DETERMINATION OF THE RISK FACTORS OF PNEUMONIA AND THE EVALUATION OF THE COST EFFECTIVENESS OF CURRENT TREATMENT APPROACH FOR BACTERIAL PNEUMONIA IN CHILDREN FIVE YEARS AND YOUNGER

By

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ALRI	Acute Lower Respiratory Tract Infection
ARI	Acute Respiratory Infection
AM	Alveolar Macrophages
CBC	Complete Blood Count
CEA	Cost Effectiveness Analysis
CER	Cost Effectiveness Ratio
CHERG	Child Health Epidemiology Reference Group
CI	Confidence Interval
COPD	Chronic Obstructive Airway Disease
CRP	C Reactive Protein
C/S	Culture and Sensitivity Test
CS	Cigarette Smoking
DF	Degree of Freedom
DPT	Diphtheria, Pertussis and Tetanus
ESR	Erythrocyte Sedimentation Rate
Exp. B	Exponential B (Odds Ratio)
FBC	Full Blood Count
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
CPGs	Clinical Practice Guidelines
Hib	Haemophilus influenzae type B
HKL	Kuala Lumpur Hospital
ICER	Incremental Cost Effectiveness Ratio
IDSA	Infectious Disease Society of America
IPHKL	Institute of Pediatric in Kuala Lumpur Hospital
K.-S Test	Kolmogorov–Smirnov test
LOS	Length of Stay
MMR	Measles, Mumps and Rubella
OR	Odds Ratio
OPV	Oral Polio Vaccine
MYR	Malaysian Ringgit
RR	Relative Risk
SE	Standard Error
SGA	Small for Gestational Age
SHS	Second Hand Smoking
UNICEF	The United Nations of Children Fund
WHO	World Health Organization

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KAJIAN BAGI MENENTUKAN FAKTOR-FACTOR RISIKO RADANG PARU-PARU DAN PENILAIAN KOS KEBERKESANAN RAWATAN SEDIA ADA RADANG PARU-PARU DISEBABKAN BAKTERIA DI KALANGAN KANAK-KANAK BERUMUR LIMA TAHUN DAN KEBAWAH

ABSTRAK

Pneumonia atau radang paru-paru, merupakan salah satu penyebab utama morbiditi dan kematian, terutama sekali di negara-negara membangun. Pencegahan pneumonia dan kecacatan disebabkan olehnya boleh dicapai dengan mengurangkan faktor-faktor risiko penyebab pneumonia dan menilai golongan yang berisiko tinggi. Penilaian faktor-faktor risiko tersebut adalah salah satu dari tiga matlamat kajian kes kawalan berdasarkan umur dan jantina secara retrospektif ini. Seramai 260 orang kanak-kanak berumur lima tahun dan kebawah yang disahkan menghidap pneumonia mengikut panduan kod ICD-10 terlibat dalam kajian, 43% (n=113) dari mereka menghidap pneumonia disebabkan virus dan 57% (n=147) lagi disebabkan oleh bakteria. Faktor-faktor risiko pneumonia telah diuji menggunakan 'Chi-square' dan 'Binary Logistic Regression'. Imunisasi tidak lengkap telah ditemui sebagai alat ramalan risiko yang paling penting berbanding faktor-faktor risiko lain yang telah dianalisis (OR=3.71, p<0.001). Faktor-faktor lain yang menjadi penting dalam kajian ini ialah kehadiran ke pusat jagaan harian kanak-kanak (p=0.001), kurang berat badan berbanding umur (p=0.001), kurang penyusuan ibu (p=0.016) dan bapa perokok (p=0.04). Matlamat kedua kajian ini adalah untuk mengenal pasti antibiotik pilihan yang paling berkesan dan berkos rendah di antara jenis-jenis antibiotik yang lain untuk rawatan pneumonia disebabkan bakteria. Hanya dua antibiotik sahaja yang dimasukkan ke dalam analisis iaitu *cefuroxime* dan *C-penicillin* mengikut sampel yang didedahkan oleh kedua-dua ubat. Bagi kumpulan *cefuroxime*, purata jumlah keseluruhan kos rawatan ialah RM 838.90 (IQR. 787.9,

1834.57), dan bagi kumpulan *C-penicillin*, puratanya ialah RM 1153.85 (IQR. 791.61, 1523.9). Penggunaan *cefuroxime* menghasilkan kejayaan rawatan pesakit yang lebih baik (84% berbanding 73% kadar kejayaan rawatan) dan dengan kos yang lebih rendah. Nisbah keberkesanan kos untuk *cefuroxime* dan *C-penicillin* ialah masing-masing RM 998.70 dan RM 1580.60 yang menunjukkan bahawa *cefuroxime* mempunyai kos keberkesanan lebih rendah berbanding *C-penicillin*. Nilai ICER bersamaan - 2,863, di mana nilai negative ICER menunjukkan kesan penjimatan. Kesinambungan rawatan terkini dengan garis panduan kebangsaan adalah matlamat lain kajian ini, dan ia mendedahkan bahawa 82% (n=127) daripada kes pneumonia disebabkan bakteria telah dirawat mengikut garis panduan.

DETERMINATION OF THE RISK FACTORS OF PNEUMONIA AND THE EVALUATION OF THE COST EFFECTIVENESS OF CURRENT TREATMENT APPROACH FOR BACTERIAL PNEUMONIA IN CHILDREN FIVE YEARS AND YOUNGER

ABSTRACT

Pneumonia is a major cause of morbidity and mortality especially in developing countries. The prevention of pneumonia and its later disabilities can be achieved by the reduction of risk factors and evaluating subjects of high risk. Risk factors evaluation was one of the three aims of this retrospective age and gender matched case control study. A total of 260 children five years and younger diagnosed with pneumonia according to ICD-10 were involved, 43% of them (n = 113) having pneumonia of viral origin and 57% (n = 147) having bacterial pneumonia. Pneumonia risk factors were determined using Chi-square and Binary Logistic Regression. Incomplete immunization found to be the most significant risk predictor among all the analyzed factors (OR = 3.71, $p < 0.001$). The other factors that were significant in this study are day care attendance ($p = 0.001$), low weight for age ($p = 0.001$), lack of breast feeding ($p = 0.016$) and paternal smoking ($p = 0.04$). The second objective of this study was to determine the most cost effective choice among the current antibiotics used for bacterial pneumonia management. The only two antibiotics that were evaluated are cefuroxime and C-penicillin according to the revealing samples of the both drugs. For the cefuroxime group the median of the total management cost is MYR 838.90 (IQR. 787.90, 1834.57), for the C-penicillin group the median is MYR 1153.85 (IQR. 791.61, 1523.9). Cefuroxime use resulted in better patient outcome (84% versus 73% treatment success rate) and at lower cost. The cost effectiveness ratio for cefuroxime and C-penicillin are 998.70 and 1580.60 respectively, this indicate that cefuroxime is more cost effective than C-penicillin. The

incremental cost effectiveness ratio is equal to - 2,863, minus value of ICER indicate saving effects. Concordance of the current treatment pattern with the national guidelines was the third objective of this study, and it reveals that about 82% (n = 127) of the bacterial pneumonia cases were treated according to the guidelines.

CHAPTER I

INTRODUCTION

1.1 BACKGROUND

Acute Lower Respiratory Tract Infection is one of the three main causes of death among children globally. Lower Respiratory Tract Infection (LRTI) is the third leading cause of death among children worldwide and it is the first leading cause of death among children in low income countries (WHO, World Health Statistics 2008). The most common severe form of LRTI is pneumonia. It is responsible for the two million deaths among children under five years of age worldwide annually (Williams *et al*., 2002). The estimated annual treatment costs for treating Community Acquired Pneumonia (CAP) in the U.S. alone is USD12.2 billion (Colice *et al*., 2004). In developing countries, more than 25% of children have an episode of clinical pneumonia for the first 5 years of their life. Many of these disease episodes are severe and potentially fatal (Rudan *et al*., 2004). Therefore, this has led to the conclusion that pneumonia is the cause of 21% of child deaths in the developing world (Williams *et al*., 2002) which makes pneumonia as the largest single cause of childhood mortality. In Malaysia, the prevalence of ARI among children under five years of age is estimated to be 28% to 39.3% (Azizi *et al*., 2002, Malaysian CPGs on Pneumonia and Respiratory Tract Infections in Children, 2002), and pneumonia is the third leading cause of death among Malaysian children under five (Hussain *et al*., 2008).

1.1.1 Pneumonia Definition

Pneumonia is an inflammation and consolidation of the lung tissue due to an infectious agent. The inflammation involves the lung tissues and the terminal airspaces. The inflammatory cascade triggers the leakage of plasma and the loss of surfactant, thereby resulting in air loss and consolidation.

An inhaled infectious organism must bypass the host's normal non-immune and immune defense mechanisms in order to trigger the infection of pneumonia. The non-immune mechanisms include the aerodynamic filtering of inhaled particles based on the size, shape, and the electrostatic charges: the cough reflex, mucociliary clearance, and several secreted substances (eg, lysozymes, complement, defensins). Macrophages, neutrophils, lymphocytes, and eosinophils carry out the immune mediated host defense (Dennis, 2009).

Pneumonia can result from a variety of causes, including infection with bacteria, viruses, fungi, parasites, and chemical or physical injury to the lungs. Its cause may also be officially described as idiopathic, which is unknown when infectious causes have been excluded (Nicholas and Joseph, 2009). Pneumonia that develops outside the hospital setting is considered as community acquired pneumonia while pneumonia that develops 48 hours or more after admission to the hospital is termed as nosocomial or hospital acquired pneumonia (American Thoracic Society and the Infectious Diseases Society of America, 2005). Community acquired pneumonia is divided into 2 groups, typical and atypical. Typical organisms include *S pneumoniae* (*pneumococcus*), *Haemophilus* and *Staphylococcus* species. Atypical refers to pneumonia caused by

Legionella, Mycoplasma, and *Chlamydia* species (Woodhead, 2002). In developing countries, the case of fatality rate among children with viral pneumonia ranges from 1.0 to 7.3 percent (Stensballe, Devasundaram, and Simoes, 2003), with bacterial pneumonia ranging from 10 to 14 percent and with mixed viral and bacterial infections from 16 to 18 percent (Ghafoor *et al*., 1990).

Therefore, a prompt treatment of pneumonia with a full course of appropriate antibiotics is lifesaving. In fact, an early treatment is most vital in order to improve the chances of avoiding the development of serious complications and deaths. Although drug management is available, only about half of the children infected with pneumonia receive appropriate medical care, and according to the available information, it was discovered that less than 20 per cent of children with pneumonia received antibiotics treatment as recommended (WHO/UNICEF, 2006). Expanding treatment coverage is not impossible, and even could be done at a relatively low cost. It is estimated that if the antibiotic treatment were delivered to all children with pneumonia, this will help in saving the life of around 600,000 children each year, at a cost of USD 600 million (Gareth *et al*., 2003). In addition, if efforts for protection could be made through delivering preventive intervention against death from pneumonia globally, this will be able to double the number of lives saved up to 1.3 million. The act of identifying the risk factors and intervening modifiable risk factors is anticipated to play a greater role in reducing the number of deaths from pneumonia. Therefore, this study was designed to investigate the influencing risk factors and to evaluate the cost effectiveness of antibiotics usage.

1.2 STUDY JUSTIFICATION

Human health had improved dramatically during the last century, yet grave inequities in health still persist. It is well known that pneumonia and other respiratory infections are the main causes of morbidity and mortality among children worldwide. They occupy most of the consultation time at the primary care as well as in the hospital setting (Azizi *et al*., 2002, Malaysian CPGs on Pneumonia and Respiratory Tract Infections in Children, 2002). The effort to manage these ailments imposes enormous burden on health resources. It is undeniable that pneumonia is a fatal disease. It kills more children than any other illness, more than AIDS, malaria and measles combined (WHO/ UNICEF, 2006). It has been estimated that over two million children had died from pneumonia each year accounting for almost one for every five deaths worldwide. Yet, not much attention is paid to this fatal disease (WHO/ UNICEF, 2006). Most of the previous researches on pneumonia focused only on the general aspects of management. However, this research is focusing on the treatment and the risk factors of pneumonia. The overuse and misuse of antibiotics has contributed to the increase in bacterial resistance patterns (Ball *et al*., 2002), as well as associated with increased costs, including the cost of the antibiotics and the increase in overall costs of medical care because of treatment failures and adverse events, particularly if hospitalization is required (Nicolau, 2002). Hence, resources must be deployed effectively in order to make a progress in health, to meet new challenges and to redress inequities.

This requires knowledge about which therapeutic interventions will actually work to contribute information on the total cost involved. This can be achieved through the application of cost effectiveness analysis of various antibiotics, which will be examined in this research.

1.3 OBJECTIVES OF STUDY

1.3.1 General Objectives

The general objectives of this study are, firstly, to determine the risk factors of pneumonia (both viral and bacterial) among children five years old and younger hospitalized during year 2008 in the pediatric institute of Hospital Kuala Lumpur (HKL) and secondly, to evaluate the cost effectiveness of antibiotics prescribed for hospitalized children in the pediatric institute and the concordance of antibiotic used for bacterial pneumonia with the Malaysian Clinical Practice Guidelines on Pneumonia and Respiratory Tract Infections in Children, 2002.

1.3.2 Specific Objectives

The specific objectives are as follows:

- To determine the most influencing risk factor.
- To determine other modifiable risk factors
- To determine influencing non-modifiable risk factors which will help in defining individuals and groups at higher risk for whom controlling or treating their modifiable risk factors are of priority.

- To calculate the cost effectiveness of antibiotics prescribed for hospitalized children with bacterial pneumonia.
- To evaluate antibiotics prescribed for bacterial pneumonia management according to age groups for children 5 years and younger in concordance with the national guidelines (Azizi *et al*., 2002, Malaysian CPGs on Pneumonia and Respiratory Tract Infections in Children, 2002).

1.4 LITERATURE REVIEW

Childhood pneumonia is one of the largest causes of morbidity among children five years and younger. It is responsible for almost one fifth of total mortality in this age group. Global health care agencies have focused on this disease and direct their support at the international., practical, academic and research level. However, during the search in the literature for this study, there were no much studies, systematic review or wide cohort study at the national level addressing the important issues of pneumonia in children (issues such as diagnosis, programmes for prevention, management, risk factors determination and pneumonia burden in Malaysia).

Even globally, most of the studies founded about the risk factors of pneumonia were for the period from 1990 - 2000. There are only few recent studies to address the issue of pneumonia risk factors among children. At the national level, the presence of the Malaysian Clinical Practice Guidelines on Pneumonia and Respiratory tract infections is valuable. These guidelines provide a comprehensive guidance in the local context. Updating these Guidelines is also one of the issues that need to be highlighted, as it belongs to year 2002, by now the etiology of pneumonia could have been changed which may affect the clinical applicability of these guidelines.

1.4.1 Epidemiology of Pneumonia

Rudan *et al.,* (2004) calculated and published the first global estimate of the incidence of clinical pneumonia among children aged less than 5 years for the year 2000. It was discovered that the estimated median incidence for developing countries was 0.28 episodes per child per year. WHO, on the other hand, came up with a calculation for the

incidence of clinical pneumonia among children aged less than 5 years in developing countries worldwide (WHO regions include the African Region, the Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and the Western Pacific Region) which is close to 0.29 episodes per child per year (Table 1.1). This equates to 151.8 million new cases every year of which thirteen million (8.7%) are severe enough and require hospitalization.

It was reported that an additional 4 million cases occurred in developed countries worldwide. The incidence of clinical pneumonia was estimated to be highest in South East Asia (0.36 episodes per child per year) and lowest in European regions (0.06 episodes per child per year).

Table 1.1: Estimates of Incidence and Number of New Cases per Year of Clinical Pneumonia among Children Less Than 5 Years Old (WHO Regions)

WHO Regions	Total population aged 0-4 years (million)	Estimated incidence (episode/child/year)	Estimated number of new cases
Africa	105.62	0.33	35.13
America	75.78	010	7.84
Eastern Mediterranean	69.77	0.28	19.67
European	51.96	0.06	3.03
South East Asia	168.74	0.36	60.95
Western Pacific	133.05	0.22	29.07
Total (Developing Countries)	523.31	0.29	151.76
Total (Developed Countries)	81.61	0.05	4.08
Total	604.93	0.26	155.84

WHO Bulletin: Epidemiology and etiology of childhood pneumonia, Rudan *et al*., 2008.

The high incidence of pneumonia worldwide makes it a major public health interest. In order to assess the distribution of 156 million episodes according to regions and countries, WHO established the Child Health Epidemiology Reference Group (CHERG). This consists of a group of independent technical experts. CHERG has systematically reviewed and improved the collection of data, methods and assumptions underlying the estimates of the distribution of the main causes of death.

As a result, they provided a new regional and country pneumonia morbidity estimates for the year 2000 (despite being relatively old it is the latest global estimate for pneumonia released by WHO). They reviewed current understanding of the distribution of pneumonia's etiological agents among children aged less than 5 years. They determined the countries with the highest predicted number of new pneumonia episodes and their respective incidence (Table 1.2). These 15 countries accounted for 74% (115.3 million episodes) of the total estimated 156 million global episodes.

Table 1.2: The fifteenth Countries with the Highest Estimated Absolute Number of New Clinical Pneumonia Cases

Country	Predicted No. of New Cases (Million)	Estimated Incidence (episode/child/year)
India	43.0	0.37
China	21.1	0.22
Pakistan	9.8	0.41
Bangladesh	6.4	0.41
Nigeria	6.1	0.34
Indonesia	6.0	0.28
Ethiopia	3.9	0.35
Congo	3.9	0.39
Viet Nam	2.9	0.35
Philippine	2.7	0.27
Sudan	2.0	0.48
Afghanistan	2.0	0.45
Tanzania	1.9	0.33
Myanmar	1.8	0.34
Brazil	1.8	0.11

WHO Bulletin: Epidemiology and etiology of childhood pneumonia, Rudan *et al*., 2008.

Annually, more than half of the world's new pneumonia cases were concentrated in three countries where 44% of the world's children aged below 5 years live. These countries are India (43 million), China (21 million) and Pakistan (10 million) while Bangladesh, Indonesia and Nigeria each had 6 million cases (United Nations Millennium, 2008). The incidence of pneumonia in Malaysia, as part of Western Pacific, is 0.22 (22%) episodes/child/year which was considered high by the WHO. However, there were no statistics of pneumonia cases in Malaysia specifically. A study conducted by Maimunah *et al.,* (1997) discovered that the prevalence of ARI among children below the age of five years was estimated to be between 28% - 39.3%.

1.4.2 Risk Factors

A risk factor is defined as an attribute that is associated with the increased risk of an outcome. The relationship between the risk factor and the outcome may be either causal or non-causal. Causal risk factors are determinants of the outcome, and a successful intervention to reduce exposure to them would improve the outcomes. However, a non-causal risk factor may be associated with the outcome through confounding or reverse causation. Interventions to reduce exposure to non-causal risk factors would not necessarily improve the outcomes. In addition to this, previous studies had tested some of the risk factors of pneumonia (Azizi *et al*., 1995; Choo *et al.,* 1998; Luiz *et al*., 2004; Ana *et al* 2004; Best *et al*., 2008), but still there is a need to confirm their findings and searching the presence of other risk factors. The Malaysian Clinical Practice Guidelines on Pneumonia and Respiratory Tract Infections in Children for the year 2002 had listed the following risk factors.

i. Low weight for age (Anon, 2003)
ii. Lack of breast feeding (Karalanglin *et al*., 2009).
iii. Failure to complete immunization (Hassan and Al-Sadoon, 2001).
iv. Low birth weight (Luiz *et al.,* 2004).

Other possible factors that may have increased the risk of patients to develop pneumonia were documented by some studies. These factors are:

i. Young maternal age (Luiz *et al*., 2004).
ii. Attendance at day care centres (Ana *et al.,* 2004).

iii. Paternal smoking (Best *et al*., 2008; Peat *et al*., 2007).

iv. Maternal smoking (Strachan and Cook, 1997; Peat *et al*., 2007; Brenda, 2008).

v. Pre term birth (Gessner, Castrodale, and Soriano, 2005).

Despite recent advances in the treatment of pneumonia which offer hope in reducing its devastating effect, prevention still remain an important approach to reduce the incidence, recurrence and mortality of pneumonia (Lorente, Blot, and Rello, 2010; Hallie and James, 2010). The prevention of pneumonia and its later complications can be achieved by the reduction of risk factors, specifically the modifiable risk factors. However, non modifiable risk factors will also help to prevent pneumonia through the evaluation of those subjects of high risk who will have a priority in the prevention and management.

1.4.2.1 Lack of Breast Feeding

Infection still constitute a heavy burden and still remain as a major cause of morbidity and mortality worldwide despite current advances in medicine, nutrition, hygiene and anti infective therapy. The high susceptibility of neonates and infants to infection could be in part due to some of the contributing factors that predispose to infection. However, there is a clear deficit in various aspects of neonates' and infants' immune system which could be the main cause of this increase in susceptibility to infection. Knowing that there is a direct relation between infants' immune system development and the increase risk of infection among the newborns, infants and children demand greater understanding of breast milk immunological advantages. Breast feeding

is strongly recommended for babies during the first months of life. In addition to the immunologic advantages of breast milk, it contains all the newborn's nutritional needs. There is evidence that breast feeding decreases the risk of infections in children (Cesar *et al*., 1999; John *et al*., 1997), although some authors suggested that the effect of breast feeding might be more important in decreasing the severity of infections (measured by the rate of hospitalization) than in reducing the risk of infection (Chen, 1994).

Breast feeding provides immunity and protects children against ALRI through breast milk's unique anti-infective properties (Robert and Camille, 2007). It provides passive protection against pathogens (antibacterial and antiviral substances including secretory immunoglobulin A, lactoferrin, oligosaccharides, and cells which include macrophages, lymphocytes, and neutrophils), stimulants of the infant's immune system, and the bifidus factor which inhibits colonization by Gram negative species (Hanson *et al*., 2004).

In short, immunologic advantages of breastfeeding can be measured in terms of mortality and risk of infection among breastfed infants compared to non-breastfed infants. Three studies were conducted to provide information on ALRI (including pneumonia) and its related mortality in relation to breast feeding status. In major Brazilian case control study with large sample size, the data of infants who died of ALRI and the data of control subjects taken from the same community were compared. The odd ratio for lack of breast feeding was 3.6. This indicate that children who were not breast fed have about three and half times more likely to die of ALRI than those who received breast milk. The result was achieved after excluding of the other confounding

factor (Victora *et al.,* 1987). A case control study from Tanzania, on the other hand showed a relative risk about 1.7 for non breast fed children. Confounding factors were not controlled and this may reduce accuracy of the result. The third study is cohort study from Philippines. The relative risk for non breast fed children was 1.05 which indicates no association between lack of breast feeding and ALRI (Yoon, 1996). Other studies were conducted to provide the evidence on the association of nutrition interventions (including breast feeding) and reduction of respiratory infection risk (Froozani *et al*., 1999; Alvarado *et al*., 1999; Vitolo *et al*., 2005). However the above controversy may not be resolved by the results of these studies as they did not distinguish upper from lower respiratory tract infections. Hence the mentioned studies can not be used as evidence for this study which is focusing on pneumonia only (the main presentation of LRTI). PROBIT (Promotion of Breastfeeding Intervention Trial) is a large cluster randomized trial in the Republic of Belarus. The effect of breastfeeding promotion on ALRI outcomes was presented by 15% decrease in LRTI hospitalization (Kramer *et al*., 2001). More recently, a critical review of randomized trials of the effect of nutritional interventions on ALRI morbidity and mortality was done. This review included meta analyses and large scale randomized controlled trials on the effect of nutritional interventions (including breastfeeding promotion) on ALRI morbidity and mortality. This was based primarily on several systematic reviews that formed the evidence base for the Lancet Undernutrition Series (LUS). They concluded that exclusive breastfeeding promotion reduces ALRI morbidity (Roth *et al*., 2008). The other evidence is the global estimates of the effects of maternal and child undernutrition on infants health consequences. It revealed that lack of exclusive breastfeeding in the first half of infancy is a risk factor for ALRI incidence, morbidity and death (Black *et al*., 2008).

1.4.2.2 Incomplete Immunization

Most of the studies that were conducted for evaluating the association between immunization and respiratory infections including pneumonia, involved only one type of vaccines. This study evaluated three vaccines that shown to have association with pneumonia. The vaccines are DPT-Hib, OPV and MMR. During the search in literature, most of the papers found were about the new pneumococcal conjugate vaccine (PCVs) which is not included in this study as it is unavailable in the public health sector of Malaysia. Few papers focusing on Hib and measles vaccinations were also found. In systematic review of observation studies, the association of mortality reduction with childhood vaccines was examined. This includes 24 studies with robust methodologies on measles vaccine. There was 31- 46% reduction in mortality (after elimination of methodologically low quality data). This reduction was attributed to the reduction of measles disease and its complications, mainly pneumonia (Cooper *et al*., 2003).

A recent systematic review of published randomized controlled trials (RCTs) and quasi experimental (QE) studies was conducted to determine the effectiveness of measles vaccine. Meta analysis of these studies found that vaccination was 85% [95% confidence interval (CI) 83–87] effective in preventing measles disease (Sudfeld, Navar, and Halsey, 2010). However this review did not focus on prevention of pneumonia or LRTIs as one of the complications of measles. The WHO 2008 report has cited and categorized pneumonia risk factors and lack of measles immunization was considered as one of the definite risk factors for pneumonia (Rudan *et al*., 2008).

On the other hand, the importance of Hib vaccine in the prevention of pneumonia is related the organisms commonly causes pneumonia in this age group, those are *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumonia* (Sazwal and Black, 2003). Hence, the risk of pneumonia infection increases if this vaccine missed from immunization schedule. In Indonesia, one randomized controlled trial was conducted to address the burden of Hib disease in Asia. The result indicates a significant reduction in clinical pneumonia among vaccinated children compared to non vaccinated children (Gessner *et al*., 2005). However there was no significant reduction among radiologically confirmed pneumonia cases. A 34 to 44% risk reduction of radiologically confirmed pneumonia was detected in case control study on Hib vaccination from Bangladesh (Baqui *et al*., 2007). Hib vaccine was distributed by use of a quasi-randomized approach after adjustment for the confounding factors. Additional evidence on the effectiveness of Hib vaccine for pneumonia prevention was seen in other case control studies (Andrade *et al*., 2004; Hoz *et al*., 2004).

Majority of the available papers available that relate immunization and pneumonia were focusing on the association between immunization and pneumonia prevention. There were only few studies focusing on lack of immunization as risk factor of pneumonia. A study was conducted in Spain using sample size of 1500 cases and 1500 age and gender matched controls (Almirall *et al*., 2008). Strict diagnostic criteria were used to ensure correct diagnosis and eliminate bias that may occur due to misclassification. They were looking at the association between lower respiratory infections and a number of risk factors, including lack or incomplete immunization. The study found that there was a significant association between incomplete immunization

and the risk of pneumonia. However, further studies need to be done in order to confirm this association and to monitor the changes that may occurs due to the periodic alteration in the etiology of pneumonia.

1.4.2.3 Low Birth Weight

Grant (1994) estimated that 19% of all babies born in developing countries have low birth weight that is, a birth weight of <2500 g, up to and including 2499g (WHO, 2005a). The median prevalence ranges from 10% in the Middle East and North Africa to 34% in southern Asia. There are two main mechanisms that predispose low birth weight infants to an increased risk of respiratory infections, these are reduced immuno-competence and impaired lung function. Low birth weight babies may have a higher incidence of pneumonia because low birth weight may lead to a short duration of breast feeding and poor nutritional status.

Generally, low birth weight infants may be divided into 2 broad subgroups: preterm (<37 wk gestation) and small for gestational age (SGA). The operational definition of SGA is an infant born at term with a weight less than the standard reference weight. SGA infants are more adversely affected than preterm infants and their impairment lasts longer (Hanaa, Nafisa, and Randa, 2011). However, impairment of the immune response may arise from nutritional deficits (Yu and Upadhyay, 2004).

Report on the association between low birth weight and pneumonia incidence throughout infancy stage is poorly documented. The association between low birth weight and respiratory infections (generally) was the focus point in most of the studies

that were conducted. Despite the fact that these studies may provide the evidence on the association between low birth weight and respiratory infection (Datta *et al*., 1987; Chen *et al*., 1988; Cerqueiro *et al*., 1990; Victora et al., 1994; Fonseca et al., 1996), they are relatively old. Much of the recent studies involve determination of the association between low birth weight and mortality due to respiratory infection, or LBW and frequent hospitalization.

A study was conducted to identify risk factors of LRTI associated infant mortality in the United States of America. Deaths associated with LRTI were defined as deaths for which the International Classification of Diseases, 10th Revision (ICD-10) codes for LRTI appeared anywhere on the coded death record. LRTI includes pneumonia and influenza (ICD-10 codes J10 –J18). A total of 5420 LRTI associated infant deaths were documented in the United States during the period 1999–2004. The conclusion was made indicates that low birth weight was associated with markedly increased risk for LRTI associated death among all of the racial groups (Rosalyn *et al*., 2009).

Two studies were conducted to determine if low birth weight is associated with hospitalization due to respiratory illness. One American population based case control study from Washington was identified two levels of exposure. These are very low birth weight (VLBW < 1500 g), and moderately low birth weight (MLBW 1500-2499 g). Normal birth weight subjects (2500-4000 g) were considered unexposed. The discharge diagnosis codes were used to define respiratory hospitalization. A total of 4674 cases and 18445 controls subjects were identified. The controls were age matched to the cases and randomly selected. The odds ratio for hospitalization due to respiratory illness was

1.83 for VLBW ($P = 0.001$). For Moderately low birth weight the odds ratio was 1.34 at $P < 0.005$. This was after controlling of the confounding factors like age, sex, marital status, residence and race (Eric *et al*., 2009). Also in Washington, more recent population based study of cohort design was conducted to test if low birth weight subjects are at increased risk of respiratory disease. Diagnosis was done using ICD-9 classification. Normal birth weight subjects were randomly selected from birth certificates, frequency matched to low birth weight subjects by birth year. Identification of the exposed (low birth weight) and unexposed (normal birth weight) subjects was done and categorize to VLBW and MLBW. (Odds ratio for hospitalization was 1.39 for moderately-low-birth weight ($P < 0.001$), for very low birth weight 2.52 ($p < 0.001$). They concluded that low birth weight was associated with an increased risk of hospitalizations due to respiratory illness (Eric *et al.*, 2011). However, confounding factors were not considered and matching for age wasn't done for all paired cases and controls as done in the study of Eric *et al*., 2009.

In short, despite the similarities between the study of Eric *et al* and this study (case control design, diagnosis based on discharge codes, comparing the exposed with unexposed through logistic regression). A major different point is that this study targeting pneumonia only and not all types of respiratory tract infection as in the case of most the studies that were reviewed in this literature

1.4.2.4 Preterm Birth

Preterm birth is an important determinant of neonatal mortality and morbidity (Wang *et al*., 2004). It was advocated that the well-known unfavorable adverse outcomes of preterm birth on health would last for a long term and might appear later in life (Saigal and Doyle, 2008). The estimates of the year 2005 indicated that about 10% (12.9 million births) of all life births worldwide were preterm, 85% (11 million births) of which were concentrated in Africa and Asian regions (Stacy *et al*., 2009). They defined preterm birth as child birth occurring at less than 37 completed weeks or within 259 days of gestation. Morbidity is adversely related to gestational age as the fetus needs time to grow, and to develop its tissues and organs. Therefore, the consequences of preterm birth on later health and development during the first two years of life were crucial. It was discovered that preterm children had higher prevalence of wheezing and hospitalization for the first year of life compared to full term children. However pneumonia is more prominent and hospitalization which was reported more frequently among preterm birth children compared to children born at term, the study did not search long term effects (after the first 2 years of life) of preterm birth on pneumonia and hospitalization (Ina *et al*., 2009). In the current study, the association of preterm birth and pneumonia risk were investigated for children up to 5 years old.

1.4.2.5 Low Weight for Age

Childhood underweight is one of the leading causes of global burden of disease (Ezzati *et al*., 2002), and one of the important risk factors of pneumonia in children (Anone, 2003). In one case control study to determine the risk factors of pneumonia among Indian children, Z score for weight/age based on national center for health statistics data

was used to evaluate the implication of weight status on pneumonia risk. Cases were 127 children aged 2-35 months hospitalized with pneumonia. Controls were 135 children attending their immunization clinic. The results indicate that children with a score lower than 0 was associated with more than three folds increase in the risk of pneumonia (OR 3.26, CI 1.82-5.85) when compared to children with a score equal to or greater than 0, even after being adjusted for all the other variables (Mahalanabis *et al*., 2002). However, the controls were healthy children attending immunization clinic and not hospitalized children which makes the results prone to recalling bias. In this study, controls were hospitalized children.

During the search in literature, lack of recent studies testing the association of low weight fore age and pneumonia risk was one of the obstacles for this study. Most of the studies were focusing on the association between malnutrition and risk of pneumonia mortality. Underweight (which is represented by weight-for-age *z*-score < -2) was categorized as definite risk factor of pneumonia by WHO (Rudan *et al.,* 2008). The evidence that could further supports this association is available on some old and recent studies (Agrawal *et al*., 1995; Banajeh, Sunbali, and Sanahani, 1997; Sehgal *et al*., 1997; Yoon *et al.,* 1997; Man *et al*., 1998; Bahwere *et al*., 2004; Caulfield *et al*., 2004; Johnson *et al*., 2008; Nantanda *et al*., 2008; Naheed *et al*., 2009). one of the possible explanations for this association is that an underweight child (which is probably due to being undernourished) might have impaired immune responses and is more prone to infections than a normal weight child who is well nourished (Fanca *et al*., 2009).

1.4.2.6 Day Care Attendance

Previous epidemiological studies have used day care attendance as an indicator of the increased likelihood of early and frequent exposure to infections. It is well documented that in developed countries, exposures to common infections occur more frequently in institutional settings (Kevin *et al*., 2008). A study was conducted in Denmark to investigate the risk of respiratory and other illnesses among children (age groups: 6 weeks through 17 months, 18 through 35 months, and 36 through 59 months) who were exposed to various types of day care facilities (Mads *et al*., 2006). Children are considered exposed to day care environment if they were enrolled in day care centres, for at least 10 hours per week for the 4 weeks before the interview. Unexposed children were not enrolled in any regular child care centre with children and did not have siblings younger than 5 years of age who received regular day care**.** Although an increased risk of respiratory illness was associated with the attendance at day care centre for children in all three age groups, the risk was statistically significant only for children between 6 weeks to 17 months of age (odds ratio = 1.6; 95% confidence interval = 1.1 to 2.4).

In Brazilian case control study involving 650 Brazilian children aged less than 2 years. The risk of pneumonia among children attending day care was investigated. They found that there was a significant association between the risk of pneumonia among young children and day care centre attendance (Fonseca *et al.*, 1997). However, the study only recruited the subjects and controls from poor socioeconomic areas, and poverty could be a source of other factors (confounding factors) that may lead to the increase risk of infection like pneumonia.

Previous studies were investigated the association of daycare centre attendance and risk of respiratory infection (Fleming *et al*., 1987; Hurwitz *et al*., 1991; Hardy and Fowler, 1993; Nafstad *et al*., 1995; Fuchs *et al*., 1996; Louhiala *et al*., 1999; Celedon *et al*., 1999; Forssell, Hakansson, and Mansson, 2001; Anders *et al*., 2003; Dales *et al*., 2004). There should be further studies to evaluate the association between the risk of pneumonia among young children and day care centre attendance. Such studies should also consider the contribution of other possible confounding factors. This study evaluated only pneumonia cases not the other respiratory tract infection.

1.4.2.7 Young Maternal Age

Another factor that may increase the risk of pneumonia is young maternal age. A hospital based case control study was conducted in Southern Brazil to review 510 infants of less than two years old with radiological confirmed pneumonia. The incidence of radiological confirmed pneumonia was associated with low paternal education, the number of persons in the household and young maternal age (Victora *et al*., 1994). Another hospital based case control study was conducted by Luiz *et al.*, (2004), in Taubate University Hospital Brazil, they classified mother's age under 3 categories: less than 20 years, 20 to 34, and over 34 years old. The study found that young maternal age was one of the statistically significant risk factors. Therefore, younger mothers have twice as likely to have a child being hospitalized due to pneumonia compared to mothers who were within the range of 20 to 34 years of age. The possible explanation is that early motherhood puts young women at risk for educational underachievement (Nanchahal *et al*., 2005; Hofferth, Reid, and Mott, 2001), and poorer economic circumstances which represented by higher levels of welfare dependence, lower levels of

workforce participation, and lower income (Moffitt, 2002; Olauson *et al*., 2001). In addition early motherhood is associated with higher levels of mental health disorders (Schmidt *et al*., 2006; Boden *et al*., 2008). All these factors will absolutely have negative role in child health rendering him more prone to infection (Hofferth and Reid, 2002). In the above mentioned studies, pneumonia diagnosis was merely based on radiographic finding, hence the diagnosis might be not accurate as compared to set of diagnostic tools including confirmed culture.

1.4.2. 8 Parental Smoking

Another significant risk factor for childhood pneumonia is parental smoking (Broor *et al*., 2001; Haberg *et al*., 2007; Duijts *et al*., 2008; Puig *et al*., 2009). Smoking has many undesirable effects, not only to the smokers, but also to others who inhale the smoke known as passive smokers. Besides, parental smoking might have an affect on children's health either directly or indirectly causing infection. The direct mechanisms by which smoking increases the risk of infections include structural changes in the respiratory tract and a decrease in the immune response (Lidia and Neal, 2004; Noakes *et al*., 2007; Ruskamp *et al*., 2010). A study revealed that smokers incur a 2 to 4 fold increased risk of invasive pneumococcal disease (Satoru *et al*., 2005). Children of parents who smoke have higher frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared to the children of nonsmoker parents (Braback , Bjor, and Nordahl, 2003; Al-Shehri, Sadeq, and Quli, 2005; Carroll *et al*., 2007; Suzuki *et al*., 2009).