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Review

The burden and etiology of lower respiratory tract infections in children under five years of age in Indonesia

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Abstract

Introduction: Lower respiratory tract infections (LRTI) are a substantial threat for children worldwide. Currently, there is a lack of knowledge about the burden and etiology of LRTI in children under five years of age in Indonesia.
Methodology: We have systematically searched the available English and Indonesian scientific literature to review and summarize data on LRTI and LRTI-associated invasive disease, and bacterial carriage in the upper respiratory tract in children under five years of age in Indonesia.
Results: Overall, data on the burden and etiology of LRTI in children under five years of age in Indonesia is very limited. The data are primarily collected in Java. Data from other parts of Indonesia, including Sumatra, Kalimantan, and Sulawesi, are scarce. The case fatality rate (CFR) of LRTI in children under five years of age in Indonesia was 0.11%. Influenza was the most commonly reported viral etiological agent of LRTI in children under five years of age in Indonesia. *Klebsiella pneumoniae* was the most frequently reported bacterial agent of LRTI. *Streptococcus pneumoniae* showed the highest carriage rates.
Conclusions: Surveillance and diagnostic studies are urgently needed and should be conducted in different parts of Indonesia to improve insight in the burden and etiology of LRTI in Indonesia. These data are pivotal to increase the effectiveness of public health strategies, including vaccination and prevention of antimicrobial resistance.

Key words: Children; etiology; Indonesia; lower respiratory tract infection.

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Introduction

Lower respiratory tract infections (LRTI) are a substantial threat for children resulting in high morbidity and mortality rates worldwide. It is estimated that, globally, 15.5% of children mortality is due to LRTI [1]. Indonesia is one of the developing countries with a high contribution to global pneumonia cases [2]. Previous studies have been conducted to determine strategies to reduce the burden of LRTI in Indonesia through surveillance and vaccination [3-7]. In several epidemiological studies, carriage rates of potentially pathogenic bacteria, i.e. *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis* and also *Klebsiella pneumoniae* were measured in healthy children in Central Java, West Java, and West Sumatra provinces [8-10]. The serotype distribution of *S. pneumoniae* was studied in Jakarta and West Nusa Tenggara to determine the effectiveness of the pneumococcal vaccine [11-13]. Although the Ministry of Health of the Republic of Indonesia has tried to investigate the etiology of LRTI in children through Severe Acute Respiratory Infection (SARI) surveillance, currently, many findings have not been published in international journals and are thus not accessible through medical literature databases [14]. In order to obtain insight into what is currently known about the burden of LRTI, associated invasive disease and bacterial carriage in Indonesian children, we systematically searched all available English and Indonesian literature.

Methodology

The PRISMA checklist was followed for the development of our study protocol [15]. The systematic review protocol of this study was registered in PROSPERO under number CRD42020153212 (available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=153212).

Eligibility criteria

Studies on LRTI in children under five years of age in Indonesia were eligible for inclusion. In this paper, the term LRTI is used in its broadest sense referring to all infections in the lungs or below the vocal cord, excluding tuberculosis. Additionally, we included studies that have stratified age data of children below the age of five. Exclusion criteria were studies without age-specific data, studies without any information on pathogen identification, review articles, either systematic or narrative, and posters.

Literature search

We searched the following electronic databases: PubMed, Embase, Web of Science, Scopus, and ProQuest for studies published between January 2009 and October 2019. The search was limited to publications written in English and Indonesian. We were using a combination of search strings for lower respiratory tract infection, children, and Indonesia. In addition, we used Google Scholar to search for articles written in Indonesian using the keywords pneumonia, and anak (children).

PUBMED

1. "Respiratory Tract Infections"[Mesh:NoExp] OR "Bronchitis"[Mesh] OR "Empyema, Pleural"[Mesh] OR "Lung Abscess"[Mesh] OR "Lung Diseases, Fungal"[Mesh] OR "Lung Diseases, Parasitic"[Mesh] OR "Pleurisy"[Mesh] OR "Pneumonia"[Mesh] OR Pneumon*[tiab] OR bronchopneumon*[tiab] OR pleuropneumon*[tiab] OR Bronchitis[tiab] OR Bronchiolitis[tiab] OR CAP[tiab] OR HAP[tiab] OR VAP[tiab] OR Lower respiratory tract infection*[tiab] OR LRTI[tiab] OR Lower respiratory infection*[tiab] OR Lung disease*[tiab] OR Lung infection*[tiab] OR Pulmonary disease*[tiab] OR Pulmonary infection*[tiab]
2. child*[tw] OR schoolchild*[tw] OR infan*[tw] OR adolescen*[tw] OR pediatri*[tw] OR paediatr*[tw] OR neonat*[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl[tw] OR girls[tw] OR girlhood[tw] OR youth[tw] OR youths[tw] OR baby[tw] OR babies[tw] OR toddler*[tw] OR newborn*[tw] OR postneonat*[tw] OR postnat*[tw] OR perinat*[tw] OR preschool*[tw] OR suckling*[tw]
3. ("Indonesia"[Mesh] OR West Irian*[tiab] OR Indonesia*[tiab] OR Irian Jaya*[tiab] OR Java[tiab] OR Javanes*[tiab] OR Bali[tiab] OR Balines*[tiab] OR Sumatra*[tiab] OR Celebes*[tiab] OR Sulawesi*[tiab] OR Madoera*[tiab] OR Madura*[tiab]
4. #1 AND #2 AND #3

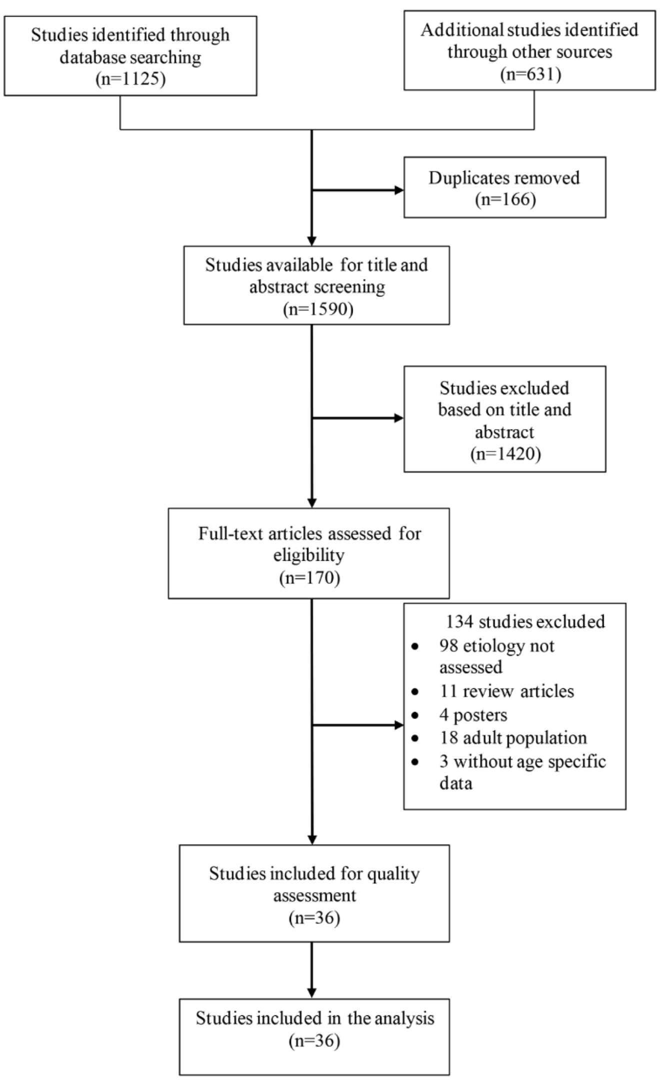
EMBASE

1. exp pneumonia/ OR lower respiratory tract infection/ or exp chest infection/ or lung infection/ OR Pneumon*.ti,ab,kw. OR bronchopneumon*.ti,ab,kw. OR pleuropneumon*.ti,ab,kw. OR Bronchitis.ti,ab,kw. OR Bronchiolitis.ti,ab,kw. OR CAP.ti,ab,kw. OR HAP.ti,ab,kw. OR VAP.ti,ab,kw. OR Lower respiratory tract infection*.ti,ab,kw. OR LRTI.ti,ab,kw. OR Lower respiratory infection*.ti,ab,kw. OR Lung disease*.ti,ab,kw. OR Lung infection*.ti,ab,kw. OR Pulmonary disease*.ti,ab,kw. OR Pulmonary infection*.ti,ab,kw.
2. babies.ti,ab,kw. OR baby.ti,ab,kw. OR boy.ti,ab,kw. OR boyhood.ti,ab,kw. OR boys.ti,ab,kw. OR Exp child health care/ OR Exp child health/ OR child*.ti,ab,kw. OR Exp child/ OR Exp childhood disease/ OR Exp childhood mortality/ OR Exp childhood/ OR girl.ti,ab,kw. OR girlhood.ti,ab,kw. OR girls.ti,ab,kw. OR Exp high risk infant/ OR infan*.ti,ab,kw. OR Exp infant disease/ OR Exp infant mortality/ OR neonat*.ti,ab,kw. OR Exp newborn disease/ OR Exp newborn morbidity/ OR Exp newborn period/ OR newborn*.ti,ab,kw. OR Exp newborn/ OR nicu.ti,ab,kw. OR paediatr*.ti,ab,kw. OR pediatr*.ti,ab,kw,hw. OR exp pediatric nursing/ OR exp pediatric rehabilitation/ OR exp newborn hypoxia/ OR exp pediatric ward/ OR exp pediatrics/ OR perinat*.ti,ab,kw. OR Exp perinatal development/ OR Exp perinatal period/ OR picu.ti,ab,kw. OR postnat*.ti,ab,kw. OR postneonat*.ti,ab,kw. OR preschool*.ti,ab,kw. OR school child.ti,ab,kw. OR schoolchild*.ti,ab,kw. OR suckling*.ti,ab,kw. OR toddler*.ti,ab,kw. OR youth.ti,ab,kw. OR youths.ti,ab,kw.
3. exp indonesia/ OR West Irian*.ti,ab,kw. OR Indonesia*.ti,ab,kw. OR Irian Jaya*.ti,ab,kw.

OR Java.ti,ab,kw. OR Javanes*.ti,ab,kw. OR Bali.ti,ab,kw. OR Balines*.ti,ab,kw. OR Sumatra*.ti,ab,kw. OR Celebes*.ti,ab,kw. OR Sulawesi*.ti,ab,kw. OR Madoera*.ti,ab,kw. OR Madura*.ti,ab,kw.
4. #1 AND #2 AND #3

WEB OF SCIENCE (AND SCOPUS)
1. pneumonia OR chest infection or lung infection OR Pneumon* OR bronchopneumon* OR pleuropneumon* OR Bronchitis OR Bronchiolitis OR CAP OR HAP OR VAP OR Lower respiratory tract infection* OR LRTI OR Lower respiratory infection* OR Lung disease* OR Lung infection* OR Pulmonary disease* OR Pulmonary infection*
2. babies OR baby OR boy* OR child* OR girl* OR infan* OR neonat* OR newborn* OR nicu OR paediatr* OR pediatr* OR perinat* OR picu OR postnat* OR postneonat* OR preschool* OR schoolchild* OR suckling* OR toddler* OR youth*
3. West Irian* OR Indonesia* OR Irian Jaya* OR Java OR Javanes* OR Bali OR Balines* OR Sumatra* OR Celebes* OR Sulawesi* OR Madoera* OR Madura*
4. #1 AND #2 AND #3

Figure 1. Flowchart of study selection.



PROQUEST
1. pneumonia OR chest infection or lung infection OR Pneumon* OR bronchopneumon* OR pleuropneumon* OR Bronchitis OR Bronchiolitis OR CAP OR HAP OR VAP OR Lower respiratory tract infection* OR LRTI OR Lower respiratory infection* OR Lung disease* OR Lung infection* OR Pulmonary disease* OR Pulmonary infection*
2. babies OR baby OR boy* OR child* OR girl* OR infan* OR neonat* OR newborn* OR nicu OR paediatr* OR pediatr* OR perinat* OR picu OR postnat* OR postneonat* OR preschool* OR schoolchild* OR suckling* OR toddler* OR youth*
3. West Irian* OR Indonesia* OR Irian Jaya* OR Java OR Javanes* OR Bali OR Balines* OR Sumatra* OR Celebes* OR Sulawesi* OR Madoera* OR Madura*
4. #1 AND #2 AND #3

Data collection

Two reviewers independently screened the title and the abstract of all retrieved studies. Disagreements between the two reviewers were solved through discussion. Studies without relevant information were excluded. Later, the full texts of the selected articles were assessed for eligibility using the same procedure as the abstract screening.

Quality assessment

Two reviewers independently assessed the risk of bias by using the Newcastle-Ottawa Scale (NOS) [16]. The final global quality score was discussed by two reviewers.

Data extraction and analysis

All the included studies were extracted using the modified Cochrane data extraction form. Extracted data included study period, research method, sample size, age group, prevalence, incidence, case fatality rate, carrier and carriage rate, etiology, and laboratory method of identification.

Results

We archived 1,756 publications from our search strategy and included 36 publications for analysis (Figure 1).

Disease Burden

Five studies and thirteen government publications report on the disease burden related to LRTI in children under five years of age in Indonesia (Table 1) [17-34].

Prevalence

The Ministry of Health of the Republic of Indonesia reports the prevalence of LRTI annually based on healthcare data collected from all provinces in Indonesia [21-24,26-32]. Mean, and standard deviation from 2009 until 2019 reports are 2.26% and 0.30%, respectively (Figure 2). National Institute of Health Research and Development reported a higher prevalence (4.5-4.8%) based on a household survey on 2013 and 2018 [25,34].

Table 1. Summary table of studies reporting disease burden.

Reference	Study period	Research method	Study Location (City, Province, Island)	Sample size	Age group	Prevalence	Incidence	Case Fatality Rate
Azmi 2016	Data from 2010 and 2011	Cross sectional using Case mix system	NA	Indonesia: 42 private and public hospitals	Children (0-4 years) and adults	NA	±5,000/100,000 discharge	0-4%
Simoes 2011	February 1999-Febryary 2001	Cross sectional	Bandung, West Java, Java	2,014	< 5 years	NA	38.54-57.25 per 1,000 child-years	NA
Susilarini 2018	May 2013-April 2016	Cross sectional	Gunung Kidul, Yogyakarta Special Region, Java; Balikpapan, East Kalimantan, Kalimantan; Deli Serdang, North Sumatera, Sumatera	911 children from total 1,527 patients	Children (0- 4 years), other 5- >70 years	NA	82-114 per 100,000 population	NA
Tan 2018	January-December 2011	Cross sectional	Bandung, West Java, Java	Indonesia: 949 episodes	<5 years	NA	886/949 confirmed CAP, 15/949 bacterial CAP	NA
Ministry of Health Republic of Indonesia 2009	2008	Cross sectional	NA	20,887,256	< 5 years	1.88% (392,923/20,887,256)	NA	NA
Ministry of Health Republic of Indonesia 2010	2009	Cross sectional	NA	17,402,735	< 5 years	2.24% (390,319/17,402,735)	NA	NA
Ministry of Health Republic of Indonesia 2011	2010	Cross sectional	NA	21,704,229	< 5 years	2.30% (499,259/21,704,229)	NA	NA
Ministry of Health Republic of Indonesia 2012	2011	Cross sectional	NA	23,315,846	< 5 years	2.39% (559,114/23,315,846)	NA	0.11% (609/559,114)
Ministry of Health Republic of Indonesia 2013	2012	Cross sectional	NA	23,471,733	< 5 years	2.34% (549,708/23,471,733)	NA	0.11% (609/549,708)
Ministry of Health Republic of Indonesia 2014	2013	Cross sectional	NA	23,366,598	< 5 years	2.44% (571,547/23,366,598)	NA	NA
Ministry of Health Republic of Indonesia 2015	2014	Cross sectional	NA	22,311,380	< 5 years	2.95% (657,490/22,311,380)	NA	0.08% (496/657,490)
Ministry of Health Republic of Indonesia 2016	2015	Cross sectional	NA	24,625,211	< 5 years	2.25% (554,650/24,625,211)	NA	0.16% (877/554,650)
Ministry of Health Republic of Indonesia 2017	2016	Cross sectional	NA	24,520,873	< 5 years	2.31% (568,146/24,520,873)	NA	0.11% (598/568,146)
Ministry of Health Republic of Indonesia 2018	2017	Cross sectional	NA	28,142,450	< 5 years	1.81% (511,434/28,142,450)	20.54 (per 1,000 children)	0.34% (1,752/511,434)
Ministry of Health Republic of Indonesia 2019	2018	Cross sectional	NA	25,190,309	< 5 years	2.00% (505,331/25,190,309)	NA	0.08% (425/505,331)
National Institute of Health Research and Development MoH Republic of Indonesia 2013	May-June 2013	Cross sectional	NA	1,027,763 household	< 5 years	4.5%	NA	NA
National Institute of Health Research and Development MoH Republic of Indonesia 2019	2018	Cross sectional	NA	300,000 household	< 5 years	4.8%	NA	NA
Purniti 2011	December 2007-January 2009	Cross sectional	Denpasar, Bali, Bali	736 patients	28 days-60 months	NA	534.2/100,000	NA

NA: Data not available (not mentioned in the publication).

Incidence

Several studies counted the incidence of LRTI. Almost all of them used different denominators: 5,000 per 100,000 discharge, 38.54-57.25 per 1,000 child-years, 82-114 per 100,000 population, 534.2 per 100,000 population, 20.54 per 1,000 children [17-19,31,33].

Case Fatality Rate (CFR)

Seven reports from the Ministry of Health of the Republic of Indonesia have CFR data of LRTI (Figure 2) [24,26,28-32]. CFR median is 0.11% (min 0.08%-max 0.34%). Similar CFR results (0-4%) are reported by Azmi et al [17].

Figure 2. Prevalence and case fatality rate (CFR) of LRTI in children under five years of age in Indonesia, data from the Ministry of Health of the Republic of Indonesia.

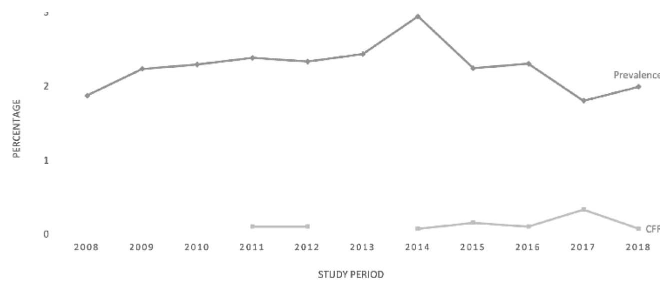


Table 2. Summary table of studies reporting etiology of lower respiratory tract infection.

Reference	Study period	Research method	Setting	Study Location (City, Province, Island)	Sample size	Age group	Etiology (number of isolates)	Laboratory method of identification
Agustiningsih 2012	July 2008-June 2009	Cross sectional	Hospital (not specified)	Jakarta, Special Capital Region, Java	62 children <5 years from 230 patients	Children (<15 years of age) and adults (>15 years old)	*K. pneumoniae* (15), *S. pneumoniae* (9), Influenza A (3), mixed virus-bacteria (21), mixed bacteria-bacteria (16)	Multiplex PCR (Seeplex®), real time PCR
Indawati 2014	January- October 2010	Cross sectional	Hospital (not specified) and primary health center	Jakarta, Special Capital Region, Java	105 children 0-5 years from total 167 patients	0-5 years and 6-14 years	Influenza A (2), Influenza B (12)	Rapid test (BinaxNOW™ Influenza A and B Test)
Nataprawira 2015	Data from October 2008-December 2014	Cross sectional	Hospital (not specified)	Bandung, West Java, Java	63 patients	0-50 months	*B. pertussis* (2)	culture
Prawira 2012	Medical record form September 2005-August 2010	Cross sectional	Hospital (not specified)	Jakarta, Special Capital Region, Java	3 children <5 years from total 26 participants	Children (0-18 years) and adults (>18 years)	H5N1 (3)	PCR
Sari 2017	Laboratory record January 2014-December 2015	Cross sectional	Hospital (NICU)	NA, Central Java, Java	225 patients	neonates	*K. pneumoniae* (49)	NA
Simoes 2011	February 1999-Febryary 2001	Cross sectional	Primary health center	Bandung, West Java, Java	2,014	< 5 years	RSV (163)	Abbott Test Pak, real time reverse transcription PCR
Susilarini 2018	May 2013-April 2016	Cross sectional	Hospital (not specified)	Gunung Kidul, Yogyakarta Special Region, Java; Balikpapan, East Kalimantan, Kalimantan; Deli Serdang, North Sumatera, Sumatera	911 children from total 1,527 patients	Children (0- 4 years), other 5->70 years	Influenza virus (114)	Real time reverse transcription PCR
Yuliarti 2012	June 2008-December 2009	Cross sectional	Hospital (not specified)	Jakarta, Special Capital Region, Java	205 patients	28 days to 60 months	*S. pneumoniae* (1)	Conventional biochemical test
Widoretno 2012	March- December 2008	Cross sectional	Hospital (not specified)	Jakarta, Special Capital Region, Java; Bandung, West Java, Java; Semarang, Central Java, Java; Makassar, South Sulawesi, Sulawesi; Kupang, East Nusa Tenggara, Timor; Tangerang, Banten, Java	215 throat specimens from 350 patients	< 5 years	Influenza A (4), RSV (20), Adenovirus (1), Bocavirus (2), Coronavirus (2), Metapneumo virus (2), Parainfluenza virus (6), Rhinovirus (10), Coxsackie-Entero virus (19), Entero-Rhino virus (10), Coxsackie-Entero-Rhino virus (3), Entero-Adeno virus (1), Entero virus-RSV (4), RSV-Corona virus (1), RSV-Enterovirus-Rhinovirus (4)	Multiplex Bead Array Assay ResPlex II v.2, Luminex®
Setyati 2012	Medical records January-June 2011	Cross sectional	Hospital (PICU)	Yogyakarta, Yogyakarta Special Region, Java	95 bacterial isolates	Children (<1 and ≥ 1 year)	*Klebsiella pneumoniae* (15)	NA
Gatera 2014	Medical record January 2011-December 2012	Cross sectional	Hospital (not specified)	Bandung, West Java, Java	24 bacterial isolates	1-5 years	*Klebsiella pneumoniae* (7), *Streptococcus pneumoniae* (9)	NA
Purniti 2011	December 2007-January 2009	Cross sectional	Hospital (not specified)	Denpasar, Bali, Bali	736 patients	28 days- 60 months	*Klebsiella pneumoniae* (1)	NA

NA: Data not available (not mentioned in the publication); NICU: Neonatal Intensive Care Unit; PICU: Pediatric Intensive Care Unit.

Etiology

Twelve studies described the etiology of LRTI in children under five years of age in Indonesia (Table 2) [18,19,33,35-43]. The studies were conducted in different settings (hospital based and/ or primary health care based). In addition, different laboratory method of identification was used. Five studies focused on viral pathogens, while six studies focused on bacteria as the main pathogen [18,19,36,38,41]. Only one study described both bacterial and viral [35]. Figure 3 shows the location and indicates the sample size of the different studies reporting on etiology of lower respiratory tract infection in children under five years of age in Indonesia.

Viral

Based on the number of studies and the number of cases described in the separate studies, influenza virus was the most common cause of viral respiratory tract infections in children under five years of age in Indonesia. Other viruses prevalent in this age group and mentioned in the different studies were respiratory syncytial virus, coxsackievirus, enterovirus, coronavirus, adenovirus, parainfluenza virus, bocavirus, rhinovirus, and human metapneumovirus [35,41].

Influenza Virus

Data regarding influenza virus infections in Indonesian children were found in five different studies [19,35,36,38,41]. Influenza A virus was the most commonly reported type. The studies identified not only H1 and H3 subtypes but also H5 [19,35,38,41]. One study conducted in an infectious disease hospital in Jakarta analyzed the clinical, laboratory, and radiologic characteristics of confirmed avian influenza (H5N1) cases. There were three patients under five years of age from all thirteen children. Two out of three died. The main clinical conditions were fever, productive cough, and dyspnea. The cause of death was acute respiratory distress syndrome [38]. Another study, also conducted in Jakarta, found influenza B in twelve patients among 167 children age 0-14 years diagnosed with influenza-like-illness and pneumonia [36].

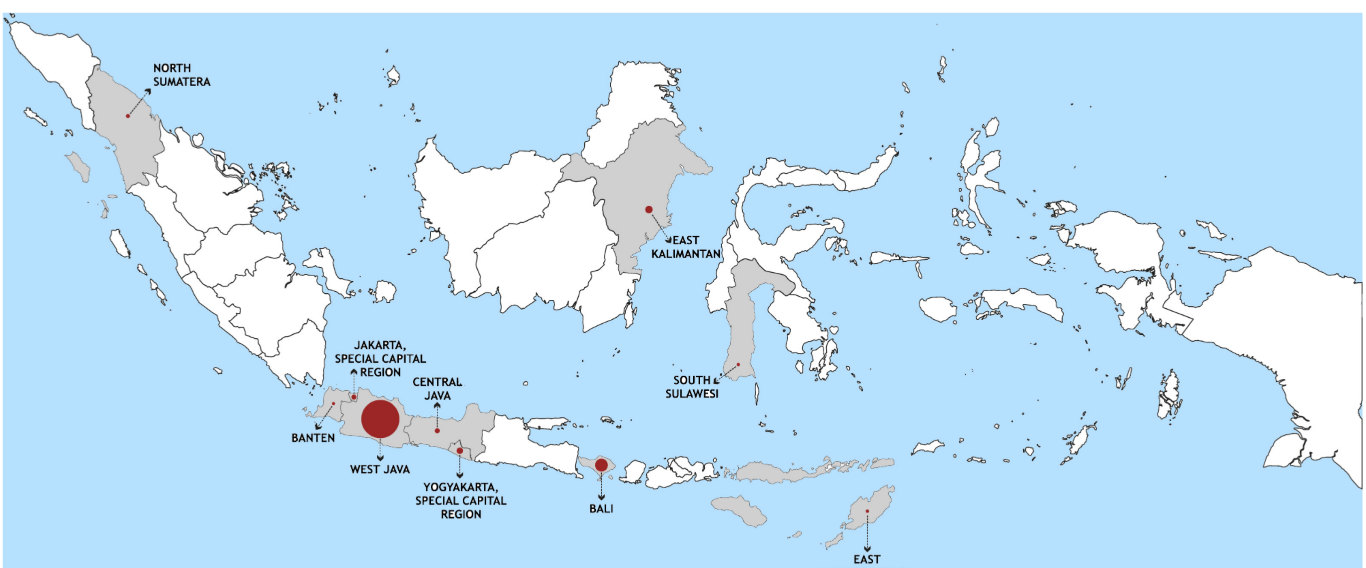
RSV

Two studies identified RSV as the causative agent of LRTI [18,41]. One large study in Bandung, West Java, consist of 2,014 participants under five years of age, revealed that in Indonesia, the incidence of LRTI due to RSV was relatively low. No RSV found as the etiology of LRTI in children under two months of age [18].

Bacterial

All studies that reported bacteria as the cause of LRTI in children under five years of age in Indonesia were hospital-based. All studies were conducted in Java Island, except two studies located in Bali and Sumatera [33,43].

Figure 3. Location and representation of total sample size of studies reporting etiology of lower respiratory tract infection.



West Java 2171, Bali 736, East Kalimantan 417, Jakarta 396, Yogyakarta 356, Central Java 276, North Sumatera 221, South Sulawesi 42, East Nusa Tenggara 13, Banten 8.

K. pneumoniae

K. pneumoniae was the most commonly reported bacterial pathogens [33,35,39,42,43] *K. pneumoniae* isolate was found in the blood of children with respiratory complaints [33,42,43], the tracheal aspirate [35,42], nasal-nasopharyngeal swab, and bronchoalveolar lavage [35].

S. pneumoniae

Only three out of twelve studies identified *S. pneumoniae,* 19 cases in total [35,40,43]. Two studies identified it from a blood culture sample (see *Invasive Disease*). The third study used multiplex PCR to detect *S. pneumoniae* among hospitalized-suspected H5N1 patients. In this study, the prevalence of *S. pneumoniae* co-occurring or co-infecting with *H. influenzae* and *K. pneumoniae* was higher than a single infection with *S. pneumoniae* [35].

B. pertussis

One study retrospectively identified *B. pertussis* associated with pertussis-like symptoms in sixty-one probable and two confirmed cases. All patients were in the paroxysmal phase when they came to the hospital; thus, only a limited number of *B. pertussis* could be detected. Seventy-nine percent of the case was at the age of 0-5 months. Only two patients had a history of pertussis vaccination. No fatality found. Unfortunately, household contacts could not be screened, and no other information related to a possible outbreak was reported [37].

Viral-bacterial co-infection

One study conducted in Jakarta aimed to find the etiology of lower respiratory tract infection in 108 children and 122 adults. The authors reported polymicrobial infections, both viral and bacterial pathogens, as measured in the nasal swab, throat swab, tracheal aspirates, and bronchoalveolar lavage. From this study, it was concluded that bacterial-viral co-infection, in particular *K. pneumoniae* and Influenza A, was the most common cause, followed by bacterial co-infection (*S. pneumoniae* and *H. influenzae*) [35].

Bacterial carriage

Studies focused on the bacterial carriage in the upper respiratory tract of children under five years of age were done in Java, Lombok, and Sumatera island (Table 3) [8-12,44-47]. Figure 4 shows the location and indicates the sample size of the different studies reporting on bacterial carriage in children under five years of age in Indonesia.

S. pneumoniae

Eight studies reported *S. pneumoniae* carriage [8-12,44,45,47]. The lowest rate in healthy children from two to twelve months old was 22%. The same study showed that the prevalence could increase to 68.4% in

Table 3. Summary table of studies reporting bacterial carriage.

Reference	Study period	Research method	Study Location (Region, Province, Island)	Sample size	Age group	Carrier, carriage rate	Laboratory method of identification
Dunne 2018	February- March 2016	Cross sectional	Bandung, West Java, Java; Central Lombok, West Nusa Tenggara, Lombok; Padang, West Sumatera, Sumatera	302 healthy children	12-24 months	*S. pneumoniae* (49.5%), *H. influenzae* (27.5%), *M. catarrhalis* (42.7%), *S. aureus* (7.3%)	qPCR
Fadlyana 2018	NA	Cross sectional	Bandung, West Java, Java; Lombok, West Nusa Tenggara, Lombok; Padang, West Sumatera, Sumatera	302 healthy children	12-24 months	*S. pneumoniae* (Padang:34.6%, Bandung:64.0%, Lombok:50.5%), *M. catarrhalis* (Padang: 31.7%, Bandung:45.0%, Lombok 51.5%),	qPCR; FTD Bacterial pneumoniae CAP qPCR kit, Fast Tract Diagnostic
Farida 2013	February- April 2010	Cross sectional	Semarang, Central Java, Java	243 healthy children, 253 healthy adults	Children (6-60 months) and adults	*K. pneumoniae* (7%), *S. pneumoniae* (43%), other Gram-Negative Bacteria (20%)	VITEK® 2, optochin test
Farida 2014	February- April 2010	Cross sectional	Semarang, Central Java, Java	243 healthy children, 253 healthy adults	Children (6-60 months) and adults	*S. pneumoniae* (43%)	Optochin test, DNA hybridization
Hadinegoro 2016	2012	Cross sectional	Central Lombok, West Nusa Tenggara, Lombok	1,200 healthy children	2 to 60 months	*S. pneumoniae* (46%)	Optochin test
Murad 2019	November 2014- January 2015	Cohort	Bandung, West Java, Java	200 healthy infants	2 months (follow up until 12 months)	*S. pneumoniae* (22% at 2 months and 68.4% at 12 months of age)	qPCR
Safari 2014	January- July 2012	Cross sectional	Jakarta, Special Capital Region, Java	90 HIV patients	4-144 months	*S. pneumoniae* (46%)	PCR
Hatmaningtyas 2013	May- June 2013	Cross sectional	Semarang, Central Java, Java	174	6-60 months	*K. pneumoniae* (0-2.9%)	Biochemical test
Hikmawati 2010	February- March 2010	Cross sectional	Semarang, Central Java, Java	75 children from total 150 participants	Children (0-5 years) and adults (45-70 year)	*S. pneumoniae* (45.3%), *H. influenzae* (12%), *Enterobacteriaceae* (10.7%), *S. aureus* (6.7%), *M. catarrhalis* (5.3%)	Biochemical test

NA: Data not available (not mentioned in the publication).

children of 12 months or older [45]. Serotype data was found in five studies [9-12,45]. The PCV 13 serotype carriage rate was 9.1 to 35.1% [45]. Three other studies in children from two to sixty months of age reported a PCV 13 coverage of 45%, 56%, and 60% [10-12]. Three of the five studies found 6 A/B serotype as the most prevalent serotype in Indonesian children [10,12,45]. Other serotypes that were frequently found in all five studies were vaccine types 19F and 23F and non-vaccine types 2 and 15B/C [9-12,45].

H. influenzae

H. influenzae carriage rates ranged from 12% up to 32.9% in two studies [9,47]. One of these studies serotyped *H. influenzae* isolate, and none of the 83 isolates was *H. influenzae* type B, which reflects the effect of the Hib vaccine on a carriage [9].

M. catarrhalis

One study in Semarang, Central Java, reports the carriage rate of *M. catarrhalis* from children under five years of age at 5.3%. The prevalence of *M. catarrhalis* from healthy children aged 12-24 months in Lombok, West Nusa Tenggara, was ten times higher than Semarang, approximately, making it the highest also compared to Bandung and Padang, West Sumatra [9,44,47].

S. aureus

S. aureus prevalence was the lowest compared to *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. The prevalence was between 6.7% until approximately 9.0%. *S. aureus* had the same prevalence in Bandung as in Central Lombok (around 8.0%) [9,47].

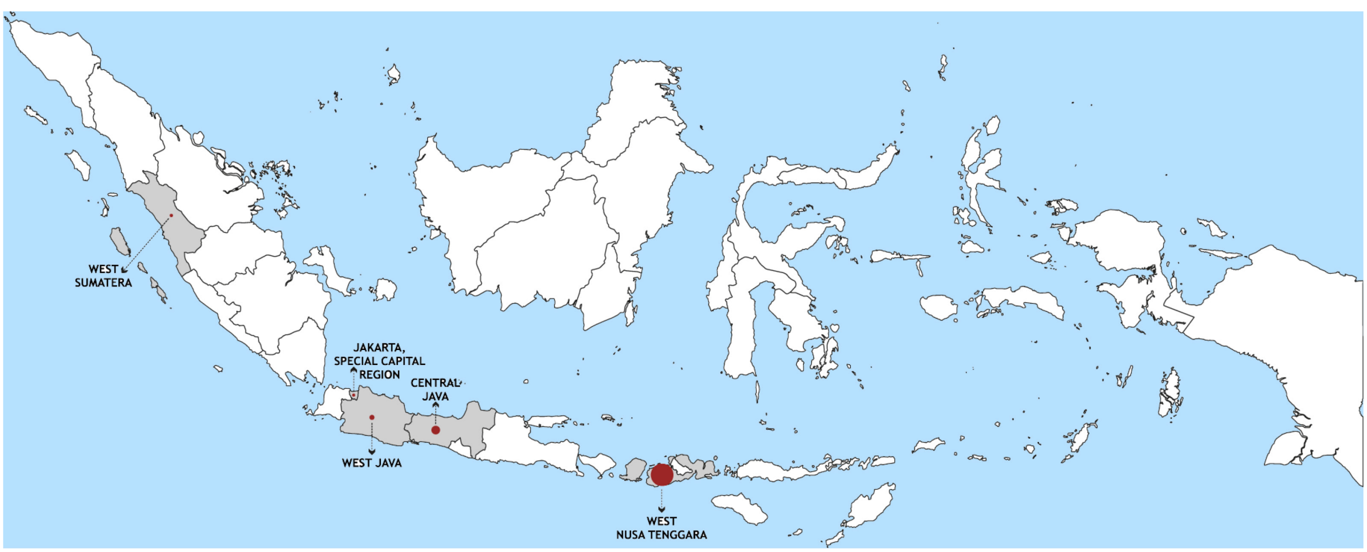
Other bacterial pathogens identified in carriage studies

Semarang was the only place where *K. pneumoniae, Pseudomonas spp. and A. baumannii* comp. were identified in asymptomatic carriers. The range of carriage rates of *K. pneumoniae* varied from 2.9% to 7.0% [8,46]. *Pseudomonas* spp. and *A. baumannii* comp. were found in 7% and 5% of the carriers, respectively [8].

Invasive Disease

Three studies located in Denpasar, Bandung, and Jakarta showed the burden of invasive pneumococcal disease (IPD) in Indonesia [33,40,43]. Two studies directly aimed to measure the burden of invasive pneumococcal disease [33,40]. No pneumococci were detected in the 736 IPD and pneumonia patients in Denpasar [33]. A study in Bandung found nine pneumococcal isolates in blood cultures from 486 patients with pneumonia [43]. A study in Jakarta found one IPD case from 205 patients diagnosed with pneumonia, meningitis, sepsis, and suspected occult bacteremia. The IPD patient was a three-month-old baby boy infected with *S. pneumoniae* serotype 7F, had bilateral lobar pneumonia and meningitis and died on the fifth day of hospitalization because of respiratory failure [40].

Figure 4. Location and representation of total sample size of studies reporting bacterial carriage.



West Nusa Tenggara 1301, Central Java 492, West Java 300, West Sumatera 101, Jakarta 90.

Discussion

The objective of this study was to collect all available data to have a complete overview of the current status of the burden and etiology of LRTI in children under five years of age in Indonesia. Furthermore, we obtained all available information about asymptomatic carriage of well-known LRTI pathogens and about invasive infections associated with respiratory complaints in this population, which are strongly related to LRTI and therefore important to include in this review.

The median CFR of LRTI in children under five years of age in Indonesia from 2011-2018 was 0.11% as reported by the Ministry of Health of the Republic of Indonesia [21-24,26-32]. This is relatively low as compared to other countries such as Malawi (6.6%) and India (8.2%) [48,49].

We found that the influenza virus was the most commonly reported viral cause of LRTI in children under five years of age in Indonesia. Although this result differs from other studies performed in other populations, which found that RSV is most common in children under five years of age [50-52]. *K. pneumoniae* was the most commonly reported bacterial cause of LRTI. This has earlier been found in other populations, as reported in a study conducted in China [53].

In healthy asymptomatic Indonesian children under five years of age, not vaccinated with a pneumococcal vaccine, *S. pneumoniae* had the highest prevalence rate. The highest carrier rate reported was 68.4% [45]. These data are in line with a previous study in Thailand, showing a carriage rate of 67.6–83.6% [54]. Although we noticed substantial carriage rates with *S. pneumoniae* in healthy children under five years of age in Indonesia, it is not the most commonly identified bacterial cause of LRTI in children under five years of age in Indonesia. This is likely an underrepresentation due to the use of insensitive diagnostic methods. Interestingly *K. pneumoniae,* the most commonly reported cause of LRTI, is also found in asymptomatic carriers in Indonesia. It is speculated that this is due to the consumption of contaminated food and water [8]. The coverage of vaccine serotypes (based on PCV13) was between 45-60%. A similar conclusion was reached from a study reporting prevalence of *S. pneumoniae* in South East Asia, in which a coverage of 65% was found [55].

Unfortunately, there is a lack of information regarding the incidence of LRTI-related invasive disease in children under five years of age in Indonesia. Therefore no conclusions can be drawn based on the available literature. This strongly demands for more studies identifying the etiology of LRTI-related invasive disease.

Although we only included a total of 36 English and Indonesian articles, we are confident that this is all relevant literature available at this moment. Reviewing this literature gives a better understanding of what is known about the burden and etiology of LRTI in children in Indonesia. However, at the same time we have to conclude that there is an important lack of information regarding the burden and etiology of LRTI, especially because most studies are done in certain regions of Java, while there is hardly any information available from other regions. Based on this review we recommend to improve the diagnostics of respiratory tract infections in children in Indonesia and to enhance the capacity of infectious disease surveillance, in particular in other provinces than Jakarta, West and Central Java.

Conclusions

Surveillance and diagnostic studies are urgently needed and should be conducted in different parts of Indonesia to improve insight in the burden and etiology of LRTI in Indonesia. These data are pivotal to increase the effectiveness of public health strategies, including vaccination and prevention of antimicrobial resistance.

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