BMJ Open

Prevalence of respiratory bacterial infections in people with lower respiratory tract infections in Africa: the BARIAFRICA systematic review and meta-analysis protocol

Serges Tchatchouang,[1,2,3] Jean Joel Bigna,[4] Ariane Nzouankeu,[1] Marie-Christine Fonkoua,[1] Jobert Richie Nansseu,[5] Marie S Ndangang,[6] Sebastien Kenmoe,[2] Véronique B Penlap,[3] Richard Njouom[2]

For numbered affiliations see end of article.

Correspondence to
Professor Richard Njouom;
njouom@pasteur-yaounde.org

ABSTRACT

Introduction The burden of lower respiratory tract infections (LRTIs) is a substantial public health concern. However, the epidemiology of LRTI and its bacterial aetiologies are poorly characterised, particularly in the African continent. Providing accurate data can help design cost-effective interventions to curb the burden of respiratory infections in Africa. Therefore, the aim of this systematic review and meta-analysis will be to determine the prevalence of respiratory Bacterial Aetiologies in people with low Respiratory tract Infections in Africa (BARIAFRICA) and associated factors.

Methods and analysis We will search PubMed, EMBASE, Web of Science, African Journals Online, Cumulative Index to Nursing and Allied Health Literature, and Global Index Medicus to identify studies that reported the prevalence (of enough data to compute this estimate) of respiratory bacterial infections in people with LRTIs in Africa from 1 January 2000 to 31 March 2018, without any linguistic restrictions. Study selection, data extraction and risk of bias assessment will be conducted independently by two investigators. Heterogeneity will be evaluated using the χ^2 test on Cochran's Q statistic and quantified with H and I^2 statistics. Prevalence will be pooled using a random-effect meta-analysis model. Subgroup and meta-regression analyses will be used to identify sources of heterogeneity of prevalence estimates. This study will be reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Ethics and dissemination Since this study will be based on published data, it does not require ethical approval. This systematic review and meta-analysis is intended to serve as a basis for determining the burden of LRTIs, for identifying data gaps and for guiding future investigations in Africa. The final report will be published in peer-reviewed journals, presented in conferences and submitted to relevant health policy makers.

PROSPERO registration number CRD42018092359.

Strengths and limitations of this study

► To the best of our knowledge, this work will be the first systematic review and meta-analysis reporting the prevalence of respiratory bacterial infection in people with lower respiratory tract infections in Africa.
► This study will inform and guide policy and practice in decision-making, and guide researchers in future investigations in the field of respiratory bacterial infections.
► Two review authors will independently assess the study selection, data extraction and risk of bias in included studies.
► The study will be limited by the broad spectrum of definition of cases of lower respiratory tract infection according to the authors of included articles.

INTRODUCTION

Respiratory tract infections are common conditions among humans, with a high burden in terms of public health.[1] Depending on their location, diseases can be divided into upper and lower respiratory tract infections (LRTIs).[2] LRTIs including bronchitis, bronchiolitis and pneumonia[3] are heavy burden diseases, and also cause significant economic losses in low-income/middle-income countries and especially those in Sub-Saharan Africa.[4 5] In Sub-Saharan Africa, LRTIs rank third after HIV/AIDS and malaria in terms of causes of mortality. LRTIs are the leading cause of death in nine African countries.[6] A systematic analysis in 2015 found that LRTIs caused 2.74 million deaths and 103 million disability-adjusted life-years (DALYs) worldwide, making them the fifth leading cause of death overall and the second leading cause of DALYs.[7] Compared

to other regions, the burden of these infections is higher in Sub-Saharan Africa and Asia, where the highest mortality are among children under 5. For instance, 546.8 and 511.3 deaths per 100 000 were reported in Somalia and Chad, respectively. Meanwhile, the lowest reported mortality was in Finland in Western Europe, with 0.65 deaths per 100 000.[7] Several bacteria have been identified as the aetiology of LRTIs, including *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter* species, *Streptococcus viridans*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus* species.[7] [8] The epidemiology of LRTIs in Africa can be specific based on sociodemographical, environmental and ecological specificities. A systematic review performed between 2000 and 2015 showed the prevalence of respiratory pathogens in children under 5 living in Sub-Saharan African countries.[9] Apart from the fact that the systematic review focused only on children, it did not take into account data from entire Africa and did not perform any meta-analysis of the included studies. To the best of our knowledge, there is no previous review that assessed respiratory bacterial aetiologies in people with LRTIs in Africa. We present here a protocol for a systematic review and meta-analysis to summarise data on the prevalence of respiratory Bacterial Aetiologies in people with low Respiratory tract Infections in Africa (BARIAFRICA), with the aim to provide accurate data for designing cost-effective interventions to curb the burden of respiratory infections in Africa and to guide future research.

Review questions

1. What is the prevalence and aetiologies of respiratory bacterial infections among people with LRTIs living in Africa?
2. What are the sources of heterogeneity of the prevalence of respiratory bacterial infections in people with LRTIs in Africa?

METHODS AND ANALYSIS
Design and registration

This systematic review and meta-analysis protocol will be conducted following the Centre for Reviews and Dissemination guidelines.[10] The present BARIAFRICA systematic review and meta-analysis protocol was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[11] The study protocol was registered with PROSPERO registration number CRD42018092359.

Criteria to consider studies for this review
Inclusion criteria

1. Types of studies: We will consider cross-sectional studies, case–control studies, baseline data of cohort studies, surveillance data, as well as control group (without any intervention) of clinical trials.
2. Types of participants: We will consider studies conducted in people with clinically diagnosed LRTIs residing

in Africa regardless of age group and settings. LRTIs had to be diagnosed by a physician.
3. Types of outcomes: We will consider studies reporting the prevalence of respiratory bacterial infections regardless of laboratory diagnostic technique used (or enough data to compute this estimate). Prevalence will be calculated as the number of respiratory bacterial infection on the number of people with LRTI among which specific bacteria were searched.
4. Studies that have been published from 1 January 2000 until 31 March 2018.
5. Studies published regardless of language of publication.

Exclusion criteria

1. Studies conducted during or after outbreak period.
2. Case reports, letters, conference abstracts, comments, editorials and case series (<30 participants).
3. Studies with imported cases of respiratory bacterial infections.

Search strategy for identifying relevant studies

The search strategy including the name of all African countries and their synonyms will be applied in electronic databases. The name of the country in the language relevant to that region will also be applied. Relevant articles will be searched by combining keywords in the field of lower respiratory infections and the names of African subregions. The following databases will be used: Medline through PubMed, EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature, African Journals Online, and Global Index Medicus. The search strategy used in PubMed is presented in online supplementary table 1. The search strategy will be adapted for other databases. The reference list of the eligible articles and relevant reviews will be manually searched to identify additional studies.

Selection of studies for inclusion in the review

Using the Rayyan application,[12] two review authors will independently select records based on titles and abstracts. Any disagreement will be solved by discussion and consensus, or will involve a third review author as an arbitrator. Studies in language different from English or French will be translated using Google Translate and considered for eligibility. Two review authors will independently evaluate the full text of the selected records. Discrepancies will be resolved by consensus or by an arbitration of a third review author. The agreement between the two first review authors will be estimated by Cohen's kappa coefficient.[13]

Risk of bias assessment

The evaluation of included studies for risk bias will be done using an adapted version of the risk of bias tool for prevalence studies developed by Hoy *et al.*[14] Based on this tool, studies will be rated as low risk, moderate risk and high risk with scores ≤5, 6–8 and >8, respectively. The defined questions will be scored with 0 for no and 1 for yes. The total score of each article will be calculated by the

sum of its points. Discrepancy in risk of bias assessment among the review authors will be solved by discussion and consensus, or by arbitration of a third review author.

Data extraction and management
Study characteristics such as name of the first author, year of publication, study population, number of bacteria searched, age range, study design, setting, diagnostic criteria and outcomes measured, location, country in which the study was conducted, criteria for sample selection and sample size, city, latitude, longitude, altitude, clinical presentation, number of clinical isolates, comorbid conditions/underlying conditions, number of patients tested, number of patients infected with bacteria, diagnostic technique used, and male proportion will be recorded. Prevalence by country will be calculated for multinational studies. Where cases and samples for estimating prevalence will not be available, we will contact the corresponding author of the study to request the missing information. The countries will be grouped into regions according to the United Nations Statistics Division (UNSD). Lower respiratory infections will be classified as bronchitis, bronchiolitis and pneumonia. Data extraction will be done independently by two review authors. Disagreements between the two review authors will be solved by discussion, or if necessary will involve a third review author for arbitration.

Data synthesis
Data will be analysed using the *'meta'* and *'metafor'* packages of the R statistical software (V.3.4.4, R Foundation for Statistical Computing, Vienna, Austria). Unadjusted prevalence will be recalculated based on the information on crude numerators and denominators provided by individual studies. Prevalence will be reported with their 95% confidence and prediction intervals. To keep the effect of studies with extremely small or extremely large prevalence estimates on the overall estimate to a minimum, the variance of the study-specific prevalence will be stabilised with the Freeman-Tukey double arcsine transformation before pooling the data with the random-effects meta-analysis model.[15] Only studies conducted in populations with close clinical presentation/underlying conditions and with same laboratory diagnostic technique will be pooled together. If it is not possible to conduct meta-analysis, data will be synthesised using a narrative approach. Egger's test will be used to detect the presence of publication bias.[16] A p value <0.10 on Egger's test will be considered indicative of statistically significant publication bias. Heterogeneity will be evaluated by the χ^2 test on Cochran's Q statistic,[17] which will be quantified by H and I^2 values. The I^2 statistic estimates the percentage of total variation across studies due to true between-study differences rather than chance. In general, I^2 values greater than 60%–70% indicate the presence of substantial heterogeneity.[18]

In the case of substantial heterogeneity, subgroup and meta-regression analyses will be used to investigate sources of heterogeneity. Subgroup analyses will be performed for the following subgroups: children versus adults, UNSD African regions, level of country income, clinical presentation, setting (primary care, intensive care and emergency units, inpatients, outpatients) and study period of inclusion. Univariable and multivariable meta-regression analyses will be used to test for an effect of study and participants' characteristics (year of publication, seasonality, setting, clinical presentation, comorbid conditions, number of screened bacteria, age groups, population, UNSD regions, absolute latitude (distance to equator), latitude, longitude and altitude). To be included in multivariable meta-regression analysis, a p value <0.25 in univariable analysis will be required. For categorical variables, the global p value will be considered for inclusion in multivariable models. We will apply a manual forward selection procedure to identify factors independently associated with the variation of the overall prevalence. We will successively add in the model the more significantly associated variables. The final model that will be considered is the one with the lowest Bayesian Information Criterion. A p value <0.05 will be considered statistically significant. Following crude overall prevalence, we will conduct two sensitivity analyses to assess the robustness of our findings. The first one will include only studies with low risk of bias and the second only studies reporting data of a full year(s) period (complete season(s)).

Potential amendments
We do not plan to make any changes to this protocol. However, if substantial changes occur during the review, they will be reported in the published results.

Patient and public involvement
Patients and the public were not involved in the conception and design of this protocol.

ETHICS AND DISSEMINATION
This work relies on published data and therefore does not require an ethical approval. The findings will be published in a scientific peer-reviewed journal. They will be also submitted to conferences and to relevant public health actors.

CONCLUSIONS
Taking into account the burden of LRTIs in Africans, the findings from this systematic review and meta-analysis will be useful for health stakeholders and will provide information that can lead to efficient strategies for controlling the burden of LRTIs in Africa. As all settings in Africa are not able to diagnose bacterial aetiologies in people with LRTI, knowledge of major respiratory bacterial infections can help in this case to orientate the first-line treatment. Different definitions of LRTIs and inclusion

criteria would lead to substantial heterogeneity during meta-analysis.

Author affiliations
[1]Department of Bacteriology, Centre Pasteur of Cameroon, International Network of Pasteur Institutes, Yaoundé, Cameroon
[2]Department of Virology, Centre Pasteur of Cameroon, International Network of Pasteur Institutes, Yaoundé, Cameroon
[3]Department of Biochemistry, Faculty of Science, University of Yaoundé I, Yaoundé, Cameroon
[4]Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, International Network of Pasteur Institutes, Yaoundé, Cameroon
[5]Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon
[6]Department of Medical Information and Informatics, Rouen University Hospital, Rouen, France

Contributors ST, JJB, SK and RN conceived the protocol, and AN, MSN, VBP and M-CF designed the protocol. ST, JJB and SK drafted the manuscript. ST, JJB, SK, MSN, AN, VBP, M-CF and RN revised the successive drafts of the manuscript. All authors approved the final version of the manuscript.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Khan S, Priti S, Ankit S. Bacteria etiological agents causing lower respiratory tract infections and their resistance patterns. *Iran Biomed J* 2015;19:240–6.
2. Neumark T. *Treatment of respiratory tract infections in primary care with special emphasis on Acute Otitis Media (Medical Dissertations)*: Linköping University, 2010.
3. Kocsis B, Szabo D. New treatment options for lower respiratory tract infections. *Expert Opin Pharmacother* 2017;18:1345–55.
4. WHO. *Estimating the burden of respiratory diseases. Practical Approach to Lung Health: manual on initiating PAL Implementation*. Geneva: WHO, 2008:138.
5. Bates M, Mudenda V, Mwaba P, *et al*. Deaths due to respiratory tract infections in Africa: a review of autopsy studies. *Curr Opin Pulm Med* 2013;19:229–37.
6. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385:117–71.
7. GBD 2015 LRI Collaborators. 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;17:1133–61.
8. Uzoamaka M, Ngozi O, Johnbull OS, *et al*. Bacterial etiology of lower respiratory tract infections and their antimicrobial susceptibility. *Am J Med Sci* 2017;354:471–5.
9. Sanou AM, Cissé A, Millogo T, *et al*. Systematic review of articles on etiologies of acute respiratory infections in children aged less than five years in Sub-Saharan Africa, 2000-2015. *EC Microbiology* 2016;6:556–71.
10. Centers for reviews and dissemination. CRD's guidance for undertaking reviews in healthcare. 2009.
11. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
12. Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
13. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005;37:360–3.
14. Hoy D, Brooks P, Woolf A, *et al*. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934–9.
15. Barendregt JJ, Doi SA, Lee YY, *et al*. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–8.
16. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
17. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101–29.
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.