

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

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## 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 Relevant unpublished papers and conference proceedings will also be checked.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.

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## INTRODUCTION

Pulmonary hypertension (PH) is the increase in vascular resistance in the pulmonary circulation. It is defined by a mean pulmonary

## Strengths and limitations of this study

- This review would possibly be limited by scarcity of studies directly evaluating the incidence and the aetiologies of pulmonary hypertension in Africa.
- Another possible limitation could be the predominance of clinic-based studies, the poor-quality data and the heterogeneity of diagnostic method of pulmonary hypertension.
- There may be a likelihood of under-representation of some geographical areas and predominance of studies with non-random selection of participants.

arterial pressure  $\geq 25$  mm Hg at rest by right heart catheterisation.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3–12</sup>

In a recent systematic review with meta-analysis of the prevalence and incidence of pulmonary hypertension in HIV-infected people living in Africa,<sup>5</sup> 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,



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therapeutic and prognostic aspects of PH via the Pan African Pulmonary hypertension Cohort study.<sup>13</sup> While Africa may potentially carry the highest burden of PH owing to the endemicity of its main aetiologies and risk factors in the region,<sup>3-12</sup> 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.<sup>12</sup> 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  $\geq 25$  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).<sup>14</sup> 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

**Table 1** PubMed/Medline search strategy for studies published from inception to 30 September 2016

Search no	Search terms
1	"Pulmonary hypertension" OR "Pulmonary arterial hypertension"
2	(Africa OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR "Guinea Bissau" OR "Ivory Coast" OR "Cote d'Ivoire" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe OR "Central Africa" OR "Central African" OR "West Africa" OR "West African" OR "Western Africa" OR "Western African" OR "East Africa" OR "East African" OR "Eastern Africa" OR "Eastern African" OR "North Africa" OR "North African" OR "Northern Africa" OR "Northern African" OR "South African" OR "Southern Africa" OR "Southern African" OR "sub Saharan Africa" OR "sub Saharan African" OR "subSaharan Africa" OR "subSaharan African") NOT ("guinea pig" OR "guinea pigs" OR "aspergillus niger")
3	#1 AND #2

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.

- ▶ Prevalence/incidence of PH: where only primary data (sample size/person time of follow-up and number of cases) will be provided, these parameters will be used to calculate the prevalence/incidence estimate. Where prevalence/incidence rates or relevant data for estimating them will not be available, we will contact the corresponding author of the study to request the missing information.
- ▶ Aetiologies of PH: reported number of each aetiology of PH as classified by Simonneau *et al.*<sup>2</sup>

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 binomial (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.<sup>15</sup>

Heterogeneity will be evaluated by the  $\chi^2$  test on Cochran's Q statistic<sup>16</sup> which is quantified by  $I^2$  values, assuming that  $I^2$  values of 25%, 50% and 75%, respectively, represent low, medium and high heterogeneity.<sup>17</sup> 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.<sup>18</sup> Funnel plot analysis and Egger's test will be done to detect publication bias.<sup>19</sup> 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.<sup>20</sup> 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.<sup>5 21</sup>

## 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.<sup>22</sup>

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**Contributors** JJB and JJN conceived and designed the protocol. JJB drafted the manuscript. JJB, JRN, LNA and JJN 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.

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