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REVIEWS

Systematic review and meta-analysis on the etiology of bacterial pneumonia in children in sub-Saharan Africa

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Abstract

Introduction. Before the introduction of vaccination to protect children from pneumonia, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (HiB) were the most frequent aetiological agents causing bacterial pneumonia in children under five years old. However, the etiology of childhood pneumonia appears to be changing and non-vaccine-type *S. pneumoniae*, non-typeable *H. influenzae*, and *Staphylococcus aureus* are becoming more relevant.

Objective. We conducted a systematic review aimed at identifying the common causes of bacterial pneumonia in children in sub-Saharan Africa.

Methods. We searched PubMed, Web of Science and African Index Medicus and included primary studies conducted since January 2010 that reported on the bacterial causes of pneumonia in children under five from sub-Saharan Africa. We extracted data items (about the study setting, pneumonia diagnosis, sampling, microbiological methods, and etiological agents) as well as study quality indicators.

Results. *Streptococcus pneumoniae* was the most common bacteria in blood cultures from children with pneumonia (8%, 95% CI: 4-14%), and *H. influenzae* was second (3%, 95% CI: 1-17%). Children's nasopharynx commonly contained *S. pneumoniae* (66%), *Moraxella catarrhalis* (62%), and *H. influenzae* (44%).

Conclusion. *S. pneumoniae* and *H. influenzae* cause bacterial pneumonia in sub-Saharan African children. Our review also highlights the prevalence of potentially pathogenic bacteria in the nasopharynx of children under five and calls for more research into how nasopharyngeal colonization causes pneumonia.

Keywords: Pneumococcus, Staphylococcus, Haemophilus, Moraxella, Children, subSaharan Africa, Pneumonia.

INTRODUCTION

Pneumonia is an acute infection of the lungs and tissues of the lower respiratory tract. This condition disproportionately affects young children, in whom both incidence and mortality are high(1). Childhood pneumonia is one of the leading causes of illness and death among children less than five years of age. According to the Global Burden of Disease (GBD) estimates, more than 100 million children under the age of five years suffered from pneumonia in 2015, and approximately 700,000 died (1). The burden of childhood pneumonia is particularly high in sub-Saharan Africa (SSA) where the incidence and mortality are much higher than in any other region of the world (1,2). The region accounts for about half of all childhood pneumonia deaths, while only 20% of the global under-five population lives in SSA (1,3).

Pneumonia in children can be caused by multiple organisms, of which bacteria and viruses are the most important. Although viral agents are responsible for most of the pneumonia cases, it is bacterial agents that are responsible for most of the severe cases resulting in hospitalization and death (4). According to the 2015 GBD estimates, 64% of pneumonia-related deaths in children below five years were due to bacterial causes (1). Before the introduction of vaccination to protect children from pneumonia, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (HiB) accounted for most of bacterial pneumonia in children under five (3,4). With the use of highly effective pneumococcal conjugate vaccines (PCVs) and conjugate vaccines against *H. influenzae* type B (HiB), the incidence of pneumonia due to vaccine-type (VT) S. pneumoniae and HiB have declined (2,3,5,6). However, under the influence of these vaccines, the etiology of childhood pneumonia appears to be changing (2). Serotypes of *S. pneumoniae* not included in PCV, non-typeable or non-type B *H. influenzae*, and *Staphylococcus aureus* are becoming more relevant etiological agents of childhood pneumonia (2,7).

Knowledge of the common causative agents of pneumonia guides the choice of antibiotics to treat pneumonia. This is especially important in SSA where many cases of childhood pneumonia are treated empirically, without microbiological guidance. It is therefore essential that frontline health workers and policy-makers have up-to-date knowledge of organisms causing pneumonia in children. In this systematic review, we aim to summarize the current evidence on the causes of bacterial pneumonia in children under five years of age in SSA after the introduction of conjugate vaccines.

MATERIALS AND METHODS

Protocol and registration

The review was developed in line with the PRISMA guidelines (8). The original review protocol, as well as its amendments, were registered in PROSPERO (CRD42020203924).

Eligibility criteria

We looked for records that were published after 2010 and reported on cases of pneumonia in children in SSA who were between the ages of four weeks and five years old. Studies that focused solely on infants younger than four weeks old were not considered because the epidemiological profile of pneumonia is distinct in this age group (9). The inclusion criteria for studies were that they had to report on the prevalence of bacterial causes of pneumonia in the relevant population, either with or without comparison. Studies that used culture or molecular methods on blood or any type of respiratory sample (nasopharyngeal swabs, induced sputum, lung aspirate) were eligible to be included in the review. We only considered primary research and took into account the following types of studies: case series, surveillance studies, cross-sectional studies, case-control studies, cohort studies, and interventional studies. Modelling studies and reviews were not eligible.

Supplementary information The online version of this article (Tables/Figures) contains supplementary material, which is available to authorized users.

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Information sources

We searched the following electronic databases without language restrictions: MEDLINE using the PubMed interface (last search 10 October 2020), Web of Science database (last search conducted 16 October 2020), and African Index Medicus (last search 2October 2020). The MEDLINE search was restricted to articles published after 1 January 2010; no restrictions were applied to other searches. We manually searched the reference lists of included records for other potentially relevant records.

Search

Our search strategy combined the key themes of the review question: (a) bacterial pneumonia (b) children and (c) sub-Saharan Africa. For each of the themes, we applied alternate terms and spelling combinations, including truncations and wildcards to improve sensitivity. This search strategy was applied to MEDLINE and Web of Science; in the search of African index Medicus, we omitted the theme of SSA. Full details of the search strategies and syntaxes are available as supplementary material (Supplement 1).

Study selection

Screening of titles and abstracts and full-text screening for eligibility was conducted by blinded double-voting, with a third vote to resolve disagreements. CO, BE and OI screened the titles and abstracts while VW resolved disagreements. Potentially eligible records from the title and abstract screening were considered for full-text assessment. The assessment of the full-texts was conducted by BE, OI and VW, with CO acting as a tiebreaker to resolve disagreements. MJ and CO subsequently searched the reference list of records included in the review for potentially relevant records. We used the Covidence platform (https://www.covidence.org/about-us-covidence/) to organize the screening and selection of records.

Data collection process

We developed a data extraction form, implemented it in Covidence, and refined it after a pilot phase using five included records. Next, one member of the review team extracted the relevant data items from all the included papers and a second member checked the extracted data. Disagreement between the primary extraction and data check was resolved by consensus between voting members in consultation with a third member of the team. No additional information was sought from investigators or authors.

Data items

The following categories of information were extracted: (a) study characteristics (study aim, design, and start and end date), (b) characteristics of the study population (description of cases, pneumonia case definition, method of recruitment, the severity of pneumonia and number of children screened for pneumonia if applicable); (c) type of outcome measure (sample type, method of sample collection, method of bacterial identification, total number of samples collected, number of samples with positive test results for bacteria, and number of specific bacterial isolates). For case-control studies, we extracted similar data items for the control subjects.

Risk of bias in individual studies

Two members of the review team assessed the risk of bias, with disagreement resolved by consensus. We used the Joanna Briggs Institute (JBI) quality assessment tools for assessing the quality of included studies (10). As this review focuses on the cases with pneumonia we used the JBI tool for case-series for both case series and case-control studies.

Summary measure and analyses

Since this review aimed to summarize the prevalence of specific bacterial agents among cases with pneumonia, our main summary measure was the proportion of pneumonia cases with specific isolates. We first conducted meta-analyses of these proportions per sample type and per pathogen, using a random-effects model and after a variance-stabilizing transformation (double arcsine transformation). Second, for case-control studies of nasopharyngeal isolates, we also conducted a meta-analysis of the crude odds ratios of bacterial isolation comparing children with and without pneumonia. We assessed heterogeneity by computing Cochrane's Q and I^2 statistics which measure the proportion of the variation between studies that is due to heterogeneity and not by chance (11,12). R (package metafor) and STATA v. 16 were

used to conduct the analyses and to produce forest and funnel plots (13).

Risk of bias across studies

Assessing the risk of publication bias in meta-analyses of prevalence studies is not straightforward, as the prevalence is expected to vary across studies and funnel plots may not be relevant (14). We, therefore, discussed the possible presence of bias across studies and the implications it may have had on our findings without making a quantitative evaluation. For the second type of meta-analysis in this review, i.e. the association between pneumonia and nasopharyngeal isolation of S. pneumoniae (expressed as odds ratio (OR)), we did construct a funnel plot. To assess the funnel plot symmetry, we relied mostly on visual inspection of the plot, with support from formal statistical tests (formal tests for asymmetry are underpowered when the funnel plot has fewer than 10 studies)(14).

RESULTS

Study selection

Eleven studies (reported in 12 records) were eligible for inclusion in the review (15,16,25,26,17-24). The search of PubMed, Web of Science and African Index Medicus retrieved 2279 records, 229 of which were duplicates. After title and abstract screening of 2050 records, we excluded 1954 because they were irrelevant. We assessed the remaining 96 full-text records and excluded 84 (Figure 1) because they did not report on bacterial causes of pneumonia (n=3), were conducted before 2010 (n=22), were not primary research (n=13), and included persons outside the eligible age range (n=7). Three additional reports were identified from manual searching of references, but all three were excluded after full-text assessment (not shown in PRISMA chart).

Study characteristics

The table below provides an overview of the studies included in the systematic review.

Population

Two of the 11 studies in this review were multicenter (PERCH and GABRIEL networks) and nine were single-centre studies (Table 1). Three studies were conducted before the introduction of PCV in the corresponding countries (17,25,26). Concerning study design, there were nine case-control studies and two case series. All studies recruited children in hospital and all were conducted prospectively. The diagnosis of pneumonia was mostly based on standard World Health Organization (WHO) definitions of clinical (n=6) or radiological (n=6) pneumonia; one study (27) used a physician-based diagnosis. Taken together, the 11 studies contained information about 5362 pneumonia cases.

Outcomes

Three types of samples were used to determine the aetiological agents: nasopharyngeal samples (n=9), blood (n=5), and induced sputum (n=1). The laboratory methods used were PCR (n=10) and culture (n=7), with 4 studies using more than one laboratory method

Quality appraisal of included studies

The quality appraisal of the included studies is summarized in Figure 2. An important dimension of quality concern in the review was in case inclusion, some included studies did not provide enough information to make a judgement on completeness of case inclusion and consecutive case inclusion. Incomplete or non-consecutive case inclusion is a potential source of selection bias in case-control and case series studies.

SYNTHESIS OF RESULTS

Bacterial pathogens isolated from nasopharyngeal swabs

The most frequently identified bacteria from NPS were *S. pneumoniae* and *M. catarrhalis*. As shown in Table 2 and Figure 3, the results of individual studies varied between all bacterial pathogens considered, with *S. pneumoniae* and *H. influenzae* showing wide variability. S. pneumoniae was isolated in an estimated 66% of children with pneumonia, while H. influenzae was isolated in about 44% of cases. M. catarrhalis was isolated in an estimated 62% of children, based on two studies(19,23). Of the studies reporting on either S. pneumoniae or H. influenzae, five studies reported on serogroups (15,18,22,24,28). Vaccine-type serotypes still accounted for a large

proportion of S. pneumoniae isolates, especially serotype 6A, 6B, 19A, 19F and 23F.

Bacterial pathogens isolated from blood

The FOREST POT of bacterial agents isolated from blood among cases showed a relatively high proportion of S. pneumoniae and H. influenzae (Figure 4). S. pneumoniae was isolated from blood in an estimated 8% of cases (95% CI: 4% - 14%); while H. influenzae was isolated in an estimated 3% of cases (95% CI: 1% – 17%). S. aureus was less frequently isolated from blood samples, except for one study, where S. aureus was found in 5% of cases (15). M. catarrhalis was identified in the blood sample of 1 of 2189 children included in this analysis.

Association between bacterial nasopharyngeal carriage and pneumonia in children in SSA

We conducted separate analyses of the association between nasopharyngeal isolates of each bacterial agent and pneumonia by computing pooled odds ratio (OR) for case-control studies. As shown in Figure 5, we found no evidence in favour of an association between nasopharyngeal carriage and pneumonia: the pooled OR was very close to 1.0. Also, in these meta-analyses, there was considerable heterogeneity in 3 of our analyses (I^2= 86-93%; P<0.01).

Risk of bias across studies

During this review, we found no indications of publication bias. Visual inspection of the funnel plot (Figure 6) suggested no obvious asymmetry and the Peters test was not statistically significant (p = 0.62).

DISCUSSION

Summary of evidence

The main findings of this systematic review are: (a) bacterial pathogens remain a relevant cause of pneumonia in children in SSA, and (b) the usual bacterial culprits persist. *S. pneumoniae* was the most commonly detected organism in blood samples from children with pneumonia. *S. pneumoniae* was also the most common organism identified from nasopharyngeal swabs in both cases and non-cases. When we compared nasopharyngeal isolates from children with pneumonia and those without pneumonia, we found no obvious difference in the proportion of children in whom *S. pneumoniae, H. influenzae, S. aureus* and *M. catarrhalis* were isolated from the nasopharynx. We were unable to describe isolation patterns in severe versus non-severe pneumonia cases as nearly all the studies in the review were on children with severe pneumonia.

Before the introduction of PCV, nasopharyngeal colonization by *S. pneumoniae* among children in SSA was high, even in healthy children (29,30). The ubiquitous nature of pneumococcal carriage implies that inferring etiology based on nasopharyngeal samples is problematic. Our review shows that in SSA, nasopharyngeal carriage is largely similar in children with and without pneumonia. One previous study found that in some instances, bacteria may be more easily isolated by culture from healthy children than from those with pneumonia (28). A possible explanation for this is the use of antibiotics before sample collection among children with pneumonia. However, comparing the frequency of carriage reported in our review with those reported before conjugate vaccine introduction suggests that overall carriage has not changed much (29–32).

We also report on the continued importance of *S. pneumoniae* and *H. influenzae* as bacterial agents causing pneumonia in children in the region. Studies conducted before conjugate vaccine introduction showed that these pathogens were the most commonly identified among children with pneumonia (4,33). We also found that vaccine-type serogroups of *S. pneumoniae* are still important colonizers of the nasopharynx.

CONCLUSIONS

Despite the widespread implementation of vaccination against *S. pneumoniae* and *H. influenzae* in the past decade, these bacteria continue to colonize the nasopharynx of children and cause pneumonia. This, therefore, suggest that in resource-limited settings without microbiological support, the current empirical approach to the treatment of childhood pneumonia remains reasonable. The mechanisms by which bacterial colonization results in pneumonia remains

unclear, and the importance of *M. catarrhalis* as a causal agent needs further investigation. Rapid diagnostic tests based on biomarkers of bacterial infection could be a potential game-changer in the antibiotic management of childhood pneumonia.

LIMITATIONS

The small number of studies included in the meta-analysis combined with the random-effect model applied greatly increases the level of uncertainty around our meta-analysis estimates. Another limitation of our review was that the samples collected and the method of bacterial identification differed between studies. The different methods of bacterial identification have different levels of accuracy and this may account for some of the heterogeneity in observed results. The study designs and case definition applied across studies also varied. On the quality assessment of individual studies, nearly all had at least one area of concern. The most commonly observed quality concerns were in the areas of consecutive case recruitment and complete case inclusion. Therefore, there is the potential for selection bias within these studies (Table 2).

There was no evidence of publication bias amongst the assessed studies. However, there persists the possibility of bias due to language bias. Indeed, we observed that only one record screened for full-text inclusion was published in French. This could result in an under-representation of studies from parts of SSA and a bias toward English predominant areas. Furthermore, with the small number of countries presented in this review, it is unclear how representative they are of the wider SSA region.

INFORMATION

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated during the current review are available in Figshare.

Authors' contributions. CO conceptualized the review, developed the review methodology, searched the online databases, screened records, extracted data items, conducted risk of bias assessment, conducted the meta-analysis and prepared the draft manuscript. BE, IO, and VW screened records, extracted data items, conducted risk of bias assessment, and reviewed the manuscript. MJ conducted the manual literature search, screened manual records, and reviewed the manuscript. BS reviewed the protocol, and reviewed the manuscript. KV conceptualized the review, developed the review methodology, conducted the meta-analysis, guided interpretation of results, and reviewed the manuscript.

Competing interests. The authors declare that they have no competing interests.

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REFERENCES

1. Troeger C, Forouzanfar M, Rao PC, Khalil I, Brown A, Swartz S, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis. 2017;17(11):1133–61.

2. Marangu D, Zar HJ. Childhood pneumonia in low-and-middle-income countries: An update. Paediatr Respir Rev. 2019;32:3–9.

3. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Heal Organ. 2008;86(5):408–16.

4. Howie SRC, Morris GAJ, Tokarz R, Ebruke BE, Machuka EM, Ideh RC, et al. Etiology of severe childhood pneumonia in the Gambia,

West Africa, determined by conventional and molecular microbiological analyses of lung and pleural aspirate samples. Vol. 59, Clinical Infectious Diseases. 2014. p. 682–5.

5. Alicino C, Paganino C, Orsi A, Astengo M, Trucchi C, Icardi G, et al. The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on hospitalization for pneumonia in children: A systematic review and meta-analysis. Vaccine. 2017.

6. Onwuchekwa C, Edem B, Williams V, Oga E. Estimating the impact of pneumococcal conjugate vaccines on childhood pneumonia in sub-Saharan Africa: A systematic review. F1000Research. 2020;

7. Mackenzie GA, Hill PC, Sahito SM, Jeffries DJ, Hossain I, Bottomley C, et al. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies. Lancet Infect Dis. 2017 Sep;17(9):965–73.

8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339.

9. Duke T. Neonatal pneumonia in developing countries. Arch Dis Child Fetal Neonatal Ed. 2005;90(3):211–9.

10. JBI. Critical Appraisal Tools | Joanna Briggs Institute. (JBI). 2020.

11. Hedges L V., Pigott TD. The power of statistical tests in meta-analysis. Psychol Methods. 2001;

12. Cafri G, Kromrey JD, Brannick MT. A meta-meta-analysis: Empirical review of statistical power, type I error rates, effect sizes, and model selection of meta-analyses published in psychology. Multivariate Behav Res. 2010;

13. Nyaga VN, Arbyn M, Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. Arch Public Heal. 2014;

14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. Cochrane Handbook for Systematic Reviews of Interventions. 2019.

15. Bénet T, Sylla M, Messaoudi M, Picot VS, Telles JN, Diakite AA, et al. Etiology and factors associated with pneumonia in children under 5 years of age in Mali: A prospective case-control study. PLoS One. 2015;10(12):1–15.

16. Marangu D, Zar HJJ, Levine OSS, O'Brien KLL, Deloria-Knoll M, Murdoch DRR, et al. Authors : Ac c te d us cr ip t Ac c ep te us cr t. Clin Infect Dis [Internet]. 2020 Apr;8(1):1–10. Available from: http://dx.doi.org/10.1016/S2214-109X(18)30247-X

17. Elfving K, Shakely D, Andersson M, Baltzell K, Ali AS, Bachelard M, et al. Acute uncomplicated febrile illness in children aged 2-59 months in Zanzibar - Aetiologies, antibiotic treatment and outcome. PLoS One. 2016;11(1):1–21.

18. Negash AA, Asrat D, Abebe W, Hailemariam T, Hailu T, Aseffa A, et al. Bacteremic Community-Acquired Pneumonia in Ethiopian Children : Etiology , Antibiotic Resistance , Risk Factors , and Clinical Outcome. :1–8.

19. Ngocho JS, Minja L, van der Gaast – de Jongh CE, Rahamat-Langendoen JC, Langereis JD, Mmbaga BT, et al. Viral-bacterial (co-)occurrence in the upper airways and the risk of childhood pneumonia in resource-limited settings. J Infect [Internet]. 2020;81(2):213–20. Available from: https://doi.org/10.1016/j.jinf.2020.06.013

20. Morpeth SC, Knoll MD, Scott JAG, Park DE, Watson NL, Baggett HC, et al. Detection of pneumococcal DNA in blood by polymerase chain reaction for diagnosing pneumococcal pneumonia in young children from low-

and middle-income countries. Clin Infect Dis. 2017;64(January):S347–56.

21. Bénet T, Sánchez Picot V, Messaoudi M, Chou M, Eap T, Wang J, et al. Microorganisms Associated with Pneumonia in Children <5 Years of Age in Developing and Emerging Countries: The GABRIEL Pneumonia Multicenter, Prospective, Case-Control Study. Clin Infect Dis. 2017;65(4):604–12.

22. Pimenta FC, Moiane B, Lessa FC, Venero AKL, Moura I, Larson S, et al. Dried blood spots for Streptococcus pneumoniae and Haemophilus influenzae detection and serotyping among children < 5 years old in rural Mozambique. BMC Pediatr. 2020;20(1):1–8.

23. Zar HJ, Barnett W, Stadler A, Gardner-Lubbe S, Myer L, Nicol MP. Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: A nested case-control study of the Drakenstein Child Health Study. Lancet Respir Med. 2016;

24. O'Brien KL, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Higdon MM, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019;

25. Hammitt LL, Kazungu S, Morpeth SC, Gibson DG, Mvera B, Brent AJ, et al. A preliminary study of pneumonia etiology among hospitalized children in Kenya. Clin Infect Dis. 2012;54(SUPPL. 2).

26. Selva L, Benmessaoud R, Lanaspa M, Jroundi I, Moraleda C, Acacio S, et al. Detection of Streptococcus pneumoniae and Haemophilus influenzae Type B by Real-Time PCR from Dried Blood Spot Samples among Children with Pneumonia: A Useful Approach for Developing Countries. PLoS One. 2013;8(10):6–12.

27. Carrim M, Wolter N, Benitez AJ, Tempia S, du Plessis M, Walaza S, et al. Epidemiology and molecular identification and characterization of mycoplasma pneumoniae, South Africa, 2012-2015. Emerg Infect Dis. 2018;24(3):506–13.

28. Adebanjo T, Lessa FC, Mucavele H, Moiane B, Chauque A, Pimenta F, et al. Pneumococcal carriage and serotype distribution among children with and without pneumonia in Mozambique, 2014-2016. PLoS One. 2018;13(6):2014–6.

29. Adegbola RA, DeAntonio R, Hill PC, Roca A, Usuf E, Hoet B, et al. Carriage of Streptococcus pneumoniae and other respiratory bacterial pathogens in low and lower-middle income countries: A systematic review and meta-analysis. PLoS One. 2014;

30. Roca A, Hill PC, Townend J, Egere U, Antonio M, Bojang A, et al. Effects of community-wide vaccination with PCV-7 on pneumococcal nasopharyngeal carriage in the Gambia: A cluster-randomized trial. PLoS Med. 2011;

31. Usuf, E., Badji, H., Bojang, A., et al. Pneumococcal carriage in rural Gambia prior to the introduction of pneumococcal conjugate vaccine: A population-based survey. Trop Med Int Heal. 2015;

32. Usuf E, Bottomley C, Adegbola RA, Hall A. Pneumococcal carriage in sub-Saharan Africa - A systematic review. PLoS One. 2014;9(1).

33. DeAntonio R, Yarzabal JP, Cruz JP, Schmidt JE, Kleijnen J. Epidemiology of community-acquired pneumonia and implications for vaccination of children living in developing and newly industrialized countries: A systematic literature review. Human Vaccines and Immunotherapeutics. 2016.

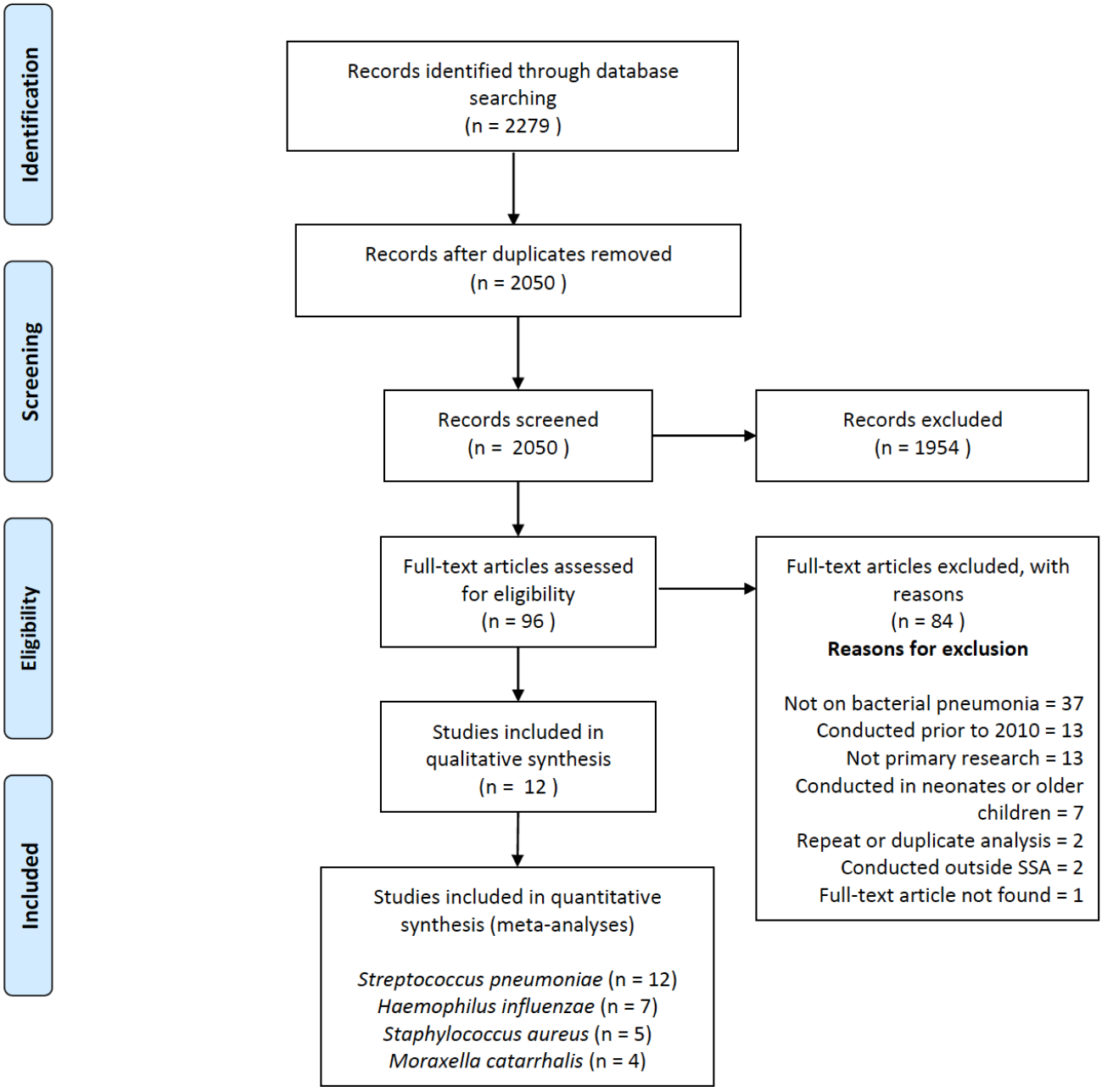

FIGURE 1: PRISMA diagram depicting the study selection process.

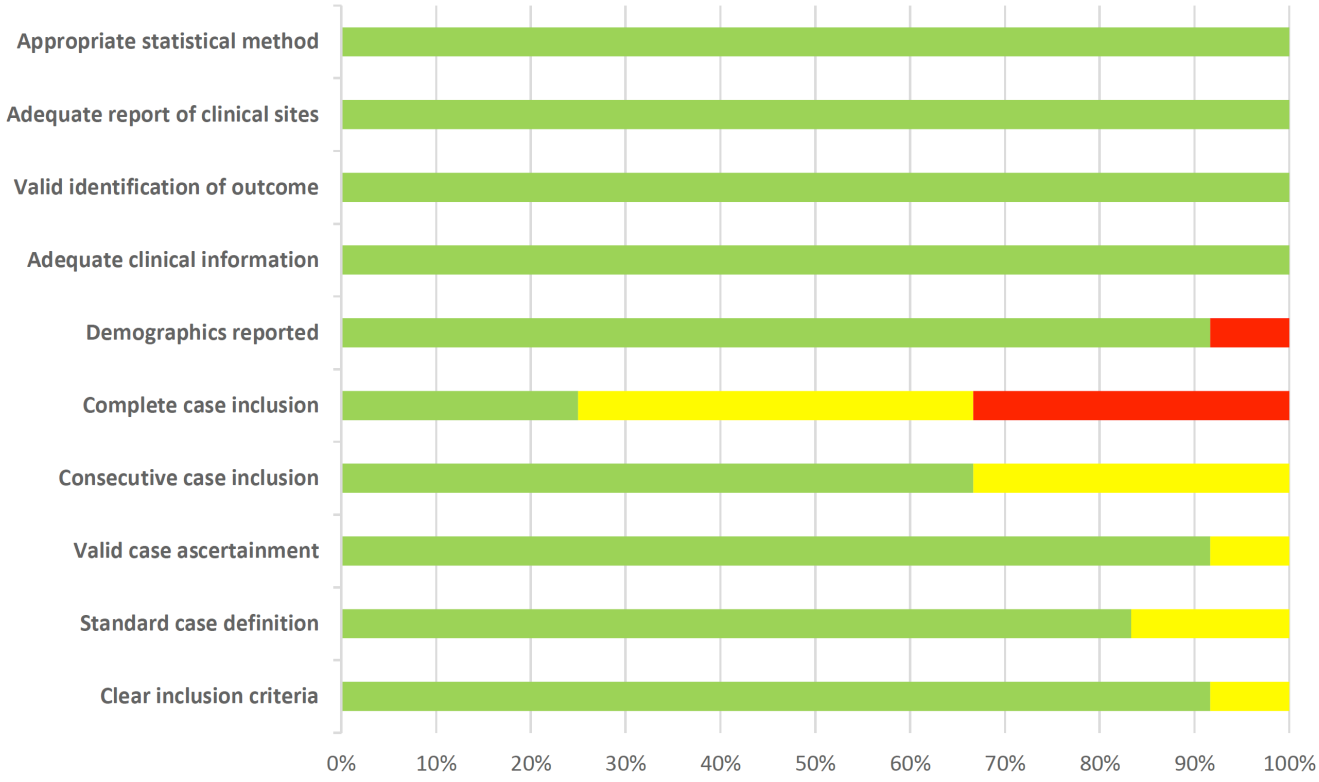

FIGURE 2: Quality appraisal of studies included in the review.

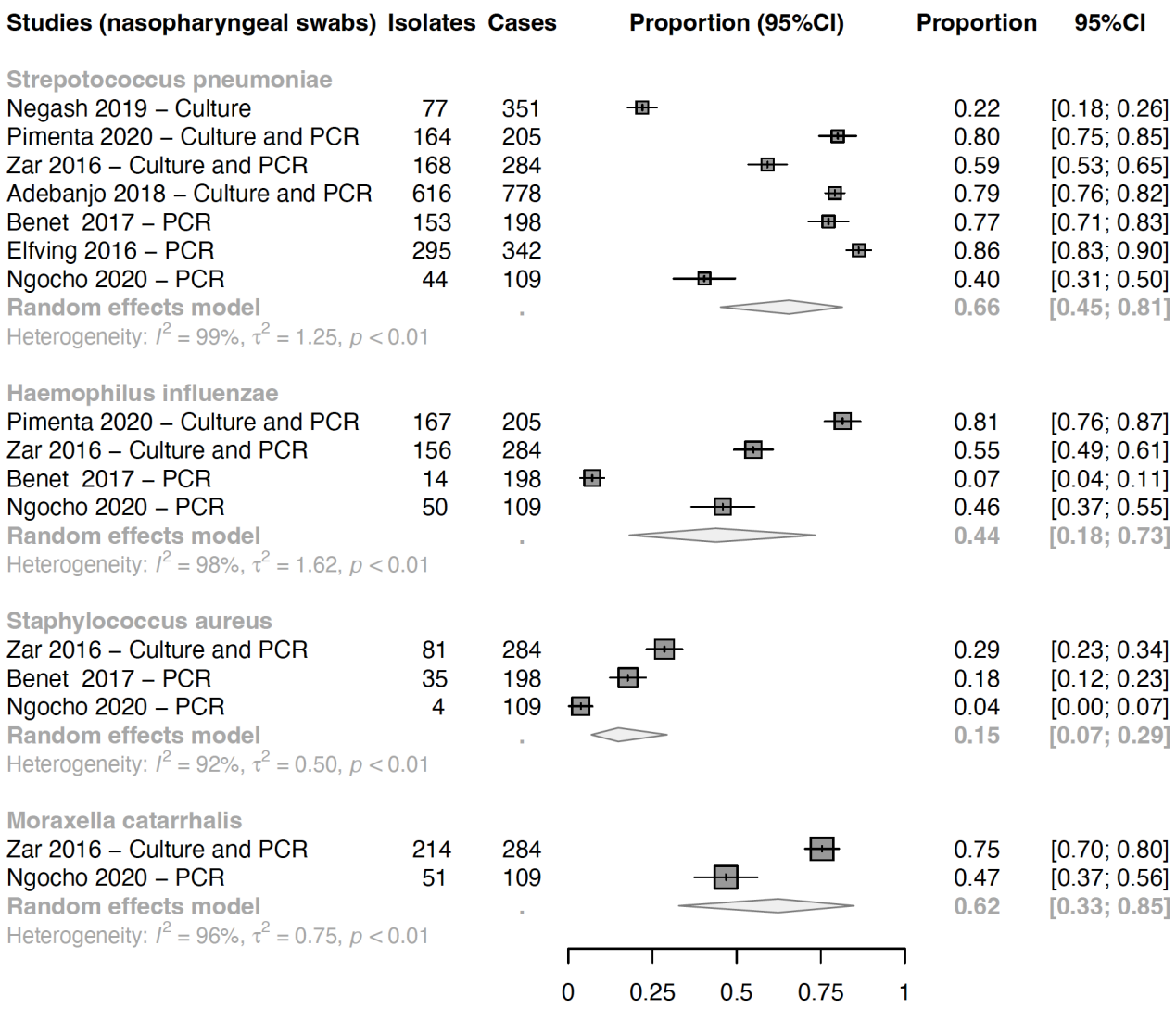

FIGURE 3: Bacteria isolated from Nasopharyngeal swabs.

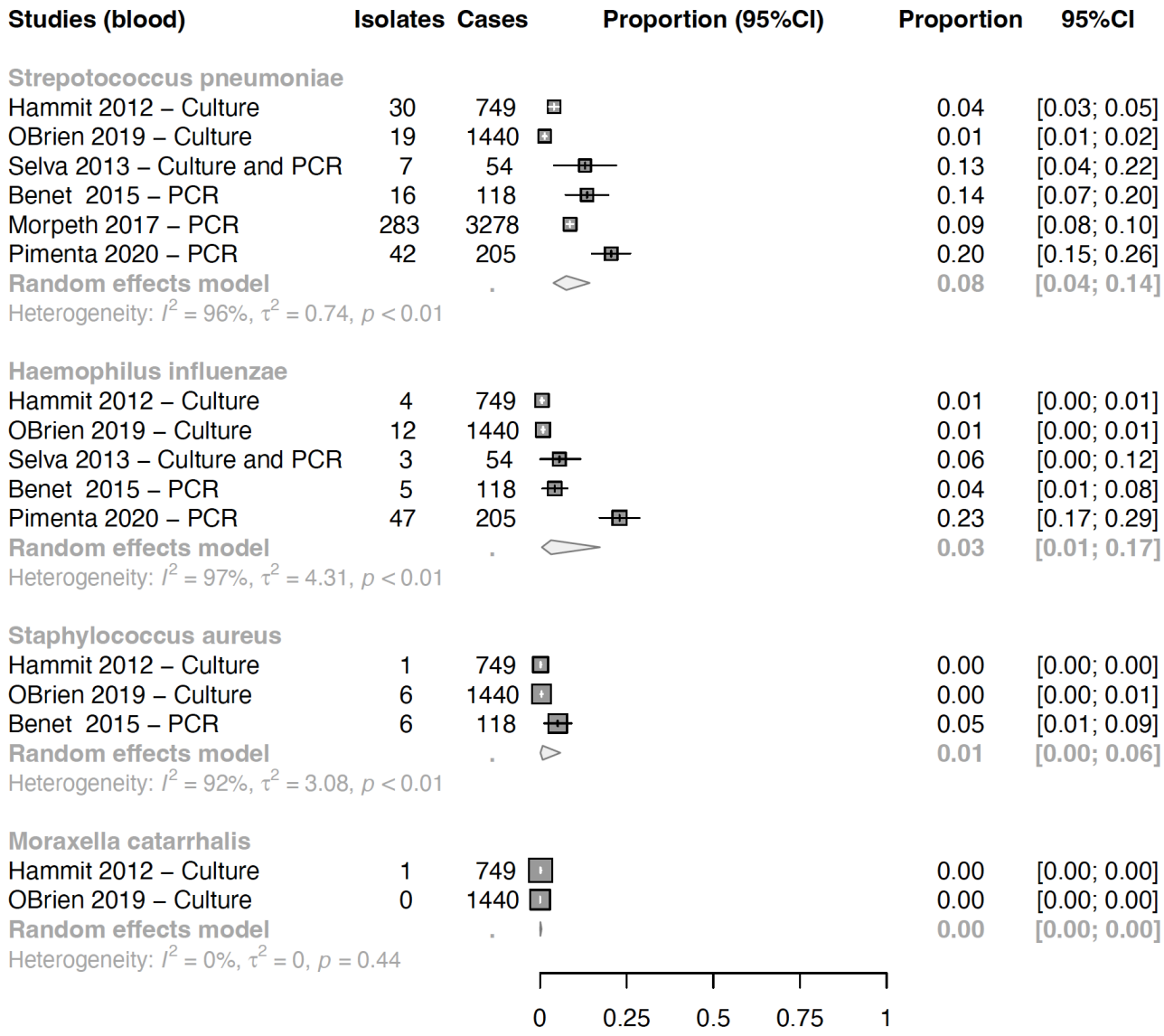

FIGURE 4: Bacteria isolated from blood samples.

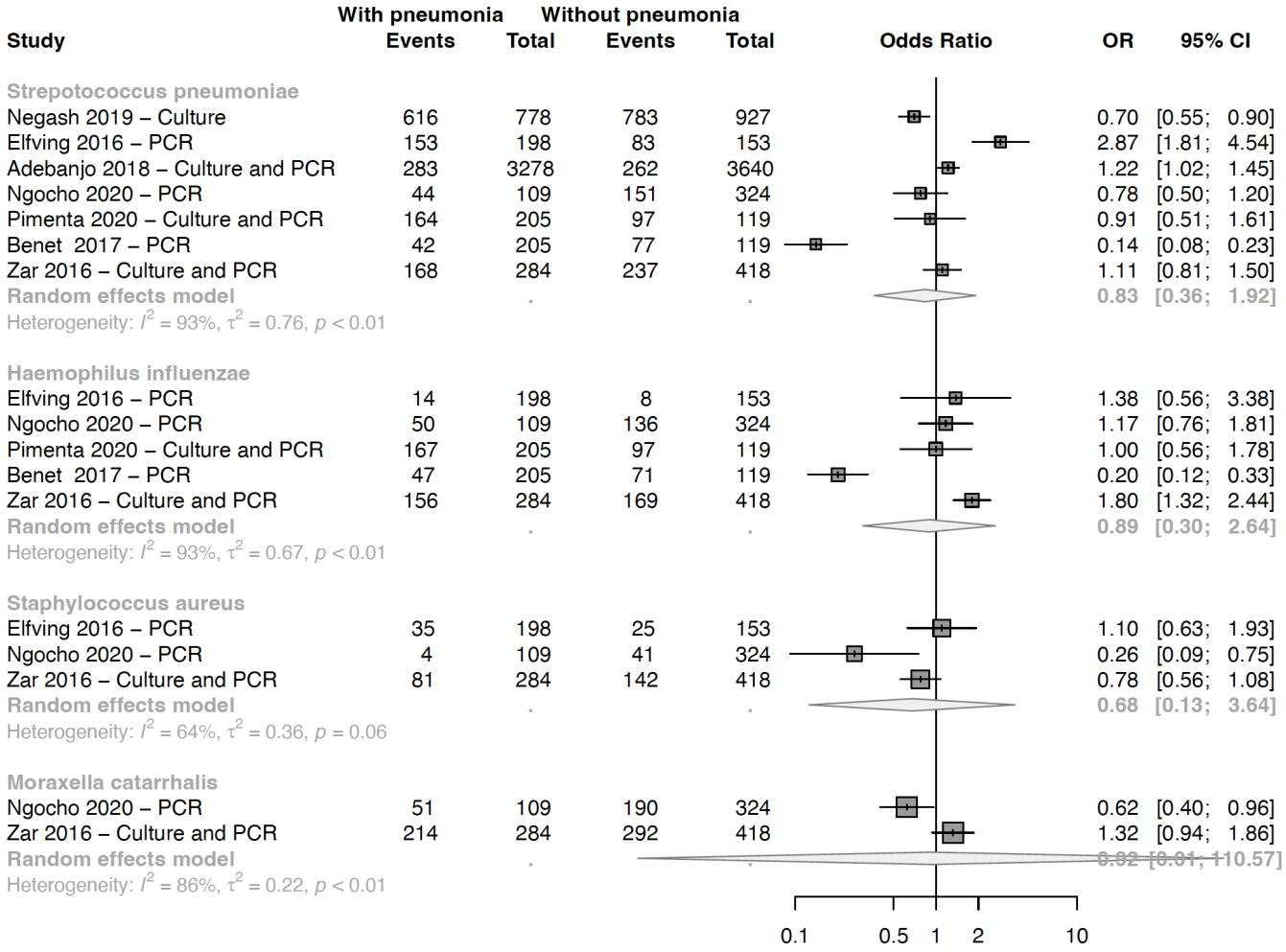

FIGURE 5: Association between nasopharyngeal bacterial isolate and pneumonia.

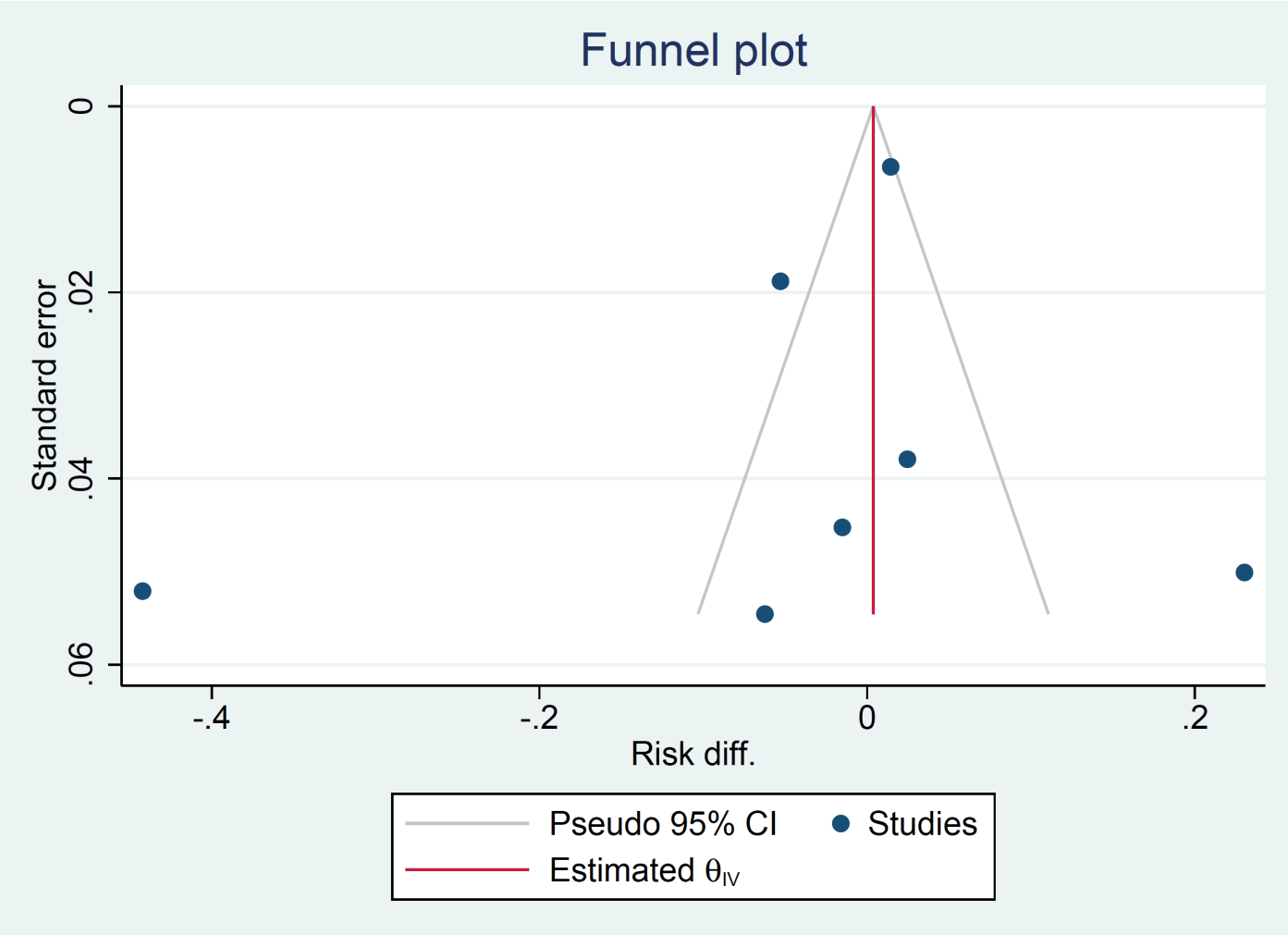

FIGURE 6: Funnel plot showing the dispersion of OR for *S. pneumoniae* isolation and pneumonia.

FIGURE 7:

Table 1. Summary of included studies.

Source	*Country(ies)*	*Study design*	*Age*	*Case definition*	*No. of cases*	*Study period*	*PCV introduction (PCV 10/PCV 13)*
Adebanjo et al. 2018	Mozambique	Case-control study	6 weeks – 59 months	Hospitalized with radiological pneumonia (WHO definition)	778	Jan 2014 - Apr 2016	2013
Benet et al. 2015	Mali	Case-control study	4 weeks – 59 months	Hospitalized with radiological pneumonia (WHO definition)	118	Jul 2011 - Dec 2012	2011
Benet et al. 2017*	Mali, Madagascar	Case-control study	4 weeks – 59 months	Hospitalized with radiological pneumonia (WHO definition)	198	May 2010 - Jun 2014	Mali (2011), Madagascar (2012)
Elfving et al. 2016*	Tanzania	Case-control study	4 weeks – 59 months	Radiological pneumonia (WHO definition)	42	Apr 2011 - Jul 2013	2013
Hammit et al. 2012*	Kenya	Case-control study	4 weeks – 59 months	Hospitalized with severe pneumonia	964	Jan 2010 - Dec 2010	2011
Morpeth et al. 2017*	Mali, Gambia, Zambia, South Africa, Kenya	Case-control study	4 weeks – 59 months	Hospitalized with severe pneumonia (WHO definition)	3278	Aug 2011 - Jan 2014	Mali (2011), Gambia (2011), Zambia (2013), South Africa (2011), Kenya (2011)
Negash et al. 2019	Ethiopia	Case series	4 weeks – 59 months	Hospitalized with radiological pneumonia (WHO definition)	351	Sep 2016 - Aug 2017	2011
Ngocho et al. 2020	Tanzania	Case-control study	4 weeks – 59 months	Hospitalized with radiological pneumonia (WHO definition)	109	Jan 2017 - Dec 2017	2013
O'Brien et al. 2019*	Mali, Gambia, Zambia, South Africa, Kenya	Case-control study	4 weeks – 59 months	Hospitalized with severe pneumonia (WHO definition)	1452	Jun 2011 - Jan 2014	Mali (2011), Gambia (2011), Zambia (2013), South Africa (2011), Kenya (2011)
Pimenta et al. 2020	Mozambique	Case series	4 weeks – 59 months	Hospitalized with severe pneumonia (WHO definition)	205	2014 - 2015	2013
Selva et al. 2013*	Mozambique	Case-control study	4 weeks – 59 months	Hospitalized with clinical pneumonia (WHO definition)	217	Feb 2010 - May 2012	2013
Zar et al. 2016	South Africa	Case-control study	6 weeks – 59 months	Clinical pneumonia (WHO definition)	314	May 2012 - Dec 2014	2010

(*) these studies included the period before the introduction of pneumococcal vaccines; WHO (World Health Organization).

Table 2. Results of individual studies.

Study ID	Study design	Sample	Lab. method(s)	Population	Total observations	Sp	Hi	Sa	Mc	Others
Adebanjo et al. 2018	Case-control	NPS	Culture and PCR	WHO radiological pneumonia	778	616	NA	NA	NA	NA
			Culture	Controls	927	783	NA	NA	NA	NA
Benet et al. 2015	Case-control	Blood	PCR	WHO radiological pneumonia	118	16	5	6	NA	NA
Benet et al. 2017	Case-control	NPS	PCR	WHO radiological pneumonia	198	153	14	35	NA	1
		NPS	PCR	Control	153	83	8	25	NA	2
Elfving et al. 2016	Case series	NPS	PCR	WHO clinical pneumonia	342	295	NA	NA	NA	NA
Hammit et al. 2012	Case-control	Blood	Culture	WHO clinical pneumonia	749	30	4	1	1	18
		Induced sputum	PCR	WHO clinical pneumonia	417	16	14	0	16	
Morpeth et al. 2017	Case-control	Blood	PCR	WHO clinical pneumonia	3278	283	NA	NA	NA	NA
		Blood	PCR	controls	3640	262	NA	NA	NA	NA
Negash et al. 2019	Case series	NPS	Culture	WHO radiological pneumonia	351	77	NA	NA	NA	NA
Ngocho et al. 2020	Case-control	NPS	PCR	WHO radiological pneumonia	109	44	50	4	51	2
		NPS	PCR	Control	324	151	136	41	190	1
Pimenta et al. 2020	Case-control	Blood (DBS)	PCR	WHO clinical pneumonia	205	42	47	NA	NA	NA
		Blood (DBS)	PCR	Control	119	77	71	NA	NA	NA
		NPS	Culture and PCR	WHO clinical pneumonia	205	164	167	NA	NA	NA
		NPS	Culture and PCR	Control	119	97	97	NA	NA	NA
O'Brien et al. 2019	Case-control	Blood	Culture	WHO radiological pneumonia	1440	19	12	6	0	15
Selva et al. 2013	Case-control*	Blood	Culture and PCR	WHO clinical pneumonia	54	7	3	NA	NA	NA
Zar et al. 2016	Case-control	NPS	Culture and PCR	WHO clinical pneumonia	284	168	156	81	214	10
		NPS	Culture and PCR	Control	418	237	169	142	292	15

(*) only case numbers are reported. NA (Not Applicable), Sp (*Streptococcus pneumoniae*), Hi *(Haemophilus influenzae)*, Sa *(Staphylococcus aureus)*, Mc *(Moraxella catarrhalis)*, NPS (Nasopharyngeal swab), PCR (Polymerase chain reaction), WHO (World Health Organization).

FIGURE 8: