BMJ Open

Pneumococcal pneumonia and carriage in Africa before and after introduction of pneumococcal conjugate vaccines, 2000-2019: protocol for systematic review.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030981.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Oct-2019
Complete List of Authors:	Kalata, Newton; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme Nyazika, Tinashe Kenny; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme; Liverpool School of Tropical Medicine, Clinical Sciences Swarthout, Todd; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme; Liverpool School of Tropical Medicine Everett, Dean ; University of Edinburgh Western General Hospital, The Queens Medical Research Institute; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme French, Neil; University of Liverpool Faculty of Health and Life Sciences, Centre for Global Vaccine Research, Institute of Infection and Global Health; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme Heyderman, Robert; University College London, Division of Infection and Immunity; University of Malawi College of Medicine, Malawi Liverpool Wellcome Trust Clinical Research Programme Gordon, Stephen; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme; Liverpool School of Tropical Medicine, Clinical Sciences Jambo, Kondwani; University of Malawi College of Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme; Liverpool School of Tropical Medicine, Clinical Sciences
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology
Keywords:	Streptococcus pneumoniae, Carriage, Pneumococcal conjugate vaccine, Pneumococcal pneumonia, Mortality, Africa

Pneumococcal pneumonia and carriage in Africa before and after introduction of pneumococcal conjugate vaccines, 2000-2019: protocol for systematic review.

Newton L. Kalata[1‡], Tinashe K. Nyazika[1,2‡¶], Todd D. Swarthout [1,2], Dean Everett[1,3], Neil French[4], Robert S Heyderman[5], Stephen B Gordon[1,2], Kondwani C. Jambo[1,2]

Affiliations

1. Malawi-Liverpool-Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, Blantyre, Malawi
2. Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
3. The Queens Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom
4. Centre for Global Vaccine Research, Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom
5. NIHR Global Health Research Unit on Mucosal Pathogens, Division of Infection & Immunity, University College London, London, United Kingdom

‡ Equal contributions and joint first authors

Correspondence: ¶Tinashe K. Nyazika, Malawi Liverpool Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, P.O Box 30096, Chichiri, Blantyre, Malawi.
Email: tknyazika@gmail.com

Abstract

Introduction: Africa harbours a high burden of pneumococcal disease, with associated high mortality rates. Despite 34 countries introducing the pneumococcal conjugate vaccine, which reduces the risk of pneumococcal carriage (a prerequisite for disease) of some of the most pathogenic pneumococcal serotypes, it remains uncertain whether they will achieve the sustained direct or indirect protection necessary to reduce pneumococcal carriage to levels sufficient to interrupt transmission and disease. We will therefore summarise the available data on the impact of the pneumococcal conjugate vaccine in reducing vaccine serotype carriage and pneumococcal pneumonia in Africa between 2000-2019.

Methods and analysis: Using a pre-determined search strategy, we will conduct a comprehensive search of PubMed, MEDLINE database, the Excerpta Medica Database (EMBASE), the ISI Web of Science (Science Citation Index), Scopus and the African Index Medicus to identify published studies reporting the prevalence of *Streptococcus pneumoniae* carriage (vaccine type and non-vaccine type), incidence rates of pneumococcal pneumonia and mortality among children, adults and HIV-infected (all-ages) pre- and post-PCV introduction (published between 1st January 2000 and 31st December 2019) in African countries that have introduced pneumococcal conjugate vaccines (PCV7/10/13) in their routine national immunisation programs. The studies retained and data extracted will be assessed for bias using pre-validated tools and checklists. Heterogeneity across studies will be assessed using the χ^2 test on Cochrane Q statistic. A random effect meta-analysis will be used to estimate the overall prevalence of pneumococcal carriage and incidence of pneumococcal pneumonia across studies with similar characteristics. Results will be reported in compliance with the Meta-Analysis Of Observational

Studies in Epidemiology (MOOSE) guidelines. The protocol has been prepared in accordance to the 2015 guidelines on Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Ethics and dissemination: This systematic review will not require ethical approval as we will be using already published data. The final manuscript will be submitted for publication in a peer-reviewed journal and presented at conferences.

PROSPERO registration number: CRD42019130976

Keywords: *Streptococcus pneumoniae,* Carriage, Pneumococcal conjugate vaccine, Pneumococcal pneumonia, mortality, Africa

Strengths and limitations

- To the best of our knowledge, this study will be the first systematic review that will comprehensively compare and explore the impact of PCV on carriage, pneumococcal pneumonia (invasive and non-invasive) and mortality associated with the disease pre-and post-vaccine introduction in adults and other at risk groups living in Africa.
- Small number of studies eligible across regions could impact the quality of our estimates.
- Presence of high heterogeneity across studies, particularly in countries where PCV7, PCV10 or PCV13 were in use around the same time and were serotyping was only done for vaccine-type pneumococcal strains.

Introduction

Streptococcus pneumoniae ("the pneumococcus") is a common coloniser of the nasopharynx and a major cause of morbidity and mortality among children under the age of 5 years worldwide.[1,2] High rates of pneumococcal disease are found in Africa and other low- and middle-income countries (LMICs), which harbour an accumulation of factors conducive for high and persistent pneumococcal carriage and transmission including, high-density living conditions, poverty and high HIV seroprevalence.[3–5] In 2015, pneumococcal pneumonia accounted for 55.4% (95% Uncertainty Interval (UI): 31.5–79.1) of lower respiratory deaths in all ages.[1] Implementation of treatment strategies, which focus on early detection and antimicrobial therapy of suspected pneumonia cases, has been difficult in Africa.[6] Therefore, introduction of an effective vaccine against pneumococcal carriage for children is crucial in this region as carriage is a prerequisite for disease.

With support from Gavi (the Vaccine Alliance), 34 African countries introduced the pneumococcal conjugate vaccines (PCV7/10/13) into their extended immunisation programmes between 2009 and 2015 [7,8] in line with WHO recommendations.[9] These vaccines have been shown to be highly effective in reducing both incidence of pneumococcal disease and prevalence of carriage by some of the most pathogenic of the 97 known pneumococcal serotypes.[10] Furthermore, the vaccine indirectly protects the PCV-unvaccinated population against pneumococcal carriage and disease by reducing pneumococcal transmission from PCV-vaccinated children who are at greater risk of carriage and, therefore, sources of transmission.[2,11–13] However, PCV's indirect protection on other high-risk populations (including HIV-infected individuals) remains to be seen in Africa.[11,14] Studies conducted in Africa

have demonstrated high nasopharyngeal (NP) carriage of pneumococcus among the HIV-infected adults on antiretroviral therapy (ART), with estimated point prevalence ranging between 40-80%.[12,15] Therefore, it remains uncertain whether the introduction of PCV in Africa will achieve the sustained direct or indirect protection necessary to reduce pneumococcal carriage to levels sufficient to interrupt transmission and disease.[16]

Systematic reviews that have been done so far on the impact of PCV in Africa have focused on carriage and clinical pneumonia endpoints in children.[17,18] None have summarised these data in the adult or important at-risk populations like HIV-infected individuals. We therefore plan to synthesise the available published data and update the evidence on the impact of the PCV vaccine introduction on pneumococcal carriage (VT and NVT), pneumococcal pneumonia and associated mortality in Africa between 2000–2019.

Objectives

General objectives

1. To summarise available data on the impact of the pneumococcal conjugate vaccine on the prevalence of pneumococcal carriage (VT and NVT) and its impact on pneumococcal pneumonia and associated mortality in Africa between 2000–2019.

Specific objectives

Using data published between 2000 and 2019, this review will assess the impact of PCV by:

1. Comparing the trend in pneumococcal carriage prevalence in Africa before and after PCV introduction.
2. Comparing the trends in the incidence and/ prevalence of pneumococcal pneumonia (invasive and non-invasive) in Africa before and after PCV introduction.
3. Estimating the mortality associated with pneumococcal pneumonia in Africa.

Methods

Information sources, search strategy and study identification

We will conduct a comprehensive literature search in PubMed, MEDLINE database, the Excerpta Medica Database (EMBASE), the ISI Web of Science (Science Citation Index), Scopus and the African Index Medicus to identify all studies published between 1st January 2000 to 31st December 2019, meeting our inclusion and exclusion criteria using the literature search strategy outlined in **table 1**. Using a structured screening guide, we will screen the reference lists for eligible articles and relevant reviews as well as conference abstracts to identify additional sources of information. Search results will be compiled and managed using the EndNote X9 citation software.

Eligibility criteria of relevant studies

Inclusion criteria

Population: Children (1-15 years), adults (15-64 years) the elderly (>65yrs), and HIV-infected individuals (all ages) residing in African countries.

Intervention: Pneumococcal conjugate vaccines (PCV 7, 10, and 13) introduction into the country's routine infant immunisation programmes.

Comparators: 10-year period (2000-2010) before PCV introduction versus 10 year-period (2011-2019) after PCV introduction.

Outcomes: Percentage difference in the pooled point prevalence of pneumococcal carriage post when compared to pre PCV introduction; adjusted prevalence ratios in the pooled prevalence of pneumococcal pneumonia between post and pre PCV introduction; and adjusted mortality rate ratios for post and pre PCV introduction.

Type of studies: We will include randomised control trials (RCTs), non-randomised trials and observational studies reporting prevalence of pneumococcal carriage and/or incidence rates for disease and/or deaths and were published between 1st January 2000 and 31st December 2019 without language restriction.

Serotyping methods: For pneumococcal carriage, identification and serotyping of *S. pneumoniae* must be from a pernasal swab using culture (as per WHO guidelines [19], polymerase chain reaction (Lyt-A gene amplification), microarray or based on whole genome sequencing (WGS).

Pneumococcal pneumonia: For a pneumococcal pneumonia diagnosis among adults, a minimum of either (i) symptoms consistent with an acute chest infection (at least cough or dyspnoea) or (ii) new infiltrates on radiograph and (iii) pneumococcal antigen detection in either blood, urine or pleural fluid. For children (1-15 years), the case definition is the criteria for adults plus symptoms of fast breathing, chest-indrawing and nasal flaring. These definitions have been adopted in order to increase the specificity of identifying pneumococcal pneumonia but are limited in their sensitivity.

Study exclusion criteria

1. Any study reporting impact data of vaccines within 12-months of PCV introduction into routine extended programme of immunisation and data reported in such a way that impact cannot be defined without data from within 12 months of PCV introduction.
2. Studies with small sample size (less than 50 participants), letters, commentaries, narratives and editorials, will be excluded as they are likely to have biased estimates, and this could affect our estimates.

3. Studies that did not distinguish between pre- and post-PCV introduction periods in the data presented.

Data extraction

Three independent reviewers (NLK, TKN and TDS) will assess the articles for inclusion based on a pre-determined inclusion and exclusion criteria. Those included after initial screening will be further evaluated for methodological quality and presence of bias. Refer to section *Appraisal of quality of reporting and the risk of bias for methods* below for further details. Discordance will be resolved by discussion between reviewers to reach consensus or by a fourth member of the team (KJ). All articles retrieved will be stored and managed using Endnote X9 throughout the review process. A standardised data extraction form designed specifically for each outcome of interest, will be used to collect information on the following parameters:

1. Study identification: name of first author, year of publication, year of participant inclusion, country, type of publication, language of publication.
2. Study characteristics: study design (e.g. cross-sectional, cohort, case control, clinical trial), setting (hospital, outpatient, population, institution (e.g. school or care facility), urban/rural), period of surveillance/recruitment, sample size, age (mean or median; range), proportion of HIV-infected participants and method of confirmation (if any), proportion on ART (if any), proportion PCV-vaccinated (if any), proportion with natural pneumococcal carriage (VT, NVT, total), diagnostic method for pneumococcal carriage detection and serotyping (culture, PCR, DNA microarray, WGS), diagnostic criteria for pneumococcal pneumonia, duration of follow up for cohort studies, mortality rates.
3. Epidemiological estimates of pneumococcal carriage: prevalence of VT and NVT carriage

4. Epidemiological estimates for pneumococcal pneumonia: prevalence and/or incidence of pneumococcal pneumonia and/or mortality in all subpopulations, where reported (infants below age of 1 year, children 1-4 years, children 5-15 years and adults (16+ years), the elderly and HIV infected. When estimates are not available or cannot be computed, the corresponding authors will be contacted to request for any missing information of these estimates.

Appraisal of quality of reporting and the risk of bias

We will assess the quality of reporting of the studies using either the Strengthening the Reporting of Observation studies in Epidemiology (STROBE) or the Consolidated Standard of Reporting Trials (CONSORT) checklist depending on the nature of the study (observational study or clinical trial).[20–22]

We will use the 10-item risk of bias tool for prevalence studies developed by Hoy et al [23] to assess the risk of bias for all the studies included using the full text publications. Bias risk scores will be presented in a table and inter-rater agreement will be assessed using a weighted Cohen's kappa statistic.[24–25]

Data analyses and reporting

We will use the metaprop command provided within the STATA software *v*15 to analyse the data.[26] Heterogeneity of studies with similar study characteristics will be evaluated by the $\chi 2$ test on Cochrane's Q statistic [27] and quantified using I^2 values assuming that I^2 of 25%, 50% and 75% represent low, medium and high heterogeneity respectively.[28] Study specific estimates will be pooled through a random effect meta-analysis to obtain an overall summary estimate of the prevalence of *S. pneumoniae* carriage, incidence of pneumococcal pneumonia and mortality after stabilizing the variance of individual studies using the Free man-Tukey

double arcsine transformation.[29] For impact of PCV on carriage, the percentage change in point prevalence will be calculated to compare pooled prevalence estimates in the before and after PCV introduction periods. Mortality rate ratios will be calculated to compare pooled mortality rates for the periods before and after PCV introduction. Meta-analysis results will be presented on a forest plot. Visual analysis of funnel plot and Egger's test will be done to detect small study effect.[30,31] All tests will be two-sided and statistical significance will be defined as $p<0.05$. In case of marked heterogeneity, a descriptive analysis will be done instead of a meta-analysis.

We will report our results according to the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[32] The process with which studies were selected will be summarised using a flow diagram. Reasons for study exclusion will be described and quantitative data will be presented in summary tables and graphs (for trends) where appropriate.

Ethics and dissemination

This systematic review will not require ethical approval as we will be using already published data. The findings will be summarised in a manuscript and submitted in peer-reviewed journals and presented at relevant conferences.

Patient and public involvement

This systematic review will use published scientific data and will not involve patients or members of the public.

Contributions: NLK, TKN, KCJ and TDS conceived the study and drafted the manuscript. The manuscript was revised by DE, SBG, NF, RSH and KCJ. All authors approved the final version of the manuscript. TKN is the guarantor of the manuscript.

Acknowledgement: The Malawi Liverpool Wellcome Trust (MLW) receives a strategic grant from the Wellcome Trust (UK).

Funding: There was no targeted funding for this work.

Conflict of interests: No competing interests were reported by authors.

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. Heinsbroek E, Tafatatha T, Phiri A, Swarthout TD, Alaerts M, Crampin AC, et al. Pneumococcal carriage in households in Karonga District, Malawi, before and after introduction of 13-valent pneumococcal conjugate vaccination. *Vaccine* 2018;36(48):7369–76.

3. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2015;386(9995):743–800.

4. Melegaro A, Gay NJ, Medley GF. Estimating the transmission parameters of pneumococcal carriage in households. *Epidemiol Infect* 2004;132(3):433–41.

5. Hill PC, Townend J, Antonio M, Akisanya B, Ebruke C, Lahai G, et al. Transmission of *Streptococcus pneumoniae* in rural Gambian villages: a longitudinal study. Clin Infect Dis 2010;50(11):1468–76.

6. Pio A. Standard case management of pneumonia in children in developing countries: the cornerstone of the acute respiratory infection programme. *Bull World Health Organ* 2003;81(3):298–300.

7. Loharikar A, Dumolard L, Chu S, Hyde T, Goodman T, Mantel C. Status of New Vaccine Introduction — Worldwide, September 2016. *Morb Mortal Wkly Rep* 2016;65(41):1136–40.

8. Susan A. Wang, arsten F. Mantel, Marta Gacic- Dobo. Progress in Introduction of Pneumococcal Conjugate Vaccine—Worldwide, 2000-2013. *Morb Mortal Wkly Rep* 2013;62(16):308–11.

9. WHO. Pneumococcal vaccines WHO position paper 2012 – Recommendations. Vaccine 2012;30(32):4717–8.

10. Chaguza C, Cornick JE, Andam CP, Gladstone RA, Alaerts M, Musicha P, et al. Population genetic structure, antibiotic resistance, capsule switching and evolution of invasive pneumococci before conjugate vaccination in Malawi. *Vaccine* 2017;35(35 Pt B):4594–602.

11. Verani JR, Massora S, Acácio S, Santos RT dos, Vubil D, Pimenta F, et al. Nasopharyngeal carriage of *Streptococcus pneumoniae* among HIV-infected and –uninfected children <5 years of age before introduction of pneumococcal conjugate vaccine in Mozambique. *PLOS ONE* 2018;13(2):e0191113.

12. Heinsbroek E, Tafatatha T, Chisambo C, Phiri A, Mwiba O, Ngwira B, et al. Pneumococcal Acquisition Among Infants Exposed to HIV in Rural Malawi: A Longitudinal Household Study. *Am J Epidemiol* 2016;183(1):70–8.

13. Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. Changing Epidemiology of Invasive Pneumococcal Disease Among Older Adults in the Era of Pediatric Pneumococcal Conjugate Vaccine 2005;294(16):2043–51.

14. Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. *N Engl J Med* 2015;372(12):1114–25.

15. Swarthout TD, Fronterre C, Lourenço J, Obolski U, Gori A, Bar-Zeev N, et al. High residual prevalence of vaccine serotype *Streptococcus pneumoniae* carriage 4 to 6 years after introduction of 13-valent pneumococcal conjugate vaccine in Malawi: a prospective serial cross-sectional study. bioRxiv 2018 doi.10.1101/445999

16. Olayinka F, Ewald L, Steinglass R. Beyond new vaccine introduction: the uptake of pneumococcal conjugate vaccine in the African Region. *Pan Afr Med J* 2017; 27:1–4.

17. 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; 43:5776–85.

18. Ngocho JS, Magoma B, Olomi GA, Mahande MJ, Msuya SE, de Jonge MI, et al. Effectiveness of pneumococcal conjugate vaccines against invasive pneumococcal disease among children under five years of age in Africa: A systematic review. *PLoS ONE* 14(2):e0212295

19. Satzke C, Turner P, Virolainen-Julkunen A, Adrian PV, Antonio M, Hare KM, et al. Standard method for detecting upper respiratory carriage of *Streptococcus pneumoniae*: Updated recommendations from the World Health Organization Pneumococcal Carriage Working Group. *Vaccine* 2013;32(1):165–79.

20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ 2007*; 335(7624):806–8.

21. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.

22. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals.

Cochrane Methodology Review Group, editor. *Cochrane Database Syst Rev* 2012 doi.10.1002/14651858.MR000030.pub2

23. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012; 65(9):934–9.

24. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psychol Bull* 1968;70(4):213–20.

25. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Medica* 2012;276–82.

26. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; 72:39.

27. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006;11(2):193–206.

28. Delgado-Rodríguez M, Sillero-Arenas M. Systematic review and meta-analysis. *Med Intensiva* 2018;42(7):444–53.

29. White IR. Multivariate Random-effects Meta-analysis. *Stata J* 2009;9(1):40–56.

30. Sterne JAC, Egger M. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *J Clin Epidemiol* 2001;10.

31. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; 343: d4002–d4002.

32. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283:2008–12.

385

Table 1	Search strategy
Search	Search terms and combinations
1	("Pneumococc*" OR "*Strep** pneumo" OR "*S.* pneumo*" OR "*Streptococc**")
2	("Pneumococcal vaccines" OR "streptococcal vaccines" OR "Pneumococcal conjugate vaccine")
3	(("Africa" OR "Africa*" OR "Algeria" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cape Verde" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Democratic Republic of Congo" OR "Congo" OR "Ivory Coast" OR "Djibouti" OR "Egypt" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Morocco" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Tunisia" OR "Uganda" OR "Zambia" OR "Zimbabwe") NOT ("pig*" OR "Papua"))
4	("carriage" OR "Carriage" OR "coloniz*" OR "Coloniz*" OR "colonis*" OR "Colonis*" OR "acquisition" OR "acquir*" OR "carrier state" OR "Carrier state")
5	("Pneumococc* pneumonia" OR "Community acquired pneumonia" OR "Non-invasive pneumonia" OR "Invasive pneumococc* pneumonia" OR "CAP" OR "IPD")
6	("mortality rate" OR "case fatality" OR "death rate")
7	Carriage: #1 AND #2 AND #3 AND #4
8	Pneumococcal pneumonia and associated mortality: #1 AND #2 AND #3 AND (#5 AND/OR #6)
9	Filters: Publication date from 2000/01/01 to 2019/06/30; Humans

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	16

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9-10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.