Prevalence, incidence and aetiologies of pulmonary hypertension in Africa: a systematic review and meta-analysis protocol

Jean Joel Bigna,1,2 Jean Jacques Noubiap,3 Jobert Richie Nansseu,4,5 Leopold Ndemnge Aminde6,7

ABSTRACT

Introduction There are no data summarising the epidemiology of pulmonary hypertension (PH) among adults residing in Africa. Establishment of accurate epidemiological data on PH in this region may guide decision-making toward interventions to curb the burden of PH in Africa. The aim of this systematic review is to determine the prevalence, incidence and aetiologies of PH among people residing in Africa.

Methods and analysis This systematic review and meta-analysis will follow the MOOSE guidelines for reporting. Relevant abstracts published until 30 September 2016 will be searched in PubMed/Medline, EMBASE (Excerpta Medica Database), African Journals Online and Africa Index Medicus. Full texts of eligible studies will then be accessed through PubMed, Google Scholar, HINARI and the respective journals’ websites. Relevant unpublished papers and conference proceedings will also be checked. Data will be analysed using STATA version 13 software. The study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence/incidence and aetiologies of PH across studies. Heterogeneity of studies will be evaluated by the $\chi^2$ test on Cochrane’s Q statistic. Funnel plot analysis and Egger’s test will be done to detect publication bias. Results will be presented by geographical region (central, eastern, northern, southern and western Africa).

Ethics and dissemination The current study is based on published data; ethical approval is, therefore, not required. This review will guide policy, practice and research by providing information on the magnitude of PH among people residing in Africa. Findings will be presented in evidence tables of individual studies as well as in summary tables. The final report of this systematic review, in the form of a scientific paper, will be published in a peer-reviewed journal. Furthermore, findings will be presented at conferences and submitted to relevant health authorities.

Review registration number PROSPERO CRD42016049351.

INTRODUCTION

Pulmonary hypertension (PH) is the increase in vascular resistance in the pulmonary circulation. It is defined by a mean pulmonary arterial pressure ≥25 mm Hg at rest by right heart catheterisation.1 Its clinical classification is related to the five main aetiologies including left heart diseases, respiratory diseases and/or hypoxaemia, chronic thromboembolic disease, unclear multifactorial mechanisms and pulmonary arterial hypertension.2 Its epidemiology in Africa is not well described to date, but its main aetiologies include schistosomiasis, HIV/AIDS, rheumatic heart diseases, chronic hepatitis B and C, hereditary haemoglobinopathies and tuberculosis which are endemic in Africa.3–12

In a recent systematic review with meta-analysis of the prevalence and incidence of pulmonary hypertension in HIV-infected people living in Africa,3 we found a prevalence of 14% among HIV-infected adults in the cardiology units in Africa. Following the publication of this review among HIV-infected patients, to the best of our knowledge, we have not found a review that includes all populations living in Africa. We therefore found it necessary to carry out a review of PH in other different populations. This review will also allow us to determine the epidemiology of PH in Africa and to compare different populations. Recently, researchers in Africa explored the clinical, aetiological,
therapeutic and prognostic aspects of PH via the Pan African Pulmonary hypertension Cohort study. While Africa may potentially carry the highest burden of PH owing to the endemcity of its main aetiologies and risk factors in the region, only 1% of publications on PH originate from this region. Indeed, some evidence suggests that Africa would be the most affected part of the world. Since there are limited data in Africa, it is of significant importance to have an estimate of the overall prevalence of PH on the African continent. This synthesis of data will further assist in identifying caveats in current evidence requiring further research in order to have better knowledge on PH in Africa. In addition to increasing awareness among clinicians and promoting research in this area, such epidemiological estimates are particularly relevant for priority setting and to guide the implementation of health policies and interventions to reduce the burden of this disease in this region.

OBJECTIVE
The objective of this study is to conduct a systematic review and meta-analysis to determine the prevalence, the incidence and aetiologies of PH among Africans residing in Africa.

REVIEW QUESTIONS
This review of studies published until 30 September 2016 will seek to answer the following questions: (1) What is the prevalence of PH among people residing in Africa? (2) What is the incidence of PH among people residing in Africa? (3) What are the main aetiologies of PH in among people residing in Africa?

CRITERIA FOR CONSIDERING STUDIES FOR THE REVIEW
Inclusion criteria
► Cross-sectional, case–control or cohort studies conducted in adults (18 years or older) residing in African countries and reporting prevalence or incidence of PH, or enough data to compute these estimates, or studies reporting PH aetiologies.
► Diagnosis of PH should be based on right heart catheterisation with a mean pulmonary arterial hypertension ≥25 mm Hg or Doppler echocardiography examination with pulmonary arterial systolic pressure >35 mm Hg.
► Published and unpublished studies reported from inception to 30 September 2016. No language restriction will be applied.

Exclusion criteria
► Studies conducted among populations of African origin residing outside Africa.
► Studies not performed in human participants.
► Case series with small sample sizes (less than 30 subjects), reviews, letters, commentaries or editorials.
► Studies lacking primary data and/or explicit method description.
► Duplicates (for studies published in more than one paper, the most comprehensive and reporting the largest sample size will be considered).
► Studies whose key data will not be accessible even after request from authors.

SEARCH STRATEGY FOR IDENTIFYING RELEVANT STUDIES
The search strategy will be implemented in two stages.

Bibliographic database searches
An expert Liberian will conduct a comprehensive and exhaustive search of PubMed/MEDLINE, EMBASE (Excerpta Medica Database), African Journals Online and African Index Medicus to identify all relevant articles published on PH in Africa until 30 September 2016, without any language restriction. Both text words and medical subject heading terms will be used. Key search terms will be ‘Africa’, ‘pulmonary hypertension’, and ‘pulmonary arterial hypertension’. Individual country names for the 54 African countries will also be used as additional key search terms for more abstracts on the subject. Abstracts of all eligible papers will be reviewed, and full texts of articles will be accessed through PubMed, Google Scholar, HINARI or journals’ websites. The main search strategy is shown in table 1.

Searching for other sources
References of all relevant original and review articles will be scrutinised for additional potential data sources, and their full texts will be accessed in a similar way. Conference proceedings will also be checked to identify relevant unpublished/ unidentified papers. Authors whose full-text papers will not be accessible by the numerous internet-based sources will be contacted via email to provide them or related data. In case of no feedback from these authors, the corresponding studies will be excluded.

SELECTION OF STUDIES FOR INCLUSION IN THE REVIEW
Assessment of eligible papers will be independently conducted by two members of the team and using an assessment guide to ensure that the selection criteria are reliably applied by all the investigators. They will also consensually retain the studies that will be included in the review, and any disagreement will be solved by arbitration of a third assessor.

ASSESSMENT OF METHODOLOGICAL QUALITY AND DATA REPORTING
The Newcastle-Ottawa Scale (NOS) will be used to evaluate the methodological quality of studies included in this review (see online supplementary appendix 1). An adapted version of this NOS will be used in this study. It is formulated by a star allocation system, assigning a maximum of 10 stars for the risk of bias in three areas: selection of study participants (3 stars maximum), control...
of confounders (2 stars maximum) and the outcome of interest, here PH (5 stars maximum). There is no validation study that provides a cut-off score for rating low-quality studies; a priori, we will consider 0–4, 5–7 and 8–10 stars as high, moderate and low risk of bias, respectively.

**DATA EXTRACTION AND MANAGEMENT**

Search results will be compiled using citation management software, EndNote X7.2.1. A data extraction sheet will be used to collect information about the following:

- General information: authors, year of publication, year of participants’ inclusion, country, regions in Africa, type of publication, language of publication (full text).
- Study characteristics: study design, setting, sample size, mean or median age, age range, proportions of male participants, diagnostic criteria for PH, disease specific/profile-specific to the study population.
- Aetiologies of PH: reported number of each aetiology of PH as classified by Simonneau *et al.*

In case of multinational studies, we will separate the results to show the prevalence/incidence within individual countries. The corresponding author of the study will be contacted to request data for individual countries. Where it will not be possible to disaggregate the data by country, the study will be presented as one, and the countries in which the study was done will be shown.

### Data synthesis including assessment of heterogeneity

Data will be analysed using Stata software (Release 13). A meta-analysis will be conducted for data obtained from studies in which PH was defined identically in the same population. SEs for the study-specific estimates will first be determined from the point estimate and the appropriate denominators, assuming a binominal (or Poisson for incidence data) distribution. Then, the study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence/incidence across studies, after stabilising the variance of individual studies using the Freeman-Tukey double arc-sine transformation.

Heterogeneity will be evaluated by the $\chi^2$ test on Cochrane’s Q statistic which is quantified by $I^2$ values, assuming that $I^2$ values of 25%, 50% and 75%, respectively, represent low, medium and high heterogeneity. Where substantial heterogeneity will be detected, a subgroup analysis will be performed to detect its possible sources using the following grouping variables: age group, sex (male vs female), study setting (hospital vs community based), geographical area (central, eastern, northern, southern and western Africa), disease-specific/profile-specific populations and study methodological quality. Inter-rater agreement for study inclusion and data extraction will be assessed using Cohen’s kappa ($\kappa$) coefficient. Funnel plot analysis and Egger’s test will be done to detect publication bias. A p value <0.05 will be considered indicative of statistically significant publication bias. Results will be presented overall and by geographic region (central, eastern, northern, southern and western Africa). We plan to do a narrative synthesis in the event of limited data for a meta-analysis fulfilling one of the objectives.

### RESULTS REPORTING AND PRESENTATION

The resulting systematic review and meta-analysis will follow the MOOSE guidelines for reporting. The study selection process will be summarised using a flow diagram.
Reasons of studies' exclusion will be described. Quantitative data will be presented in evidence tables of individual studies as well as in summary tables and forest plots where appropriate. We plan to report on quality scores and risk of bias for each eligible study.

**DISCUSSION**

This review will guide policy, practice and research by providing information on the magnitude of PH among Africans residing in Africa. Some difficulties may arise during the review. It is possible that most studies will essentially be hospital based or contain poor-quality data when available. Another possible limitation may be heterogeneity in the diagnosis of PH. In addition, it may be difficult to find any study reporting incidence of PH or enough data to compute it as well as aetiologies of PH. Other drawbacks might include the non-random selection of participants and the under-representation of some geographic areas as found in other studies.\(^{3,21}\)

**Ethics and dissemination**

This systematic review and meta-analysis will be based on published data; as such, ethical approval is not a requirement. It is expected to serve as a basis for designing preventive and control strategies for PH and as a guide for future research based on remaining gaps. The final report of this study, in the form of a scientific paper, will be published in peer-reviewed journals. Findings will be further presented at conferences and submitted to relevant health authorities. We also plan to update the review in the future to monitor changes and guide health service and policy solutions. The present protocol has been registered with PROSPERO International Prospective Register of Systematic Reviews: registration number CRD42016049351. This protocol is written in accordance with recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.\(^{22}\)

**Author affiliations**

1. Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon
2. School of Public Health, Faculty of Medicine, University of Paris Sud XI, Le Kremlin Bicêtre, France
3. Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa
4. Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon
5. Sickle Cell Disease Unit, Mother and Child Centre of the Chantal Biya Foundation, Yaoundé, Cameroon
6. Clinical Research Education, Networking and Consultancy (CRENC), Douala, Cameroon
7. Faculty of Medicine & Biomedical Sciences, School of Public Health, University of Queensland, Brisbane, Australia

**Contributors** JJB and JNJ conceived and designed the protocol. JJB drafted the manuscript. JJB, JRJ, LNA and JNJ critically revised the manuscript for methodological and intellectual content. JJB is the guarantor of the review. All authors approved the final version of this manuscript.

**Competing interests** None declared.

**Patient consent** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

**REFERENCES**

Prevalence, incidence and aetiologies of pulmonary hypertension in Africa: a systematic review and meta-analysis protocol

Jean Joel Bigna, Jean Jacques Noubiap, Jobert Richie Nansseu and Leopold Ndemnge Aminde

BMJ Open 2017 7:
doi: 10.1136/bmjopen-2016-014768

Updated information and services can be found at:
http://bmjopen.bmj.com/content/7/6/e014768

These include:

References
This article cites 20 articles, 8 of which you can access for free at:
http://bmjopen.bmj.com/content/7/6/e014768#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Respiratory medicine (348)

Notes
To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/