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Global burden of spondyloarthritis in low-and-middle income countries: a systematic review and meta-analysis protocol

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Abstract

Introduction

In recent years, the definition of spondyloarthritis (SpA) has seen major modifications with respect of diagnostic tools and classification. With the advent of biotherapies, treatment possibilities in patients with SpA have substantially improved in the last few years, the effect being all the more beneficial when the diagnosis is made at an early course of the disease. This is then of great interest to obtain accurate data on the disease prevalence, especially in the regions where data remain scarce such as low-and-middle income countries (LMICs), in order to measure and understand the needs of health care systems. Therefore, through a global systematic review and meta-analysis, the current study aims at investigating the prevalence of SpA and Human Leukocyte Antigen B27 (HLAB27), and its association with the risk of SpA in the global population of LMICs.

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 September 2019, 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 homogenous. The Egger's test and visual inspection of funnel plots will be used to assess publication bias. Results will be presented by World Health Organization (WHO) sub-regions.

Ethics and dissemination

Since primary data are 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

Strengths and limitations of this study

- This will be the first systematic review summarizing data on the global burden of SpA in LMICs, and its association with HLAB27.
- Rigorous methods and robust statistical analyses will be used to minimize bias and provide accurate data.
- No language restriction will be applied, hence, allowing to include a maximum number of studies in this review.
- Limited number of studies on the topic may represent an important shortcoming, especially for data regarding HLAB27 status.

Introduction

Spondyloarthritis (SpA) is a common disease that affects 0.5 to 2% of the global population [1–3]. This pathology is characterized by chronic inflammatory pain and debilitating stiffness, manifesting most often in young adult men [4–6]. It is associated with a negative impact on mental health, quality of life and professional activity, generating significant costs [1,4,7,8]. The delay to diagnose this pathology is often long, up to 10 years after the symptoms' onset, thus increasing the disease burden [9,10]. In our modern era of new targeted therapies, it became essential to reduce this diagnostic delay, these treatments being all the more effective as the disease is taken care at an early-stage [11,12].

The concept and definition of SpA have evolved significantly over the past thirty years [13–15], leading to the current Assessment of Spondyloarthritis International Society (ASAS) classification criteria, and distinguishing two main forms of the disease according to its clinical and radiological phenotype: radiographic and non-radiographic forms [16,17]. The ASAS classification criteria also gives a central place to the detection of the Human Leukocyte Antigen B27 (HLAB27) in the diagnostic and early referral process [18]. SpA prevalence data seem to highlight a strong association with the frequency of HLAB27 [19,20], 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 drop to 50% in the Arab countries and become virtually zero in sub-Saharan Africa where the prevalence of the HLAB27 antigen is very low (less than 1%) [21–23]. Nevertheless, these global estimates are not generalizable to the population of low-and-middle income countries (LMICs), where the data are based on scattered studies, with small patient numbers, and in a limited sample of countries (LMICs)[24]. It is thus difficult to distinguish the exact cause of the data heterogeneity, whether linked to demographic or genetic characteristics of the population, frequent under-diagnosis due to a lack of suitable health care facilities and rheumatologists, or methodological biases in data reporting [24].

Accordingly, we propose this global systematic review and meta-analysis protocol to critically synthesize current evidence on the burden of SpA in LMICs population. 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 spondyloarthritis (and its axial form) and HLAB27 in low-and-middle-income countries?

Objectives

This systematic review and meta-analysis aims at:

1. Determining the prevalence of axial spondyloarthritis in the global population (asymptomatic or referring for inflammatory back pain) of LMICs
2. Determining the prevalence of HLAB27 in the global population (asymptomatic, symptomatic and diagnosed spondyloarthritis) of LMICs
3. Determining the association between HLAB27 and the risk of spondyloarthritis 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 [25]. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) was used to report this protocol [26]. The PRISMA-P checklist is attached as online **supplementary file 1**.

Criteria for considering studies for the review

Spondylarthritis (SpA) will be diagnosed on the basis of clinical and imaging features, in accordance with 'Assessment of SpondyloArthritis international Society' (ASAS), 'European Spondyloarthropathy Study Group' (ESSG), New York, Rome or Amor criterion [13,14,18,27]. 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 micro-lymphocytotoxicity

methods [28,29]. Study where a different definition of SpA would have been used will retrieved as well and a subgroup analysis will be conducted to assess the effect of the definition on the overall summary effect.

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

1. Population: we will include studies with adults (> 15 years) whether they are asymptomatic, symptomatic (i.e. inflammatory back pain, for example) or have a diagnosed spondyloarthritis.
2. Outcomes: we will consider studies reporting the prevalence of spondyloarthritis 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 for SpA

1. Population: we will consider adults (> 15 years) with or without any specific condition or disease.
2. Exposure will be defined as being HLAB27 positive.
3. 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. 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) will be 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 September 2019. 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 [30]) in the language relevant to each country will also be applied. **Supplementary 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 inside the Zotero software. All records obtained from various databases will be combined in a single Zotero library, and the 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 the 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-randomized Studies – of Interventions (ROBINS-I) tool for studies investigating the association between HLAB27 and SpA [31]. For studies investigating prevalence estimates, we will use the risk of bias tool developed by Hoy and colleagues [32].

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, hospitalized 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 cases of SpA, and number of HLAB27 positive cases. For multinational studies, the data will be reported for the individual countries. Where it will be impossible to disaggregate data for such studies by country, the available data will be presented as a single study, and the individual countries which 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

For measuring 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 Odds Ratios (ORs) of risk estimates [33]. ORs will be reported with their 95% confidence intervals (CIs), and 95% prediction intervals [34].

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 stabilized with the Freeman-Tukey double arc-sine transformation, before pooling the data using a random-effects meta-analysis model [35]. All pooled estimate will be reported with 95% CI and 95% prediction interval. Heterogeneity will be assessed using the χ2 test on Cochran's Q statistic, and quantified by calculating I2 [36]. Values of 25%, 50% and 75% for I2, will respectively represent low, medium and high heterogeneity. We will assess the presence of publication bias using funnel plots inspection (if ≥ 10 studies) and the Egger's test (if ≥ 3 studies) [37]. When there will be enough data, meta-regression and subgroup analyses will be performed to investigate the 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), 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 κ coefficient [38]. 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 summarized 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 are 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

Preliminary searches.

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Authors' contributions

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. 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.

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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 No
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	NA
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	13
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	5-6
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	7-8
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 repeated	7, suppl. tab 2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
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)	7-8
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	8
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

*** 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.**

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

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Abstract

Introduction: In the past decade, the definition of spondyloarthritis (SpA) has undergone major modifications in respect of 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-and-middle income countries (LMICs), in order to measure and understand the needs of their health care systems. Therefore, through a global systematic review and meta-analysis, the current study aims to investigate the prevalence of SpA and Human Leukocyte 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 homogenous. The Egger's test and visual inspection of funnel plots will be used to assess publication bias. Results will be presented by World Health Organization (WHO) sub-regions.

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

Strengths and limitations of this study

- This will be the first systematic review summarizing data on the global burden of SpA in LMICs, and its association with HLAB27.
- Rigorous methods and robust statistical analyses will be used to minimize 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.

Introduction

Spondyloarthritis (SpA) is a common disease that affects 0.5 to 2% of the global population [1–3]. This pathology is characterized by chronic inflammatory pain and debilitating stiffness, manifesting itself most often in young adult men [4–6]. It is associated with a negative impact on mental health, quality of life and professional activity, generating significant costs [1,4,7,8]. The delay to diagnose this pathology is often long, up to 10 years after the symptoms' onset, increasing the disease burden [9,10]. In our modern era of new targeted therapies, it becomes essential to reduce this diagnostic delay, these treatments being all the more effective as the disease is treated at an early-stage [11,12].

The concept and definition of SpA have evolved significantly over the past thirty years [13–15], leading to the current Assessment of Spondyloarthritis International Society (ASAS) classification criteria [16,17]. The ASAS classification criteria also gives a central place to the detection of the Human Leukocyte Antigen B27 (HLAB27) in the diagnostic and early referral process [18]. SpA prevalence data seems to highlight a strong association with the frequency of HLAB27 [19,20], 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%) [21–23]. Nevertheless, these global estimates are not generalizable to the population of low-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)[24]. It is thus difficult to distinguish the exact cause of the data heterogeneity, whether linked to demographic or genetic characteristics of the population, frequent under-diagnosis due to a lack of available health care facilities and rheumatologists, or methodological biases in data reporting [24].

Accordingly, we propose this global systematic review and meta-analysis protocol to critically synthesize 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 spondyloarthritis (and its axial form) in low-and-middle-income countries?

Objectives

This systematic review and meta-analysis aims:

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

Other objectives:

2. To determine the prevalence of HLAB27 in the global population (asymptomatic, symptomatic and diagnosed spondyloarthritis) in LMICs
3. To determine the association between HLAB27 and the risk of spondyloarthritis 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 [25]. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) was used to report this protocol [26]. The PRISMA-P checklist is attached as online **supplementary file 1**.

Criteria for considering studies for the review

Spondylarthritis (SpA) will be diagnosed on the basis of clinical and imaging features, in accordance with 'Assessment of SpondyloArthritis international Society' (ASAS), 'European Spondyloarthropathy Study Group' (ESSG), New York, Rome or Amor criterion [13,14,18,27]. 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 micro-lymphocytotoxicity methods [28,29]. 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[30]. 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 $1025 or less in 2018; lower-middle-income economies are those with a GNI per capita between $1026 and $3995; and upper-middle-income economies are those with a GNI per capita between $3996 and $12,375.

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

1. Population: we will include adults (> 15 years), whether they are asymptomatic, symptomatic (i.e. inflammatory back pain) or have a diagnosed spondyloarthritis.
2. Outcomes: we will consider studies reporting the prevalence of spondyloarthritis 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)[30] in the language relevant to each country will also be applied. **Supplementary 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-randomized Studies – of Interventions (ROBINS-I) tool for studies investigating the association between HLAB27 and SpA.[31] For studies investigating prevalence estimates, we will use the risk of bias tool developed by Hoy and colleagues.[32]

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, hospitalized 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 countriy which 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 mease 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 Odds Ratios (ORs) of risk estimates [33]. ORs will be reported with their 95% confidence intervals (95% CIs), and 95% prediction intervals [34].

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 stabilized with the Freeman-Tukey double arc-sine transformation, before pooling the data using a random-effects meta-analysis model [35]. All pooled estimate 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 I2.[36] Values of 25%, 50% and 75% for I2, will respectively represent low, medium and high heterogeneity. We will assess the presence of publication bias using funnel plots inspection (if $\geq$ 10 studies) and the Egger's test (if $\geq$ 3 studies) [37]. 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 κ coefficient [38]. 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 summarized 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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Authors' contributions

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.

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Competing interests

None declared.

Patient consent for publication

Not required.

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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 No
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	NA
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	13
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	5-6
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	7-8
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 repeated	7, suppl. tab 2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
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)	7-8
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	8
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

*** 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.**

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Additional file 2. Generic Search Strategy.

Targeted databases: PubMed, EMBASE, Global Index Medicus, and Web of knowledge

Period: from inception to 30 September 2019

Search	Search terms
#1	"ankylosing spondylitis" OR "Spondyloarthritis Ankylopoietica" OR "Ankylosing Spondylarthritis" OR "Spondylarthritis Ankylopoietica" OR "Bechterew Disease" OR "Bchterews Disease" OR "Marie Struempell Disease" OR "Rheumatoid Spondylitis" OR "Ankylosing Spondyloarthritis" OR 'spine disease' OR 'spondylarthropathy' OR spondylarthropathies OR spondylarthritis OR sacroiliitis OR "HLA-B27" OR Ankylosis
#2	Afghanistan OR Albania OR Algeria OR "American Samoa" OR Angola OR Argentina OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Belize OR Benin OR Bhutan OR Bolivia OR "Bosnia and Herzegovina" OR Botswana OR Brazil OR Bulgaria OR "Burkina Faso" OR Burundi OR Cabo Verde OR Cambodia OR Cameroon OR "Central African Republic" OR Chad OR China OR Colombia OR Comoros OR "Democratic Republic of Congo" OR Congo OR "Republic of Congo" OR "Costa Rica" OR "Ivory Coast" OR "Cote Ivoire" OR Cuba OR Djibouti OR Dominica OR "Dominican Republic" OR Ecuador OR Egypt OR "El Salvador" OR Salvador OR "Equatorial Guinea" OR Guinea OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Georgia OR Ghana OR Grenada OR Guatemala OR Guinea OR "Guinea-Bissau" OR Guyana OR Haiti OR Honduras OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya OR Kiribati OR Korea OR Kosovo OR Kyrgyz OR "Lao PDR" OR Lao OR Lebanon OR Lesotho OR Liberia OR Libya OR Macedonia OR Madagascar OR Malawi OR Malaysia OR Maldives OR Mali OR "Marshall Islands" OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palau OR Panama OR Papua New Guinea OR Paraguay OR Peru OR Philippines OR Romania OR "Russian Federation" OR Russia OR Rwanda OR Samoa OR "Sao Tomé and Principe" OR Senegal OR Serbia OR "Sierra Leone" OR "Solomon Islands" OR Somalia OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "Vincent and the Grenadines" OR Sudan OR Suriname OR Swaziland OR "Syrian Arab Republic" OR Syria OR Tajikistan OR Tanzania OR Thailand OR "Timor-Leste" OR Timor OR Togo OR Tonga OR Tunisia OR Turkey OR Turkmenistan OR Tuvalu OR Uganda OR Ukraine OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR "West Bank and Gaza" OR Gaza OR Yemen OR Zambia OR Zimbabwe
#3	#1 AND #2

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 No
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	NA
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	13
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	5-6
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	7-8
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 repeated	7, suppl. tab 2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
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)	7-8
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	8
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	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

*** 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.