

# BMJ Open Global prevalence of spondyloarthritis in low-income and middle-income countries: a systematic review and meta-analysis protocol

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**To cite:** Allado E, Moussu A, Bigna JJ, *et al.* Global prevalence of spondyloarthritis in low-income and middle-income countries: a systematic review and meta-analysis protocol. *BMJ Open* 2020;**10**:e041180. doi:10.1136/bmjopen-2020-041180

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-041180>).

Received 02 June 2020

Revised 26 August 2020

Accepted 23 September 2020



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## ABSTRACT

**Introduction** In the past decade, the definition of spondyloarthritis (SpA) has undergone major modifications with respect to new diagnostic tools and classifications. With the advent of biotherapies, treatment possibilities in patients with SpA have substantially improved in the last few years. There is great interest in obtaining accurate data on the disease prevalence, especially in regions where data remains scarce such as low-income and middle-income countries (LMICs), in order to measure and understand the needs of their healthcare systems. Therefore, through a global systematic review and meta-analysis, the current study aims to investigate the prevalence of SpA and human leucocyte antigen B27 (HLAB27) and its association with the risk of SpA in the LMIC population.

**Methods and analysis** We will include cohort, case-control and cross-sectional studies performed among adults (>15 years) living in LMICs. EMBASE, Medline, Global Index Medicus and Web of Knowledge will be searched for relevant records published until 30 April 2020, without any language restriction. The review will be reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. After screening of titles and abstracts, study selection, data extraction and risk of bias assessment by two independent reviewers, we shall assess the studies individually for clinical and statistical heterogeneity. Random-effect meta-analysis will be used to pool studies judged to be clinically homogeneous. Egger's test and visual inspection of funnel plots will be used to assess publication bias. Results will be presented by WHO subregions.

**Ethics and dissemination** Since primary data is not collected in this study, ethical approval is not required. This review is expected to provide relevant data on the epidemiology of SpA, HLAB27 and their association in the global population of LMICs. The final report will be published in a peer-reviewed journal.

**PROSPERO registration number** CRD42020163898.

## INTRODUCTION

Spondyloarthritis (SpA) is a common disease that affects 0.5%–2% of the global population.<sup>1–3</sup> This pathology is characterised by chronic inflammatory pain and debilitating

## Strengths and limitations of this study

- This will be the first systematic review summarising data on the global burden of spondyloarthritis in low-income and middle-income countries and its association with human leucocyte antigen B27 (HLAB27).
- Rigorous methods and robust statistical analyses will be used to minimise bias and provide accurate data.
- No language restriction will be applied, hence, allowing a maximum number of studies to be included in this review.
- The limited number of studies on the topic may represent an important shortcoming, especially for data regarding HLAB27 status.

stiffness, manifesting itself most often in young adult men.<sup>4–6</sup> It is associated with a negative impact on mental health, quality of life and professional activity, generating significant costs.<sup>1 4 7 8</sup> The delay to diagnose this pathology is often long, up to 10 years after the symptoms' onset, increasing the disease burden.<sup>9 10</sup> In our modern era of new targeted therapies, it has become essential to reduce this diagnostic delay, these treatments being all the more effective as the disease is treated at an early stage.<sup>11 12</sup>

The concept and definition of SpA have evolved significantly over the past 30 years,<sup>13–15</sup> leading to the current Assessment of Spondyloarthritis International Society (ASAS) classification criteria.<sup>16 17</sup> The ASAS classification criteria also gives a central place to the detection of the human leucocyte antigen B27 (HLAB27) in the diagnostic and early referral process.<sup>18</sup> SpA prevalence data seems to highlight a strong association with the frequency of HLAB27,<sup>19 20</sup> although this association is not homogeneous depending on the areas of the globe: in fact, we note a

frequent co-occurrence in Western countries (around 90%), which would lower to 50% in Arab countries and become virtually absent in sub-Saharan Africa where the prevalence of the HLAB27 antigen is very low (less than 1%).<sup>21–23</sup> Nevertheless, these global estimates are not generalisable to the population of low-income and middle-income countries (LMICs), where data is based on scattered studies, with a small number of patients and in a limited sample of countries (LMICs).<sup>24</sup> It is thus difficult to distinguish the exact cause of the data heterogeneity, whether linked to demographic or genetic characteristics of the population, frequent underdiagnosis due to a lack of available healthcare facilities and rheumatologists, or methodological biases in data reporting.<sup>24</sup>

Accordingly, we propose this global systematic review and meta-analysis protocol to critically synthesise current evidence on the burden of SpA in LMICs. This study will provide evidence-based and useful data that may raise awareness in healthcare providers, researchers and policy makers for improved detection and management of SpA in the global population of LMICs.

## REVIEW QUESTION

What is the epidemiology of SpA (and its axial form) in LMICs?

## OBJECTIVES

This systematic review and meta-analysis aims:

1. To determine the prevalence of axial SpA in the global population (asymptomatic or referring to inflammatory back pain) in LMICs.

Other objectives:

2. To determine the prevalence of HLAB27 in the global population (asymptomatic, symptomatic and diagnosed SpA) in LMICs.
3. To determine the association between HLAB27 and the risk of SpA in LMICs.

## Methods and analysis

This systematic review and meta-analysis will be reported in conformity with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.<sup>25</sup> The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) was used to report this protocol.<sup>26</sup> The PRISMA-P checklist is attached as online supplemental file 1.

## Criteria for considering studies for the review

SpA will be diagnosed on the basis of clinical and imaging features, in accordance with ‘Assessment of SpondyloArthritis international Society’ (ASAS), ‘European Spondyloarthritis Study Group’ (ESSG), New York, Rome or Amor criteria.<sup>13 14 18 27</sup> The presence of sacroiliitis will be assessed by MRI, CT scan or X-ray, according to the modified New York criteria. HLAB27 detection will be assessed by ELISA, flow cytometry assay, genetic sequence-based

or microlymphocytotoxicity methods.<sup>28 29</sup> Studies where a different definition of SpA would have been used will be retrieved as well and a subgroup analysis will be conducted to assess the effect of the definition on the overall summary effect.

Only participants from LMICs will be included as classified by the World Bank.<sup>30</sup> For the 2020 fiscal year, low-income economies are defined as those with a gross national income (GNI) per capita, calculated using the World Bank Atlas method, of US\$1025 or less in 2018; lower-middle-income economies are those with a GNI per capita between US\$1026 and US\$3995; and upper-middle-income economies are those with a GNI per capita between US\$3996 and US\$12 375.

## Specific criteria for estimating the prevalence of SpA and HLAB27 in the global population of LMICs

1. Population: we will include adults (>15 years), whether they are asymptomatic, symptomatic (ie, inflammatory back pain) or have a diagnosis of SpA.
2. Outcomes: we will consider studies reporting the prevalence of SpA and/or HLAB27 or studies having enough data to compute these estimates, which are number of SpA or HLAB27 cases and total sample size.
3. Study design: we will consider cross-sectional and cohort studies.

## Specific criteria for investigating the association between HLAB27 and risk of SpA

1. Population: we will consider adults (>15 years) with or without any specific medical condition or disease.
2. The exposure will be defined as being HLAB27 positive.
3. The comparator will be defined as a confirmed absence of HLAB27 detection. Patients with ‘confirmed absence of HLAB27 detection’ are HLAB27 negative using the same method of diagnostic as those HLAB27 positive.
4. The outcome will be the presence of SpA, including its axial form, according to prespecified diagnostic criteria.
5. We will consider cross-sectional, case-control and cohort studies. We will consider studies in which both patients HLAB27 positive (exposed group) and HLAB27 negative (non-exposed group) are included and where the proportion of patients with SpA was reported in both groups.

## Search strategy for identifying relevant studies

The search strategy will be conducted as follows.

## Bibliographic database searches

Relevant records will be identified by searching EMBASE, PubMed, Global Index Medicus and Web of knowledge from inception to 30 April 2020. Text words and medical subject heading terms related to SpA and HLAB27 will be used including: ‘ankylosing spondylitis’, ‘sacroiliitis’, ‘Bechterew Disease’, ‘Spondyloarthritis Ankylopoietica’, ‘Marie Struempell Disease’, ‘spine disease’ and

'HLA-B27'. The name of the LMICs (as defined by the World Bank Classification)<sup>30</sup> in the language relevant to each country will also be applied. Online supplemental file 2 shows the full search strategy for EMBASE that will be adapted to fit with other databases. No language restriction will be applied. For articles published in a language other than English and French, an experienced translator in the concerned language will be contacted for translation.

### Searching for other sources

We will scan the references of all relevant articles for additional relevant data sources missed during our search, and their full-texts will be retrieved. References of pertinent reviews will also be scanned.

### Selection of studies for inclusion in the review

All references identified after implementation of the search strategy will be imported into Zotero software. All records obtained from various databases will be combined in a single Zotero library, and duplicates will be removed. Two reviewers (AH and EA) will independently evaluate the studies obtained from the searches, using an assessment form to ensure that selection criteria are reliably applied. These reviewers will screen the titles and abstracts of papers obtained, after which the full texts of potentially eligible papers will be retrieved by one reviewer (AH). The two reviewers will independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion. For duplicates, studies published in more than one report, the one reporting the largest sample size will be considered. Studies with inaccessible full text either online or from the corresponding author will be excluded.

### Assessment of methodological quality and reporting of data

Methodological quality and risk of bias of included studies will be independently assessed by two reviewers using the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool for studies investigating the association between HLAB27 and SpA.<sup>31</sup> For studies investigating prevalence estimates, we will use the risk of bias tool developed by Hoy and colleagues.<sup>32</sup>

### Data extraction and management

A data extraction form will be used to collect information on the surname of the first author, year of publication, country where the study was conducted, study design, study area (rural, urban), sampling method, timing of data collection, population setting (general population, hospitalised patients), type of population (healthy asymptomatic, inflammatory back pain, SpA-diagnosed patients), method of SpA diagnostic, method of HLAB27 detection, mean or median age, proportion of males, specific characteristics of the study population, sample size, number of SpA cases and number of HLAB27-positive cases. For multinational studies, data will be reported for the individual countries. Where it will be impossible to disaggregate data for such studies

by country, available data will be presented as a single study, and each individual country that participated in the study will be reported. We will exclude studies in which relevant data are impossible to extract even after contacting the corresponding author.

### Data synthesis and analysis

In order to measure the association between HLAB27 positivity and risk of SpA, a meta-analysis using the random-effects method of DerSimonian and Laird will be performed to pool weighted ORs of risk estimates.<sup>33</sup> ORs will be reported with their 95% CIs and 95% prediction intervals.<sup>34</sup>

For prevalence synthesis, unadjusted prevalences with their respective standard errors will be recalculated based on the information of crude numerators and denominators provided by individual studies. The variance of the study-specific prevalence will be stabilised with the Freeman-Tukey double arcsine transformation, before pooling the data using a random-effects meta-analysis model.<sup>35</sup> All pooled estimates will be reported with 95% CI and 95% prediction interval. Heterogeneity will be assessed using the  $\chi^2$  test on Cochran's Q statistic and quantified by calculating  $I^2$ .<sup>36</sup> Values of 25%, 50% and 75% for  $I^2$  will, respectively, represent low, medium and high heterogeneity. We will assess the presence of publication bias using inspection of funnel plots (if  $\geq 10$  studies) and Egger's test (if  $\geq 3$  studies).<sup>37</sup> When there will be enough data, meta-regression and subgroup analyses will be performed to investigate possible sources of heterogeneity using the aforementioned variables and the study methodological quality. We plan to do subgroup analysis according to: SpA form (all forms confounded or axial form only), population type, population settings, WHO subregions and the definition used to diagnose SpA. In case of substantial clinical heterogeneity, a narrative summary of findings will be done. The inter-rater agreement for study inclusion between investigators will be assessed using Cohen's  $\kappa$  coefficient.<sup>38</sup> Data analyses will be done using the 'meta' package of the statistical software R V.3.6.2.

### Presentation and reporting of results

The study selection process will be summarised using a flow diagram. Quantitative data will be presented in tables of individual studies and in summary tables or forest plots where appropriate. The quality score of bias for each eligible study will be reported accordingly.

### Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

### Potential amendments

We do not plan to modify the protocol to avoid reporting bias. However, if necessary, any amendment in the review process will be reported for transparency.

## Ethics and dissemination

Since primary data is not collected in this study, ethical approval is not required. This review is expected to provide accurate data on SpA and HLAB27 prevalences, as well as an estimation of their association in LMICs. The final report will be published in a peer-reviewed journal.

## Review status and expected deadlines

Bibliographic database searches (April–May 2020), selection of included studies (June–August 2020), data extraction and management (September–December 2020), data synthesis and analysis (January–February 2021), manuscript submission (April 2021).

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**Acknowledgements** Thank you to Doctor Paul Chamley for his valuable proof-reading.

**Contributors** AH, SH and EA had the original idea. EA, AM, AH and JJB designed and conceived the protocol. AM, EA and AH drafted the manuscript. BC, JJB, SH and AC critically revised the manuscript for methodology and intellectual content. EA and AH are the guarantors of the review. All authors approved the final version of this manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

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

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