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SYSTEMATIC REVIEW

Bacterial etiology of pneumonia in children up to 2 months of age: a systematic review

[version 1; peer review: 2 approved with reservations]

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Abstract

Background: Following the widespread introduction of childhood pneumococcal conjugate vaccines (PCVs), a significant impact on pneumonia mortality in children under five years of age has been reported. It is still unknown whether PCVs are expected to reduce pneumonia burden in younger children, particularly ≤2 months of age, as current evidence on the role of *S. pneumoniae* in pneumonia etiology in this age group is scarce. We aimed to summarize the evidence of bacterial etiology of pneumonia in children ≤2 months of age.

Methods: We conducted a systematic review considering studies evaluating a variety of syndromes associated with pneumonia, and reporting on laboratory confirmed etiologies, considering any diagnostic method and a variety of clinical specimens. We searched Medline/PubMed, Embase, WoS, Central and Index Medicus Global published in any language till April 30th, 2021. We included studies addressing the outcomes of interest in children ≤2 months of age and reporting on clinical trials, observational studies, and case series with at least 10 events. Screening of citations and data extraction were conducted in duplicate by independent reviewers, according to the study protocol registered on PROSPERO. Descriptive analyses of the various etiologic agents by syndrome are reported.

Results: We identified 3,744 citations, of which 22 publications reporting on 13 studies were included. Study methods varied significantly. Nonetheless, gram positive organisms, in particular *S. pneumoniae*, were identified as important etiologic agents of

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pneumonia in children ≤2 months of age. Viral etiologies, in particular Respiratory Syncytial Virus, Rhinovirus, and Influenza were also identified.

Conclusions: This review provides the most comprehensive analysis to date of the etiologies of pneumonia in children ≤2 months of age, suggesting that PCV impact is expected to occur in this age group. These results also have major implications for diagnosis and treatment of pneumonia in this age group.

Keywords

Systematic Review, pneumonia etiology, bacterial pneumonia, children

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Introduction

Globally, pneumococcal infections, caused by Streptococcus pneumoniae (Pneumococcus), are one of the leading causes of morbidity and mortality in children <5 years of age[1]. A variety of clinical syndromes of varying severity are associated with pneumococcus, including pneumonia, meningitis, bacteremia, otitis media and sinusitis[2]. It has been estimated that prior to the introduction of pneumococcal conjugate vaccines (PCVs), diseases caused by pneumococcus were responsible for approximately 600,000 deaths per year globally in children 1-59 months of age[3].

Pneumonia is among the leading causes of mortality in children under 5 years of age[1,4]. The main causative pathogens attributable to pneumonia include Streptococcus pneumoniae, *Haemophilus influenzae* type B, all of which have vaccine-preventable bacterial causes, and respiratory syncytial virus[5]. Infants and young children are at highest risk for serious disease[6], with children younger than 4 months being more likely to die[7]. In addition to pneumococcus, a variety of other infectious agents are related to pneumonia in children.

In the last two decades, more than 140 countries globally have introduced PCVs into national routine immunization schedules. Several studies have demonstrated the impact of PCVs on reducing invasive pneumococcal diseases and hospitalizations due to pneumonias[2,8,9]. However, pneumonia mortality is the greatest concern for policymakers and donors, and there is limited evidence on the impact of PCVs on pneumonia deaths in children.

Recent evidence from countries in Latin American using secondary mortality data demonstrated the impact of PCVs on pneumonia mortality in children under 5 years of age[10–13]. Most studies did not include children <3 months of age assuming that perinatal causes of mortality and other etiologic agents and not pneumococcal disease are responsible for the pneumonia mortality in this age group. Nonetheless, this assumption is not fully backed up by the very little available evidence in the literature on the etiology of pneumonia in this age group. Although selected studies have indicated that respiratory viruses are the most common pathogens of pneumonia in infants and toddlers, some investigators have implicated pneumococcus and *Haemophilus* in 4–20% of cases. These findings vary significantly in developing versus industrialized countries, over time, and depending on laboratory methods used to assess etiologies.

It is still not clear whether pneumococcus is a significant cause of pneumonia in younger children, particularly neonates and children <3 months of age. Whether or not to include children in this age group in impact assessment studies will depend on evidence suggesting whether pneumococcus is a significant etiology of pneumonia and thus an important burden in children under 3 months of age.

This systematic review aims at summarizing the evidence of the bacterial etiology of respiratory infections in children under 3 months of age, in particular the role of pneumococcus as a significant etiology in this age group.

Methods

The study protocol was published in PROSPERO under registration number CRD42020158091. We followed PRISMA recommendations[14], and a completed PRISMA checklist is provided as extended data[15].

Literature search

A systematic literature review was performed to identify all available data from published studies on the etiology of bacterial pneumonia in children younger than 3 months of age. Electronic searches were conducted in the following databases: Medline/PubMed, Embase, Central and Index Medicus Global (including Lilacs-Latin America and Caribbean, Regional Index Medicus (IM), including IM Western Pacific (WPRIM), IM Africa (AIM), IM South-East Asia (IMSEAR) and IM East Mediterranean (IMEMR). A complementary search was conducted in the electronic library SciELO and in Scholar. Additionally, references of selected articles and reviews were screened. No date, location, or language limits were placed on the searches of publications through April 30th, 2021. Detailed search strategies for each database are presented in the extended data[15].

Inclusion criteria

Studies reporting primary data about respiratory infections or invasive bacterial disease/sepsis secondary to pneumonia in children under 3 months of age of both sexes, regardless of any co-morbidity, were considered. We included studies that reported on the following syndromes as disease outcomes: bacterial pneumonia, pneumonia (clinical or X-ray confirmed) pneumonitis/bronchitis, Acute respiratory illness (ARI), pulmonary complications, deaths due to pneumonia, respiratory infections, severe or hospitalized pneumonia, community acquired pneumonia (CAP), para-pneumonic pleural effusion (PPE) and/or bloodstream infection/sepsis secondary to pneumonia.

Any etiologies assessed by laboratory, considering any diagnostic method and a variety of clinical specimens were incorporated.

We included citations reporting on primary studies in which the etiology of bacterial pneumonia or invasive bacterial disease secondary to bacterial pneumonia is assessed, including mostly observational studies (descriptive studies, case series, case-control, cohort and cross-sectional studies), but also randomized controlled trials (RCTs). Case series were included only if at least 10 cases are reported in the target age-group.

Exclusion criteria

We excluded studies which did not report or did not provide data for the specific age subgroup of our interest, studies which did not report on laboratory confirmed etiology for the outcome of interest, and studies that reported on infections secondary to other non-respiratory primary focus (or which primary focus was unknown).

Case reports, guidelines/recommendations, letters and reviews were excluded. Also, laboratory studies in which the clinical syndrome is not described, and case series with less than 10 events are reported were excluded.

Studies evaluating etiology of the following syndromes/diagnosis were excluded: hospital-acquired pneumonia, necrotizing pneumonia, aspirative pneumonia, pneumocystosis, interstitial pneumonia, influenza like illness, and bronchiolitis. Also, studies evaluating an outbreak of group of cases with a specific etiologic agent already defined (ii.e. adenovirus outbreak) were also excluded. Finally, studies evaluating laboratory samples (not children with clinical syndromes) and carriage studies were excluded.

Study selections

Citations retrieved in bibliographic searches were uploaded in EndNote 20 reference manager, and deduplication were performed. Remaining citations were screened by four independent reviewers (CT, MQ, MTV, MSM) in the first step, where titles and abstracts were reviewed for inclusion criteria. Screened articles were categorized as potentially eligible, unclear, or excluded. Citations on which the pair of reviewers disagreed were discussed or assessed by a third reviewer. Full text of papers meeting inclusion criteria and those unclear were obtained. In the second step, full texts were read and assessed for information on whether they meet inclusion criteria by four reviewers (CT, MQ, MTV, MTCO) and disagreements were resolved by discussion. In this step articles were categorized as included, excluded, or uncertain. Studies were categorized as uncertain when through full review we were not able to extract the information on etiologic agents of pneumonia for the specific ≤2 month of interest, because reported results were aggregated in larger age groups. For these cases, we contacted the authors of all original studies which were published in or after 2015. The rationale was that for more recent studies, the authors might have information on etiologies for the specific age subgroup of interest, even though these were not depicted in the publication. After receiving author's response, if data were obtained, articles were included but if authors didn't answer or didn't have the data, articles were excluded. One additional round of deep full text analysis was done with the complete list of selected studies resulting in new exclusions according to inclusion criteria.

Data extraction

Data extraction was done by five independent reviewers (CT, MQ, MTV, MSM, MTCO), using abstraction forms developed specifically for this systematic review.

To avoid multiple counting of reports from the same study, citations from the same study group on data originated from the same study protocol, population or information system were grouped for extraction, and reported as a single study.

Data extracted included: country; year of publication; study design; study period; sample size; demographic information (average age, sex, ethnicity); diagnostic criteria; laboratory method for diagnosis and etiologic agent; laboratory specimen considered for diagnosis; outcome definition; secondary outcomes; availability of data for ≤2 months of age; number of study subjects; number and proportion of etiologic agents by each group of etiologies.

Study risk of bias assessment

Quality assessment of studies included in the review was conducted using the JBI critical appraisal checklist for cross-sectional, case-control, cohort, prevalence, and case series studies.

Data analysis

A descriptive analysis of study characteristics including study design, respiratory syndromes/outcomes considered, biological specimen evaluated, and laboratory method used for etiologic confirmation was conducted. For all studies, the main measure of interest was the etiologic agents identified. Descriptive data on the etiologies of respiratory infections in children under 3 months of age was analyzed and are presented as percentages. As a variety of syndromes, biological specimens, and laboratory diagnostic methods were reported in the various studies, we present the results stratified by diagnostic method.

Results

A total of 4,313 studies were retrieved in searches. After eliminating duplicates, a total of 3,744 references were screened by title and abstract review. Out of the 602 selected citations, a further 580 were excluded in two rounds of review, with 22 remaining papers eligible for data extraction reporting on 13 studies included in this review (Figure 1). A complete list of reasons for excluding studies as well as references are provided in the extended data. Out of correspondences to authors of 54 studies, 16 responses were received, but new data was obtained for only 9 studies, which are included in 22 selected papers. Detailed list of included papers by database can be found in the extended data[15].

13 (n=13) studies were considered in this review (Table 1). Studies range over four decades (1980-2020), present different study designs, and consider a wide variation of number of children enrolled and assessed. Despite target age group being younger than 3 months of age, two studies evaluated only neonates aged ≤28 days, while some studies evaluated children <3 months including neonates and others excluded neonates from the study, thus including only children >28 days to <3 months.

While one study only assessed viral etiologies[16], three studies evaluated only bacterial etiologies[17–20]. Most studies report on blood (n=12) and nasopharyngeal swabs/aspirates or nasal washing (n=8), although some studies also collected other specimens, including cerebrospinal fluid (CSF), urine, broncho-alveolar lavage (BAL), pleural effusion and lung biopsies. Added to this variability of samples available and tests conducted, there were varying methods used and for etiologic diagnosis, with most studies reporting cultures, but some also using serology and antigen testing for viral infections. Most recent studies[16,21–33] included molecular techniques, with known increased sensitivity

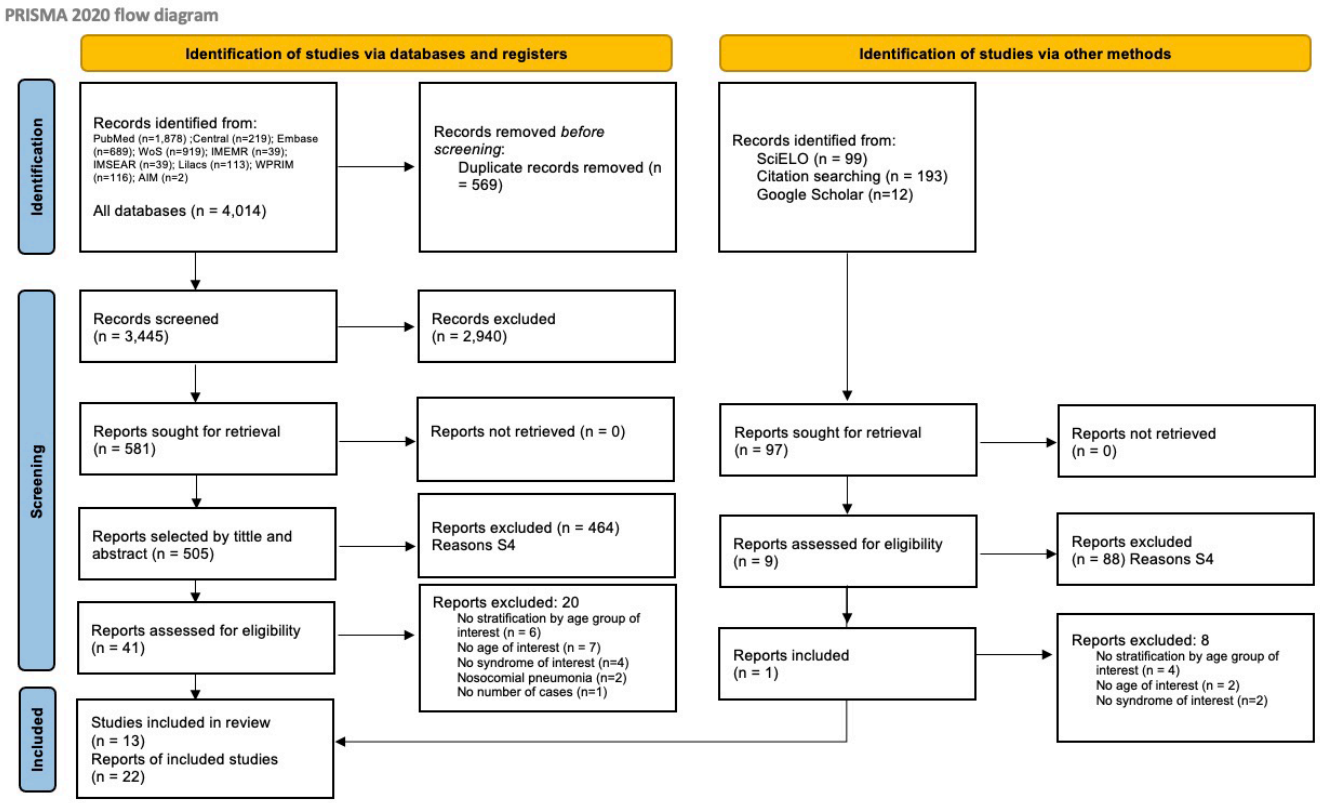

Figure 1. PRISMA Flow diagram: process of study selection.

(i.e., ability to detect pathogens) to identify many etiologic agents. The variety of study designs and methods used in the studies made it inappropriate to conduct a meta-analysis.

Etiologies identified by each study have, as expected, varied greatly considering study characteristics and methods as described above. In Table 2 below, main study characteristics and etiologic agents identified are presented (Table 2).

The only study conducted in the 1980s[34] in India, evaluated only neonates up to 28 days. This study of 44 neonates reports no *Streptococcus agalactiae* as an aetiologic agent of neonatal pneumonia, but rather demonstrates a high proportion of *S. pneumoniae* (22.4%) (using antigen testing), and Gram-negative agents (25%).

A multinational World Health Organization (WHO) study in three countries to assess etiology of severe disease in children < 3 months of age, considering also but not restricted to pneumonia, was conducted from 1991 to 1993[35]. This study is reported in different papers, one of which describes results in all countries combined[35], and country specific results, namely Ethiopia[36] and Papua New Guinea[37,38], as there are some variations in methods in each study site. This was the largest prospective study of early infant infections in developing countries, and it also reported on the absence of *Streptococcus agalactiae* and the importance of Gram-positive (61%) and Gram-negative (24%) organisms among the 167 positive blood cultures with isolates identified. Among these, *S. pneumoniae, S. aureus* and *S. pyogenes* (Gram-positives), and *E. coli* and *Salmonella* (Gram-negatives) are the most noteworthy. Viral etiologies were also important pneumonia agents, as reported in Ethiopia[36].

A retrospective laboratory-based surveillance study including children with bacterial invasive disease was conducted in Korea, and two papers report on different study periods, from 1996-2005[18], and from 2006-2010[19]. This study only considered bacterial etiologies from blood, PPE, CSF, and here *S. agalactiae* is frequently isolated in both study periods.

Another study evaluating only neonates up to 28 days of age in China from 2006-2008[20] also demonstrated a significant proportion of Gram-negative agents in children hospitalized with community acquired pneumonia, mostly *K. pneumonia* and *E. Coli.*

One study evaluated viral etiologies of hospitalized children with respiratory infections only[16]. Children aged up to 28 days were excluded, so only children aged over 28 days and under 3 months of age were considered. Molecular methods were used to assess etiologies in nasopharyngeal aspirates (NPA) (no other specimen was obtained and evaluated). A high proportion of respiratory syncytial virus (RSV) was observed in children with positive isolates.

Table 1. Summary of characteristics from 13 included studies.

Characteristics	n	%
Study period		
1980-2000	5	38.5%
2000-2010	3	23.0%
2010-2020	5	38.5%
Study design		
Prospective cohort	7	53.8%
Case control	1	7.7%
Retrospective cohort	3	23.1%
Case series	1	7.7%
Cross-sectional	1	7.7%
Sample size		
10 – 49 children	8	61.5%
50 – 150 children	1	7.7%
150 children and over	4	30.8%
Age groups		
Only neonates (≤28 days)	2	15.4%
<3 months (including neonates)	5	38.5%
>28 days to <3 months	6	46.2%
Clinical syndromes considered		
Hospitalized community acquired pneumonia	7	53.8%
Acute Respiratory illness (ARI)	1	7.7%
Sepsis secondary to pneumonia	5	38.5%
Biological specimen*		
Blood	12	92.3%
Nasal/throat swabs	8	61.5%
Broncho-alveolar lavage (BAL)	1	7.7%
Pleural effusion/aspirate	3	23.1%
Lung biopsy	1	7.7%
Urine	3	23.1%
Cerebrospinal fluid (CSF)	5	38.5%
Etiologic groups evaluated		
Bacteria only	3	23.1%
Virus only	1	7.7%
Virus and Bacteria	9	69.2%
Diagnostic methods used*		
Culture	12	92.3%
PCR/molecular	6	46.2%
Serology	5	38.5%
Antigen tests	2	15.4%

* One study may consider more than one specimen and laboratory method

Nascimento-Carvalho *et al.*[26–29] in multiple prospective cross-sectional studies conducted in Brazil during 2003–2005 and evaluating 19 different etiologies in blood and NPA using culture, serology and PCR, report the importance of viral etiologies in children hospitalized with community acquired pneumonia. Here, children aged 28 days and younger were excluded from the study, so data presented is for children from 1 to 3 months of age.

Finally, a large WHO multinational study in seven countries to assess the etiology of severe pneumonia, using a case-control design and including hundreds of children, was conducted from 2011-2014[21,24,25,31–33]. Children aged 28 days and younger were also excluded, and various specimen types and multiple laboratory methods were used to identify viral and bacterial etiologies of severe pneumonia. Findings also reinforce the importance of viral etiologies in children aged 1–3 months, but bacterial agents, particularly *S. pneumoniae* and *S. aureus,* were also reported as relevant agents.

More recent studies have similar methods, including prospective cohort designs, the use of molecular methods, and collection of various specimens including blood and NPA at a minimum[22,23,30]. While the studies in Bhutan[23] and Bolivia[22] reported a significant proportion of viral etiologies, particularly RSV and rhinovirus, the study in Malaysia[30] reported a high proportion of Gram-positive bacterial agents, particularly *S. aureus, H. influenzae, and S. pneumoniae*, isolated or combined with viral etiologies.

The risk of bias assessment of the studies is presented in Table 3. In general, studies presented high risk of bias, particularly due to design, small number of subjects, specimens collected, and laboratory methods. Many of them were conducted in different decades, when availability and accuracy of diagnostic tools varied significantly. Very few studies included controls, namely the multinational WHO Young Infant Study Group (1999)[35], and PERCH Study[21,24,25,31–33]. Given the paucity of evidence, we opted to report on all studies, and consider their limitations and potential biases in interpreting the results.

Discussion

Pneumonia is a very frequent childhood disease leading to disease burden significantly higher in children when compared to other age groups. Several studies, many of which conducted in developing countries, have evaluated pneumonia etiologies in the past decades. Understanding pneumonia etiology is key to guiding diagnosis and management approaches to pediatric pneumonia.

It is well known that pneumonia etiology varies by age. Nonetheless, very limited evidence is available for young children, particularly children under 3 months of age. Determining the etiology of community acquired pneumonia in children, including severe disease leading to hospitalizations, is very important not only to define treatment guidelines, but also to implement preventive strategies at national level, and more recently to also assess the impact of selected interventions, as pneumococcal conjugate vaccines (PCVs) are introduced.

Table 2. Characteristics of the 13 studies included in the review and main results.

Author, year of publication	Location, study period	Type of syndrome	Age group	Specimen	Lab methods	Number of children evaluated by laboratory	Bacterial etiology (%)	Etiology results (number of chilren with laboratory confirmed etiology, by etiologic agent)
Misra, S (1991)[34]	India (1986-87)	Hospitalized community acquired pneumonia with PPE	Neonates (<28 days)	Blood and Lung Aspirates	Culture, antigen test and serology for virus and bacteria	44	22 (5.7%)	10 S. *pneumoniae* 15 Gram-negatives 02 Streptococcus 04 S. epidermidis 01 Coagulase-negative *Staphylococcus*
The WHO Young Infant Study Group (1999)[35]	Ethiopia, Papua New Guinea, Gambia, Philippines (1991-93)	Severe X-ray confirmed community acquired pneumonia and/or sepsis	<3 months	Blood, urine, NPA and CSF	Culture, viral immunofluorescence for virus and bacteria	2,452 children with blood cultures	167 positive blood cultures	33 *S. pneumoniae* 34 S. aureus 29 S. pyogenes 02 Streptococcus group B 02 Streptococcus groups D/E/F 02 Streptococcus group G 17 *H. influenzae* 41 Gram-negatives
Muhe, L (1999)[36]	Ethiopia (1991-93)	Severe X-ray confirmed community acquired pneumonia and/or sepsis	<3 months	Blood, NPA and CSF	Culture, viral immunofluorescence for virus and bacteria	405 of which 202 NPA for viral etiologies and C. trachomatis	13 pneumonia and 31 sepsis by culture	**Pneumonia (n=13)** 05 S. pneumoniae 03 H. *influenzae* 09 *S. pyogenes* 05 *Salmonella spp* 10 *E. coli* 02 *S. aureus* 02 Other Gram-negatives **Sepsis (n=31)** 08 *S. pneumoniae* 02 H. influenzae 08 S. pyogenes 02 Salmonella spp 08 E. coli 02 S. aureus 01 Gram-negative **Viral Etiologies** 57/202 (28%) RSV 32/202 (16%) C. trachomatis

Author, year of publication	Location, study period	Type of syndrome	Age group	Specimen	Lab methods	Number of children evaluated by laboratory	Bacterial etiology (%)	Etiology results (number of chilren with laboratory confirmed etiology, by etiologic agent)
Lehman D (1999)[37,38]	Papua New Guinea (1991-93)	Severe X-ray confirmed community acquired pneumonia and/or sepsis	<3 months	Blood, NPA and CSF	Culture, viral immunofluorescence for virus and bacteria	845	48	13 S. pneumoniae 13 S. pyogenes 10 S. aureus 03 E.coli 03 *Enterococcus faecalis* 02 *H. influenzae* 02 *K. pneumoniae* 01 S. *agalactiae* 01 Streptococcus group G 01 Enterobacter cloacae
The PERCH Study[21,24,25,31–33]	PERCH – Kenya, Gambia, Mali, Zambia, South Africa, Thailand and Bangladesh (2011-14)	Severe X-ray confirmed community acquired pneumonia	>28 days to <3 months	Blood, NPA, urine, BAL, PE, lung aspirates, gastric aspirates	Culture, PCR, serology, Antigen tests for virus and bacteria	810 with blood cultures	349 culture positive, of which 10 bacterial	02 *S. pneumoniae* 02 *H. influenzae* 03 S. aureus 01 Salmonella spp 02 other *Enterococcus* and *Streptococcus*
Rhie, K (2018)[19]	Korea (2006-10)	Invasive bacterial infection secondary to pneumonia in hospitalized children	< 3months	Blood, PPE, CSF	Culture for bacteria only	113 with positive cultures	Only tested for bacteria	27 S. aureus 18 E. coli 55 S. agalactiae
Lee, JH (2011)[18]	Korea (1996-2005)	Invasive bacterial infection secondary to pneumonia in hospitalized children	< 3months	Blood, PPE, CSF	Culture for bacteria only	95 (in all age groups)	13 (13.7%)	07 S. aureus 02 *S. pneumoniae* 04 S. agalactiae
Wang, H (2010)[20]	China (2006-08)	Hospitalized community acquired pneumonia	Neonates (<28 days)	Blood (sample of positive sputum samples)	Culture for bacteria only	80 with positive blood cultures	Only tested for bacteria	38 K. pneumoniae 20 E. coli 16 S. aureus 06 S. epidermidis
Finianos, M (2019)[17]	Lebanon (2013-14)	Hospitalized respiratory infections	>28 days to <3 months	NPA	PCR for viruses only	25	Only tested for virus	12 RSV 05 Rhinovirus 03 Bocavirus 02 Influenza 01 Coronavirus

Author, year of publication	Location, study period	Type of syndrome	Age group	Specimen	Lab methods	Number of children evaluated by laboratory	Bacterial etiology (%)	Etiology results (number of chilren with laboratory confirmed etiology, by etiologic agent)
Nascimento-Carvalho, CM (2011, 2013, 2015, 2019)[26–29]	Brazil (2003-05)	Hospitalized community acquired pneumonia	>28 days to <3 months	Blood and throat NPA	Culture, PCR, serology for virus and bacteria	16	12 (75%)	06 C. trachomatis 01 Rhinovirus 01 Parainfluenza 03 RSV + C. trachomatis 01 RSV + S. *pneumoniae* + C. trachomatis 01 Parainfluenza + C. trachomatis 01 Enterovirus + S. *pneumoniae* + C. trachomatis 01 Rhinovirus + human metapneumovirus
Jullien, S (2020)[23]	Bhutan (2017-18)	Hospitalized X-ray confirmed community acquired pneumonia	>28 days to <3 months	Blood and NP washing	Culture, PCR, Antigen tests for virus and bacteria	13 (12 with culture and 9 with NP washing)	1 (8%)	03 RSV 02 Rhinovirus 01 RSV + Rhinovirus 01 Parainfluenza + Rhinovirus
Nathan, AM (2020)[30]	Malaysia (2014-16)	Severe X-ray confirmed community acquired pneumonia	>28 days to <3 months	Blood and induced sputum	Culture, PCR, and immunofluorescence for virus and bacteria	45	24 (48%)	08 S. aureus 06 H. *influenzae* 02 S. pneumoniae 02 S. *pneumoniae* + rhinovirus 02 S. aureus + rhinovirus 02 *S. a*ureus + RSV 01 H. influenzae + rhinovirus 01 H. *influenzae* + RSV 02 Rhinovirus 02 Metapneumovirus 01 Bocavirus 01 RSV 01 Influenza A
Gareca Perales, J (2021)[22]	Bolivia (2016-17)	Hospitalized community acquired pneumonia	>28 days to <3 months	Blood and nasal washing	Culture and PCR for virus and bacteria	47	5 (11%)	12 RSV 05 RSV + Rhinovirus 04 Rhinovirus 02 Influenza 02 B. pertussis 02 S. aureus 01 *S.* pneumoniae 01 CMV 01 Enterovirus

ALRI – acute lower respiratory illness, NPE – nasopharingeal specimen, PE – pleural empyema, PPE – para pneumonic effusion, CSF – cerebrospinal, fluid, PCR – polymerase chain reaction, BAL – broncho alveolar lavage, RSV - respiratory syncytial virus, CMV – cytomegalovirus.

Table 3. Risk of bias assessment of the 13 studies included in the review.

Author, year of publication	Location, study period	Study design	Quality assessment
Misra, S (1991)[34]	India (1986-87)	Case series	Fair
The WHO Young Infant Study Group (1999)[35]	Ethiopia, Papua New Guinea, Gambia, Philippines (1991-93)	Case control	Excellent
Muhe, L (1999)[36]	Ethiopia (1991-93)	Case control	Excellent
Lehman D (1999)[37,38]	Papua New Guinea (1991-93)	Case control	Excellent
The PERCH Study[21,24,25,31–33]	PERCH – Kenya, Gambia, Mali, Zambia, South Africa, Thailand and Bangladesh (2011-14)	Case control	Excellent
Rhie, K (2018)[19]	Korea (2006-10)	Retrospective cohort	Fair
Lee, JH (2011)[18]	Korea (1996-2005)	Retrospective cohort	Fair
Wang, H (2010)[20]	China (2006-08)	Retrospective cohort	Fair
Finianos, M (2019)[17]	Lebanon (2013-14)	Prospective cohort	Fair
Nascimento-Carvalho, CM (2011, 2013, 2015, 2019)[26–29]	Brazil (2003-05)	Cross sectional	Good
Jullien, S (2020)[23]	Bhutan (2017-18)	Prospective cohort	Good
Nathan, AM (2020)[30]	Malaysia (2014-16)	Prospective cohort	Good
Gareca Perales, J (2021)[22]	Bolivia (2016-17)	Prospective cohort	Good

Identifying the cause of pneumonia in children is difficult because of varying syndromic presentations, challenges in obtaining specimens for laboratory assessment, and the lack of rapid, commercially available, accurate laboratory tests for most pathogens, among others. A recent landscape assessment and literature review conducted by Gilani *et al.*[39] reported that published or ongoing (at the time) studies of pneumonia etiology in children present a multiplicity of case definitions, levels of clinician involvement, facility types, specimen collection, and laboratory techniques, thus reinforcing the need for the standardization of methods and analyses of pneumonia etiology in children.

Limited reviews have reported on the etiology of pneumonia in children, mostly in specific locations and in younger than 5 years of age[40]. Studies conducted in developed countries clearly demonstrate that the pattern of etiologic agents causing pneumonia in children, in particular severe pneumonia, has been changing over the past decades. While in the 1980s bacterial agents including *Staphylococcus* bacteria (*aureus* and *pyogenes*) were the main causative agents of severe pneumonia in children, over time studies began reporting an increase in the proportion of Gram-negative agents and Group B *Streptococcus* (*S. agalactiae*), which accounted for most pneumonia cases in children. Also, there is growing evidence demonstrating the importance of viral etiologies, including RSV, rhinovirus, influenza, parainfluenza, alone or in combination with bacterial pathogens, as important etiologies of pneumonia in children.

In the Canadian Guidelines for treatment of pediatric pneumonia from 1997[14], the reported main pathogens causing pneumonia in infants aged 1-3 months are, in order of frequency: *Chlamydia trachomatis*, RSV, other respiratory viruses, and *Bordetella pertussis.*

In a review article published in 2002, McIntosh[5] reports on the bacterial and viral agents causing pneumonia in children, particularly *S. pneumoniae and S. pyogenes, S. aureus and H. influenza* among bacterial agents, and RSV, influenza, parainfluenza, adenovirus, and rhinovirus among viral agents. McIntosh[5] reinforces that for treatment decision making, one should first consider the age of the child. To that end, no comprehensive review has been conducted on the etiology of pneumonia in children under 3 months of age.

This systematic review included 13 studies reported in 22 publications, conducted from 1986 through 2020 in a variety of locations, mainly in developing countries. Results were variable, depending on time in which study was conducted, study design, and laboratory methods used.

Earlier studies conducted in the 80s and 90s[34–37] demonstrate that *S. pneumoniae* is a very important etiologic agent even in neonates. Viral etiologies including RSV, influenza and parainfluenza were also observed in the WHO multicenter prospective study[35–37].

A retrospective study in Korea[18,19] conducted over 1996 to 2010 reported *S. agalactiae* as a significant agent. Nonetheless, these studies were severely biased for various reasons. First, the study was retrospective and based on laboratory surveillance, with no clinical information of patients enrolled, but rather considering invasive disease as of pulmonary focus when pulmonary or pleural specimens had been obtained. In addition, this study included both community and nosocomial infections, it not being possible to disaggregate them. Finally, only bacteria were evaluated and no viral etiologies. This study also included children younger than 28 days.

Another retrospective cohort study conducted in China[20] evaluated only bacterial etiology on young neonates aged ≤28 days. Furthermore, only sputum specimens were collected and processed, which imposes major biases in this study as well.

More recent research conducted in the past 15 years, using prospective cohort designs and better standardized methods and case definitions, and applying molecular diagnostic techniques to evaluate etiologic agents including bacterial and viral etiologies, suggests a significant proportion of viral agents causing pneumonia in children younger than 3 months of age[16,21–32,33]. Of note, Finianos *et al.*[16] in Lebanon evaluated viral agents only. Nathan *et al.*[30] in Malaysia also report a significant proportion of bacterial etiologies, particularly *S. pneumonia, H. influenza* and *S. aureus*. This was also reported by the most robust body of evidence to date on the etiology of hospitalized pneumonia in children, resulting from a WHO multinational cohort study conducted in 7 study sites from 2011-2014, the Pneumonia Etiology Research for Child Health (PERCH) study[21,24,25,31–33].

This review demonstrates that available evidence on etiology of pneumonia in young children, particularly children younger than 3 months of age is based on a variety of studies with non-standardized methodology. Syndromes and case definitions as well as age subgroups included (younger than 7 days and younger than 28 days) vary significantly among studies. Samples collected and tests performed also vary significantly, and also over time, with molecular methods available in more recent studies. Studies also vary in terms of sample size, and time and locality in which it has been conducted. All of these are known factors which may influence the reported etiology and also the ability to identify selected agents. Adequate specimens and testing methods should be used for studies evaluating etiology of pneumonia in children, in particular molecular techniques with higher sensitivity.

Despite the above limitations and challenges, this review reinforces that Gram-positive organisms, in particular *S. pneumoniae*, are still important etiologic agents of pneumonia in children under 3 months of age and should thus be considered when assessing impact of PCV in the children. In addition, viral etiologies are also important, responding for a significant proportion of pneumonia in children younger than 3 months of age.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Harvard Dataverse: Bacterial etiology of pneumonia in children up to 2 months of age: a systematic review. https://doi.org/10.7910/DVN/GIYVPD[15]

This project contains the following files:

- Search strategies.docx
- Reasons for exclusion and references.docx
- Number of included papers by database.docx

Reporting guidelines

Harvard Dataverse: PRISMA flowchart and checklist for "Bacterial etiology of pneumonia in children up to 2 months of age: a systematic review". https://doi.org/10.7910/DVN/GIYVPD

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

Author contributions

LHO and CMT conceptualized the study.

MTV, CMT, MTCO, MQ reviewed citations, read selected papers in full, extracted data from included papers, conducted quality assessment of studies, and discussed main results.

MSMS developed the search strategy, prepared the flowchart and appendices describing the number of studies screened, selected, excluded, and included in the final review. MSMS also contacted authors from study which required additional information or clarifications.

CMT drafted the manuscript. All authors revised the manuscript and provided critical inputs for the final version of the manuscript.

Acknowledgments

We thank the investigators of various studies included in this review who kindly shared detailed data from their studies and provided clarifications requested by the authors of this review.

LHO and MTCO are staff members of the Pan American Health Organization. The authors alone are responsible for the views expressed in this publication, and they do not necessarily represent the decisions or policies of the Pan American Health Organization.

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1. As stated by reviewer 1, the Abstract's conclusion sentence "suggesting that PCV impact is expected to occur in this age group" should be suppressed because the study did not directly address this issue.

2. The suggestions of the first reviewer regarding the objective of the review in assessing the bacterial aetiology of respiratory infections shall be attended by the authors.

3. The title of the manuscript and the introductions section address different objectives: bacterial aetiology of pneumonia (title) and "summarizing the evidence of the bacterial aetiology of respiratory infections in children under 3 months of age". That difference shall be solved. Also, the study's inclusion criteria address respiratory infections.

4. In Figure 1, S4 means supplement S4? I was not able to access the supplementary documents. If S4 means supplement S4, the suggested information to be included in the reasons for exclusion are described in Supplement 4.

5. Despite the study adopting the JBI critical appraisal checklist for different observational designs, Table 3 does not provide further information about the potential involved bias and threat. Such an option limited the contribution of the study's results for research recommendations. Why?

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of infectious diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 18 May 2022

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Overall, this systematic review attempted to address an important topic. However, there are methodological issues and data interpretation inaccuracies that require to be addressed in order to consider it for indexing. These are listed below.

1. Abstract:
   The following sentence in the conclusion is unjustified as the review was not designed to address it: “suggesting that PCV impact is expected to occur in this age group”. Thus must be deleted.

2. Generally, pneumonia studies are conducted in children 2-59 months of age, and those below 2 months are considered separately. For some reason, the authors have chosen to include infants less than 3 months of age in this review. Please provide the justification.

3. The last sentence of the Introduction section states that the aim of the review is to summarize “the evidence of the bacterial etiology of respiratory infections....” whereas the title suggests that the review is for pneumonia. Kindly resolve this discrepancy.

4. Please mention the date of PROSPERO registration and publication.

5. The Inclusion criteria for studies again mentions that studies dealing with “respiratory infections” would be included, whereas the Objective clearly mentions pneumonia. The terms are not synonymous.

6. It appears that citations were screened by four independent reviewers. However, the text mentions that disagreements between “pairs” of reviewers, were resolved by a “third” reviewer. Do you mean “fifth” reviewer? Or was the screening done in pairs?

7. Methods section mentions that studies were excluded if “specific ≤2 month of interest” were not available. In most other places, the authors mentioned <3 months. This discrepancy has to be resolved.

8. In Table 2, it is unclear how etiology assignment was carried out, to determine “bacterial etiology”. This point is critical because the mere presence of an organism (even from an appropriate biological specimen) is not synonymous with etiology.

9. In Table 2, please mention percentages to show the proportion with bacterial etiology among the total.

10. Table 2 does not mention the actual sample size in each study, but only the number in whom culture (or another method was used). In some studies, these numbers may be different, hence the total sample size should also be shown.

11. As an example, the first study (Misra) used blood and lung aspirates. Presumably, both were not obtained in all 44 infants, but both specimens are appropriate for etiology determination. Yes, the authors report that bacterial etiology was assigned in 22 (which is 50%). However, the percentage shown is 5.7%. This is unclear.

12. Table 2; WHO Young Infant Study. Please mention the percentage (167/2452).

13. In the above study, it appears that results from analysis of urine, NPA and CSF were not considered in etiology determination. Please confirm if this is so.

14. Table 2: Muhe: How was etiology determined in this study?

15. Table 2: Lehman. How was etiology determined in this study?

16. Table 2: PERCH. Please mention percentage (10/810) is a very small proportion.

17. Table 2; Rhie. How was it determined whether sepsis was secondary to pneumonia, or the other way around?

18. Table 2: Wang. This is an example where the knowledge of sample size is important to interpret the data properly.

19. Table 2; Finianos. It is unclear why this study is included, considering that it does not report bacterial Etiology.

20. Table 2: Nascimento-Carvalho. How was etiology determined in this study?

21. Table 2: Julien. How was etiology determined in this study?

22. Table 2: Nathan. How was etiology determined in this study?

23. Table 2: Gareca Perales. How was etiology determined in this study?

24. In Table 3; please describe how studies were categorised as having “fair”, “good” or “excellent” methodological quality.

25. The Discussion has omitted several important points viz. (A) Presence of one or more organisms in non-sterile sites (such as NPA, throat, etc) are difficult to interpret for the purpose of Etiology; (B) how to assign Etiology when multiple organisms are identified in the same specimen; (C) how to assign Etiology when different organisms are identified in different specimens from the same infant (i.e the hierarchical order of specimens); (D) limitations with methods such as urinary antigen detection; (E) selectivity of PCR (i.e. it can identify only those organisms that are looked for; (F) relationship to antibiotic therapy; (G) difficulty in neonates and young infants where sepsis often precedes radiographic pneumonia; and (H) maternal genital tract organisms, and maternal conditions such as premature rupture of membranes, etc- which can influence the organisms identified.

26. Despite the lack of evidence, the authors insist that S. pneumoniae is a major causative organism. This does not appear to be true in any of the included studies.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric respiratory disease, Childhood pneumonia, Pneumonia etiology, Systematic reviews, Evidence-based healthcare, Guidelines

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.