negative

4. IgM serology taken less than 4 days after onset of rashes are negative and second sample of IgM serology taken 6 days or more after first sample taken is negative.

3.12.4 Measles Vaccination Status

Complete vaccination: Cases that already received 2 dose of measles vaccination.

Incomplete vaccination: Cases that already received 1 dose of measles vaccination and not yet received second dose of measles vaccination.

Not vaccinated: Cases that is not yet eligible for measles vaccination at the time of diagnosis in view of have not reach age for first dose of MCV or cases did not receive any measles vaccination due to refusal or defaulter.

3.12.5 History of contact with measles cases

Any history of contact with measles cases within 7 to 21 days before the onset of rashes

3.13 Data Collection

This study used secondary data from SM2 e-measles (http://emeasles.moh.gov.my/). Permission to access the data were taken from the Director of Pahang State Health Department after ethical approval by Medical Research and Ethics Committee (MREC). Relevant data of all cases registered in Pahang e-measles database from 2016 until 2020 were extracted. Only the researcher had access to the data. Data extracted from e-measles were in Microsoft Excel worksheet and were exported and saved into IBM SPSS software version 27 with anonymous non-identifiable code for further analysis.

3.14 Statistical Analyses

Descriptive statistics were used for analysis of objective 1 and presented as proportion (percentage). Proportion of confirmed measles among notified measles cases were computed by number of confirmed measles cases from 2016 to 2020 divide by number of notified measles cases from 2016 to 2020 and the result were plotted in graph by year.

For objective 2, the incidence rate of measles in Pahang were calculated by dividing number of confirmed measles cases in a specific year by mid-year population estimation in Pahang in specific year from Department of Statistics Malaysia times 1,000,000 population. The results were plotted in graph.

For objective 3, the dependent variable in this study was confirmed measles or non-measles while the independent variable that were used in this study includes age, gender, ethnicity, urbanicity, history of contact with measles cases, history of visiting other country and measles vaccination status. All variables were categorised into two categories except for age, ethnicity, and measles vaccination status. Age was categorised into less than 1 year old, 1 year old to 6 years old, 7 years old to 12 years old, 13 years old to 17 years old and 18 years old or more. Ethnicity were categorised into Malay, Chinese, Indian and Aborigine. Measles vaccination status were categorised into complete vaccination, incomplete vaccination or not vaccinated. Simple logistic regression and multiple logistic regression were used to analyze the variables. Simple logistic regression was initially used to analyze each independent variables and the findings were presented as crude OR (95% CI). Further analyses were done by using multiple logistic regression for selected variables with *p*-value of less than 0.25 or any variables that were noted to be important variables according to the literature review. The selected variables with *p*-value less than 0.25 were ethnicity, history of contact with measles cases and vaccination status.

Multiple logistic regression was used to determine factors associated with confirmed measles among notified measles cases in Pahang. The preliminary main effect model was acquired after comparing the model using Backward Likelihood Ratio elimination and Forward Likelihood Ratio selection. Variance inflation factor (VIF), standard error and correlation matrix were used to check for multicollinearity in the analysis. All plausible two-way interaction was checked between independent variables to exclude any interaction. Then, the preliminary final model was generated. Fitness of the model was tested by using Hosmer and Lemershow goodness of fit test, receiver operating characteristic (ROC) curve and classification table. A *p*-value of more than 0.05 in Hosmer and Lemershow goodness of fit test suggests that the model is fit. The classification table with overall correctly classified percentage at 80.0% and above and ROC curve with area under the curve of 0.7 and above also suggest that the model is fit. The findings of the final model were presented with an adjusted OR, its 95% confidence interval (CI), Wald statistics and corresponding *p*-value. The adjusted OR and 95% CI was used as a measure of the strength of association between the dependent variable and their independent variables. The level of significance was set at a *p*-value of less than 0.05.

3.15 Ethical Considerations

Permission to use SM2 e-measles data for research purpose were taken from Director of Health, Pahang State Health Department. Approval for ethical clearance was obtained from Jawatankuasa Etika Penyelidikan (Manusia) of Universiti Sains Malaysia (JEPeM); JEPeM Code: USM/JEPeM/20110581 and National Medical Research Registry (NMRR), Ministry of Health Malaysia; NNMR ID: NNMR-20-

2561-57244 (Appendix B & Appendix C). The anonymous identification number instead of patient identifiers were used on subject datasheets to ensure privacy and confidentiality of data. All data were entered into a password protected computer and accessed to the computer were limited only to the researcher. Data were kept for 3 years upon completion of the study and will be destroyed after period of storage.

3.16 Study Flowchart

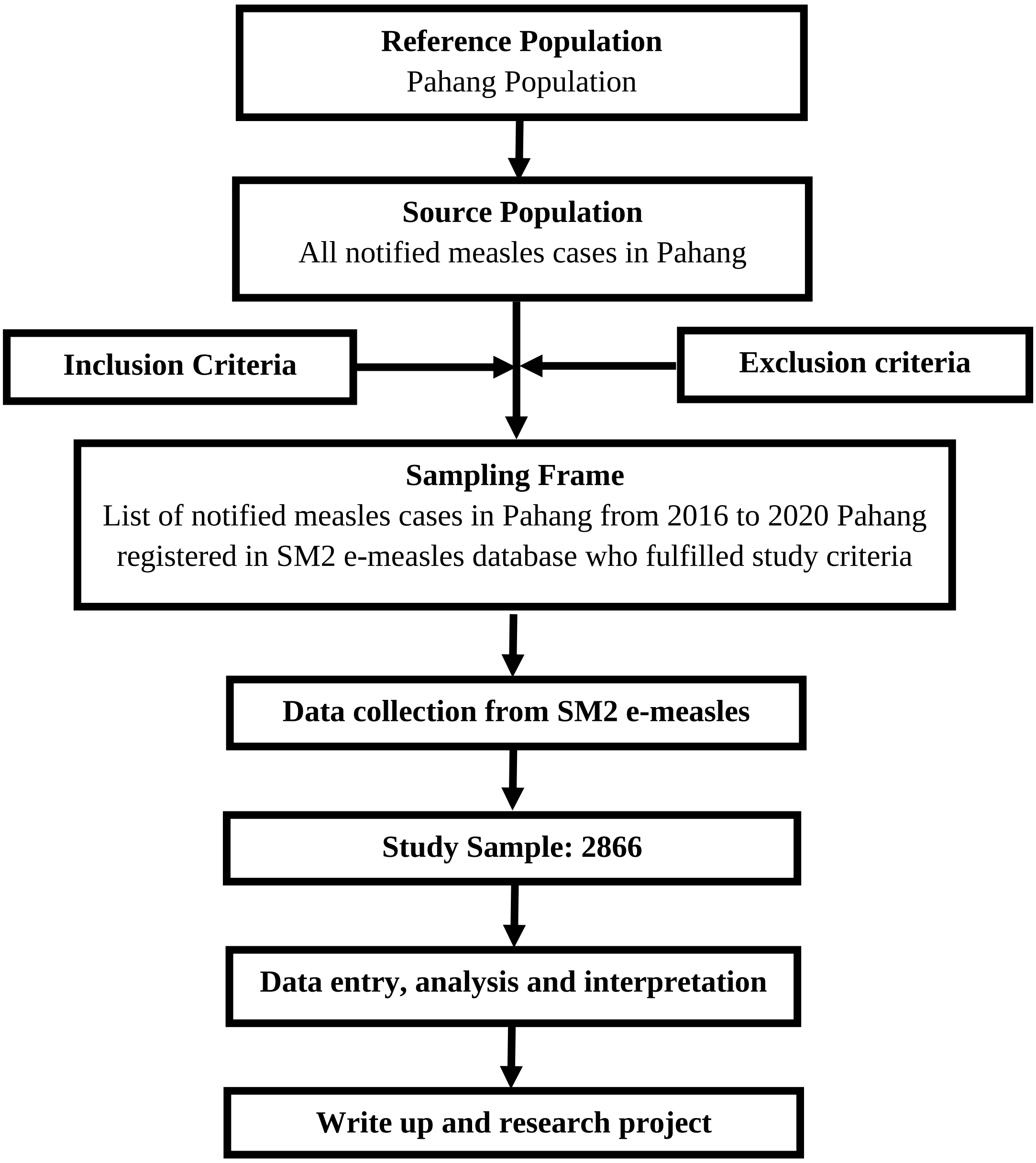


Figure 3.1: Study Flow-chart