


Risk Factors for Community-acquired Pneumonia among Children Under-five Years in Asia: A Systematic Review of Observational Studies

Muhamad Faza Soelaeman, Johan Cahyadirga
Faculty of Medicine, University of Indonesia /Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

Background: Pneumonia is the leading cause of death among less than 5 year-old children worldwide, mainly in Asia in the form of community-acquired pneumonia. As primary prevention is considered crucial in combating the disease, risk factors need to be analyzed. **Methods:** Based on the PRISMA guidelines, observational studies were explored systematically by the PubMed MEDLINE database with inclusion and exclusion criteria. The studies retrieved are then assessed with the STROBE method. **Results and Discussion:** A total of 8 studies were included, with total participants of 16.862 children. STROBE score results range from 12.2 to 19.6. Several risk factors were associated with pneumonia and risk factor; the highest odds ratio are daytime abnormal behavior (OR: 11.06, 95% CI: 1.51-81.26, p=0.018), asthma diagnosis (OR: 5.85, 95% CI: 4.83–7.08), poor economic status (OR = 4.95, 95% CI: 2.38 to 10.28, p<0.05), and smoke-related cooking process (OR = 3.97, 95% CI: 2.00-7.88, p<0.05). **Conclusion:** The most associated host risk factor was health-related conditions while the most associated environmental risk factor was the smoke-related environment. Daytime abnormal behavior, the risk factor with the highest odds ratio.

Keywords: Community-acquired pneumonia, childhood pneumonia, risk factor, Asia.

ABSTRAK

Latar Belakang: Pneumonia adalah penyebab kematian nomor satu pada anak usia di bawah 5 tahun di seluruh dunia, terutama di Asia, dalam bentuk *community-acquired pneumonia*. Pencegahan primer penyakit ini sangat penting, oleh karena itu, perlu dilakukan analisis faktor risiko pneumonia pada anak usia di bawah 5 tahun. **Metode:** Berdasarkan pedoman PRISMA, tinjauan literatur untuk studi observasional dilakukan melalui *database* PubMed MEDLINE dengan kriteria inklusi dan eksklusi yang telah ditetapkan. Studi yang diperoleh dinilai menggunakan metode STROBE. **Hasil dan Diskusi**: Sebanyak 8 penelitian memenuhi kriteria dengan total subjek 16.862 anak. Skor STROBE berkisar antara 12,2 hingga 19,6. Beberapa faktor risiko yang berhubungan dengan pneumonia; faktor risiko dengan *odds ratio* tertinggi adalah perilaku abnormal di siang hari (OR: 11,06; 95% CI: 1,51-81,26; p=0,018), asma (OR: 5,85; 95% CI: 4,83-7,08), status ekonomi buruk (OR=4,95; 95% CI: 2,38-10,28; p<0,05), dan proses memasak yang menghasilkan asap (OR=3,97; 95% CI: 2,00-7,88; p<0,05). **Simpulan:** Faktor risiko yang paling banyak dikaitkan adalah kondisi kesehatan subjek, sedangkan faktor risiko lingkungan yang paling banyak dibahas adalah lingkungan yang berhubungan dengan asap. Perilaku abnormal di siang hari yang merupakan faktor risiko dengan *odds ratio* tertinggi. **Muhamad Faza Soelaeman, Johan Cahyadirga. Faktor Risiko *Community-acquired Pneumonia* pada Anak Usia Di bawah Lima Tahun di Asia: Tinjauan Sistematik atas Studi Observasional**

Kata Kunci: *Community-acquired pneumonia,* pneumonia pada anak, faktor risiko, Asia.

INTRODUCTION

Background

Pneumonia is an important cause of morbidity and mortality among children; it is considered as a major public health issue worldwide. The World Health Organization (WHO) estimates there are 156 million new cases of pneumonia among children under five years each year with more than 1.4 million deaths, accounting for 18% of all deaths.[1,2] The majority are community-acquired pneumonia (CAP) and mostly happen in Asia, making this region a priority in combating the disease.[3,4]

Pediatric CAP, mainly caused by bacterial infection such as Streptococcus pneumoniae and viral infection such as respiratory syncytial virus (RSV), remains a challenge as around 8.7% of newly diagnosed cases are classified as severe and 11.5% progresses into severe condition.[1,2] This condition needs complex management which is difficult to achieve in primary care facilities, especially in developing countries.[5,6] Therefore, primary prevention is crucially needed. However, primary prevention is still rarely emphasized in many countries in Asia. Even though vaccines are starting to become prioritized, a broader spectrum of factors in disease transmission have not been taken into serious consideration; its

Alamat Korespondensi *email: Fazasoelaeman@gmail.com*

importance needs to be assessed in order to achieve complete protection for has children.[7,8]

Over the past decades, various studies[9,10] have investigated the possible relation between several risk factors and pneumonia among children; some discussed severe cases of pneumonia and pneumonia mortality. However, there are no systematic reviews assessing those risk factors. In addition, none of those studies are in the Asia region. As geographical and socioeconomic conditions in Asia may differ, such as childhood immunization status, nutrition, and other environmental conditions, they may lead to the epidemiologic triangle and influence disease transmission.

Objectives:
This study was conducted to obtain the most prevalent risk factor associated with CAP among children in Asia.

METHODS

Study Selection

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] Observational studies published from the year 2000 to 5 January 2023 were systematically reviewed to identify studies regarding pneumonia risk factors among children. Due to limited access, only the PubMed MEDLINE Database was explored. Keywords used are "risk factor", "pneumonia", "child", and "Asia".

The inclusion criteria are observational studies on risk factors of childhood or pediatric community-acquired pneumonia in Asia with subjects below 5 years old with a sample size of at least 50 children. Exclusion criteria are studies on respiratory diseases other than pneumonia, studies with no specified analytical method including no p-value for odds ratio (OR), non-observational studies and studies outside Asia (**Table 1**).

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Observational studies (cohort, case-control, and cross-sectional studies) on risk factors of childhood/paediatric community-acquired pneumonia in Asia with subjects below 5 years old.	Studies on respiratory diseases other than pneumonia
Studies sample size > 50	Methods for statistical analysis not specified, including studies with no p-value for its odds ratio (OR)
Studies using univariate or multivariate analysis	Non-observational studies, including surveys or case series Studies with locations outside Asia

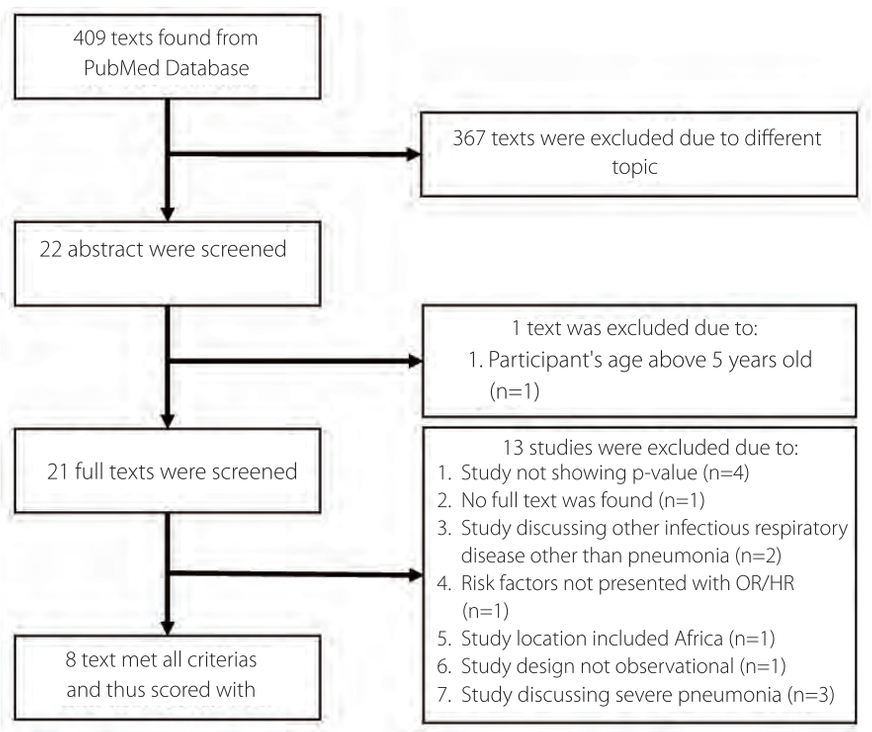

Figure 1. Selection and analytical method used in this study and its result.

Quality Assessment

The quality of the studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[12] statement checklist for cohort, case-control and cross-sectional studies which a maximum score 22.

RESULTS

Study Selection & Quality Assessment

From database explorations using the keywords "risk factor", "pneumonia", "child" and "Asia", 409 studies were found; 387 studies were excluded, leaving 22 studies whose abstracts were then reviewed. One study was excluded because participants' age was above 5 years old (n=1). Full text review was done on 21 studies, and 13 studies were excluded. Reasons for exclusion were studies without p-value (n=4), no full text available (n=1), study on other respiratory diseases (n=2), risk factors not presented with hazard ratio/HR (n=1), study location included Africa (n=1), study design was not observational (n=1), and study on risk factors for severe pneumonia (n=3). A total of 8 studies were included in the study, with 16.862 children as the total sample size (**Figure 1, 2**).

The studies were conducted in 6 different countries: the Philippines, China, Nepal, India, South Korea, and Israel. This may imply geographical and socioeconomic inclusivity within Asia. After assessment using the STROBE scoring system, the lowest quality score is 12.2 in the study by Mahalanabis D13 and the highest is 19.6 in the study by Chang J14. All qualified studies are incorporated into **Table 2**.[13-20]


DISCUSSION

The risk factors found in the study are grouped into several variables (**Table 3**). These variables were further classified into host-related and environment-related based on the epidemiology triangle. Health-related conditions include risk factors such as children's asthma, diarrhea, anemia, and stunting; pregnancy and birth conditions include risk factors such as low birth weight, preterm birth, and exposure to high temperatures during the prenatal period. Meanwhile, behavior variables include risk factors such as daytime abnormal behavior, restless sleep, and children who drink from well water. In addition, accessibility variable includes access to medical facilities, while the smoke-related environment includes smoking parents and cooking-related smoke. Health-related conditions and pregnancy and birth

Table 2. Studies characteristics with Strobe assessment score.

No	Author & Year of Publication	Study Design	Study Location	No. of Participants	Age	Risk Factors	Study Analysis	STROBE Score
1	Goldbart AD (2012)[15]	Case control	Soroka, Israel	1987	Control: 11.1 ± 16.4 months; Control: 22.2 ± 15.6 months	Daytime abnormal behavior (OR: 11.06, 95% CI 1.51-81.26, p=0.018); Rhinorrhea (OR: 3.24 95% CI 1.54-6.83, p=0.002); Restless sleep (OR: 1.68, 95% CI: 0.79-4.29, p=0.208)	SPSS 15.0 was used to analyze continous variables (t-test), unmatched samples (x2 tests or fisher exact test), multiplevariate logistic regression model, and statistic significance.	18
2	Karki S (2014)[16]	Case control	Kathmandu, Nepal	200	1 month to 5 years (median age not available in both case and control group)	Age 1-3 years (AOR: 1.51), age above 3 years (AOR: 2.60), low birth weight (AOR: 1.41), not fully vaccined (AOR: 1.52), attending child care center (AOR: 1.66). Mother Smokes (AOR: 1.51) Father smokes (AOR: 1.98), Both parents smoke (AOR: 2.21), Smokeless chulo inside house (AOR: 2.34), Smoke chulo outside house (2.76), Smoke chulo inside house (AOR: 3.76). Mother only attend primary education (AOR: 1.37), Joint family (AOR: 1.21). Buddhist religion (AOR: 1.97)	SPSS 16.0 was used to create multiple logistic regression	15.3
3	Coles CL (2005)[17]	Case control	Negev, Israel	863	Case: 20.6 months, control: 14.6 months	Anemia (AOR: 3.32, 95% CI, p<0.001), Low birth weight (AOR: 2.16, 95% CI, p=0.002), stunting (AOR= 2.22, 95% CI, p=0.04), serum retinol concentration (AOR=1.03 per mikrog/dl, 95% p < 0.001), having diarrhea 31 days prior to enrollment (AOR = 2.3, 95% CI, p=0.007)	Stata 8 Software was used for significance test on selected variables between cases and controls by using t tests, the two-tailed X2 test, or Fisher's exact test.	18.1
4	Kosai H (2015)[18]	Retrospective cohort	Biliran Island, Philippines	5249	Less than 6 years (median age NA)	Lower SES [Odds ratio: 1.11, 95% confidence interval (CI): 1.02–1.20], a preterm birth (OR: 1.87, 95% CI: 1.12–3.13), a history of asthma diagnosis (OR: 5.85, 95% CI: 4.83–7.08), drinking natural water or water from the well (OR: 1.44, 95% CI: 1.13–1.85), and a longer travel time to the closest medical facility (OR: 1.32, 95%: 1.09–1.61	Background characteristics among municipalities were compared using ANOVA, chi-square test, and Welch's test using the JMP statistical software (version 10.0.2, SAS Institute Inc., Cary, NC.).	15.4

Table 2. Studies characteristics with Strobe assessment score.

No	Author & Year of Publication	Study Design	Study Location	No. of Participants	Age	Risk Factors	Study Analysis	STROBE Score
5	Yang HJ (2013)[19]	Case control	Seoul, Korea	63	Case: 26 months; control: NA	Previous use of HDs was significant (OR, 2.73; 1.41–5.90, P = 0.00)	Nominal variables were analyzed by using a chi-square or Fisher's exact test. Univariate analyses using conditional logistic regression analysis were conducted to identify all pertinent covariates and confounders, and to assess the comparability of the cases and controls.	15.4
6	Mahalanabis D (2002)[13]	Case control	Calcutta, India	262	Case: 2-35 months; control: NA	Used wood or coal or cowdung or any combination for cooking (OR = 3.97, 95% CI = 2.00-7.88); History of asthma (OR = 5.49, CI = 2.37-12.74); Poor composite economic status (OR = 5.49, CI = 2.37-12.74)	Odds ratios and 95% confidence intervals were calculated by Cornfield's approximation	12.2
7	Miao Y (2017)[20]	Cross sectional	Changsha, China	2598	Mean:4.19 years old	Childhood pneumonia was associated with temperature during prenatal period with adjusted OR (95% CI) = 1.77	Multiple logistic regression models was used to evaluate the association between exposure to ambient air temperature during different timing windows and childhood pneumonia by adjusting covariates. Associations in the regression analysis were calculated as odds ratio (OR) with 95% confidence interval (95% CI)	19.4
8	Chang J (2018)[14]	Cross sectional	Shandong province, China	5640	Mean: 4.47 years old	Childhood pneumonia associated with main traffic road within 200m of residential area (AOR: 1.23); Childhood pneumonia associated with >100 cars parked in the ground car park per day (AOR: 1.41)	Statistical analysis performed by SPSS version 20.0. Pearson's chi-square test was used to compare differences in pneumonia prevalence. Bivariate and multivariate crude and adjusted associations between different indicators of residential ambient traffic with childhood pneumonia by SPSS.	19.6

conditions are the most mentioned risk factors in the studies, followed by the smoke-related environment. The highest odds ratio scores are from both host-related and environment-related factors (**Figure 2**) smoke.

Host-related Factor: Highest Odd-ratio Score

The risk factor with the highest hazard was abnormal daytime behavior. Goldbart, *et al*,[15] defined daytime abnormal behavior as tiredness and irritability. Together with snoring, nighttime breathing problems, restless sleep, and chronic rhinorrhea, daytime abnormal behavior are the symptoms for sleep disordered breathing (SDB).[15] Several mechanisms can explain the association between upper airway pathology and lower respiratory tract infection; One of those mechanisms is the increased risk of microaspirations. Sleep disordered breathing, such as obstructive sleep apnea, is associated with upper airway inflammation, laryngeal sensory dysfunction, and is also related to weak or absent cough reflex. These alterations may affect the oropharyngeal microflora, increase the risk of silent aspiration, and thus would lead to the inflammation of the lower airway.[21]

Inflammation is associated with induction of chemotaxis of proinflammatory cytokines. Inflammation has also been linked to degeneration of the upper airway, causing it to decrease its filtering ability. The combination


of microaspirations and a decrease in filtering ability may increase the likelihood of bacterial aspiration and thus increase the risk of pneumonia.[15,21]

The risk factor with the second highest odds ratio was diagnosis of asthma (OR 5.85). Kosai H and Mahalanabis D[13,18] stated that there is an increased risk for pneumonia among asthma patients. However, the relationship between asthma and pneumonia was not clearly elucidated in both studies. According to Obert J,[22] a probable explanation for an increased risk of pneumonia in children with asthma is due to a structural change in the respiratory epithelium. Since respiratory epithelium is one of the first lines of defense against inhaled pathogens, asthma patients with epithelial desquamation have a higher susceptibility to both bacterial and viral infection. The risk of pneumonia is also increased in asthma, which requires corticosteroid usage. In the Qian, *et al*,[23] study, there was an 83% increased risk of hospitalization for pneumonia in patients who use ICS (intranasal corticosteroid).[23] There is still no clear explanation why corticosteroids could increase the risk of pneumonia. A possible mechanism is that ICS use may alter the lung microbiome and respiratory epithelium, thus making patients even more susceptible to developing pneumonia.[24]

Environment-related Factor: Highest Odd-ratio Score and Most Discussed Risk Factor

Poor economic status is highly related to pneumonia as it has the highest odds ratio of 4.95 in Mahalanabis, *et al*, study[13] and also found in Kosai, *et al*, study.[18] Poor economic status is related to hygiene and sanitation, a possible risk factor for microbial entry to the respiratory system, thus increasing the risk of pneumonia. These factors should be seriously considered because socioeconomic status improvements may lead to better health care access, availability of clean fuel, sanitation, food, etc. and they have been linked to better outcomes of pneumonia.[13,18]

The most discussed environmental risk factor is smoke-related factor and it is the second highest odds ratio (3.97) in Mahalanabis, *et al*, study.[13] Mahalanabis, *et al*,[13] found indoor air pollution is caused by the solid fuels used that emit a large amount of smoke. Karki, *et al*,[16] elucidated that the indoor pollution was mainly caused by in-house stoves and also when both parents smoke. Chang, *et al*,[14] explained that staying in a residence close to a main traffic road, or within 200 m of an automobile shop, or within 100 m of a gas station, or having a ground car park in the residential community were significantly associated with childhood pneumonia. A plausible biological explanation is that air pollutants could cause epithelial damage by inducing oxidative stress, thus disrupting barrier dysfunction. In addition, the pro-inflammatory state induced by air pollutants will provoke inflammation and a remodelling process, possibly inducing fibrosis.[25] Damaged epithelial barrier may result in easier microorganisms invasion and thus cause pneumonia.[22] In addition, air pollutants can directly increase host susceptibility to *Streptococcus pneumoniae* infection. Air pollutants have been found to impair the phagocytic killing ability of macrophages, thus increasing *S. pneumoniae* replication.[26]

Table 3. Study variables distribution.

No	Variables	Risk Factors	Numbers of Studies with the Risk Factors
1	Host-related factors	Health-related conditions	4
		Pregnancy and birth conditions	4
		Behavior	2
		Age	1
		Vaccination	1
2	Environment-related factors	Smoke-related environment	3
		Low economic status	2
		Access to medical facility	1
		Crowdedness	1
		Mother's level of education	1
		Children attending daycare	1
		Use of humidifier disinfectant	1

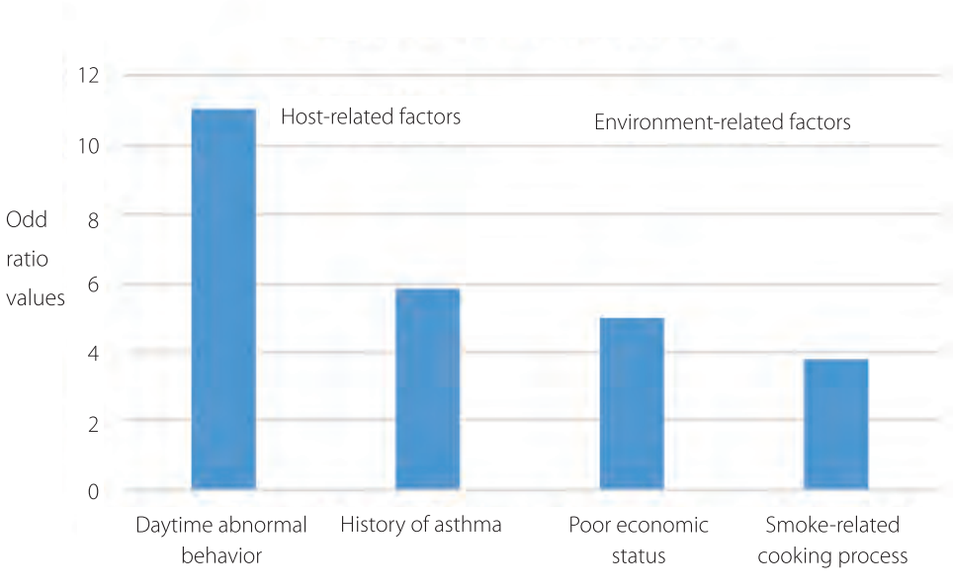

Figure 2. Highest odds ratio values.

Limitation of the Study

The most prevalent limitation of this study is the lack of literature, as there are not many studies available. Many studies have low quality and access to several studies is limited. Another limitation is the variations of countries represented. More studies should be conducted in northern, central and south-east Asian countries.

CONCLUSION

There is a wide array of risk factors for pneumonia. The most discussed host risk factor was health conditions and the most discussed environmental risk factor was the smoke-related environment. The most influential risk factor with the highest odd ratio was abnormal daytime behavior.

Suggestion

These findings could improve knowledge in society, so the government should plan a strategy to distribute this knowledge regarding risk factors of child pneumonia. Also, further studies in more countries with better qualities are suggested in order to achieve more comprehensive knowledge. A plan for pneumonia prevention should be made, whether by the government or related organizations.

Conflict of Interest

None declared.

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