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Global epidemiology of *Neisseria gonorrhoeae* in infertile populations: protocol for a systematic review

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ABSTRACT

Introduction A key target of the WHO's 'Global Health Sector Strategy on sexually transmitted infections, 2016–2021' is achieving 90% reduction in *Neisseria gonorrhoeae* (gonorrhoea for short) incidence globally by 2030. Though untreated, gonorrhoea has been linked to infertility, the epidemiology of this infection in infertile populations remains poorly understood and somewhat a neglected area of reproductive health. Our proposed systematic review aims to fill this gap by characterising comprehensively gonorrhoea infection in infertile populations globally.

Methods and analysis All available studies of gonorrhoea infection in infertile populations, including infertility clinic attendees, will be systematically reviewed informed by Cochrane Collaboration guidelines. Findings will be reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Data sources will be searched using broad index terms exploded to cover all subheadings and free text terms with no language or year restriction. Any epidemiological measure in infertile populations based on primary data will be eligible for inclusion. Measures based on different assay types will be extracted as separate studies for different analyses. Only one biospecimen type per assay type will be considered based on a predefined priority order. Samples including fewer than 10 participants or assessing infection in the upper genital tract will be excluded. Quality assessments will be conducted for all measures included in the review. Meta-analyses will be implemented using DerSimonian-Laird random effect models to estimate the mean prevalence of gonorrhoea in infertile populations globally, and stratified by WHO region, assay type, sex, infertility type, infertility diagnosis, among other factors. Detailed heterogeneity assessment will be performed, and potential sources of between-study heterogeneity will be explored using meta-regression. Review will be conducted from 26 March 2018 to 28 July 2019.

Ethics and dissemination An institutional review board clearance is not required as all data are publicly available. The findings will be disseminated through a peer-reviewed publication and international scientific meetings/workshops with key stakeholders.

PROSPERO registration number CRD42018102934

Strengths and limitations of this study

- ► To the best of our knowledge, the study is the first global systematic review of the epidemiology of gonorrhea infection in infertile populations.
- ► The significance of this study lies in that it will provide indirect supporting evidence for a potential link between gonorrhoea infection and infertility in a context where causality proved hard to establish, as prospective studies are not possible, for ethical reasons, given that gonorrhoea is a curable infection.
- ► The study will identify opportunities to address the WHO Global Health Sector Strategy on Sexually Transmitted Infections, 2016–2021.
- ► The study may be limited by gaps in evidence that is the quantity and quality of data identified for the different regions or by key infertility-related attributes, which could potentially limit the conduct of meta-analyses and meta-regressions, thus, affecting the inferences to be drawn from this study.

INTRODUCTION

Gonorrhoea is a common sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae*.[1] In 2012, the World Health Organization (WHO) estimated the rate of new gonorrhoea infections globally at 19 per 1000 women and 24 per 1000 men, suggesting the exposure of well over 75 million individuals to the infection every year.[1]

A large fraction of these infections are asymptomatic, thus evading detection and treatment, and increasing the risk for serious reproductive health outcomes such as cervicitis, pelvic inflammatory disease and subsequently infertility in women, and epididymitis, epididymo-orchitis, chronic prostatitis and subsequently infertility in men.[2–4] Infertility is estimated to affect close to 2% of reproductive age women with no prior live birth and over 10% of reproductive age women with earlier successful deliveries.[5] Data on the prevalence of infertility among men are scarce.[6] Available regional estimates are in the range of 2.5%–12%, based on survey data

among women and assuming that 20%–30% of female infertility is attributed to a male factor.[7]

Despite their health, social and economic implications,[8 9] STIs and infertility have for long languished at the bottom on health policy agendas. Recently, within the framework of the United Nations' Sustainable Development Goal 3 of 'ensuring healthy lives and promoting the well-being for all',[10] the WHO has formulated the 'Global Health Sector Strategy on STIs, 2016–2021'.[11] The strategy's goal is to end STI epidemics as a public health concern by 2030.[11] A key target is achieving, by 2030, 90% reduction in *N. gonorrhoeae* incidence.[11] Five strategic directions/actions are proposed to guide countries' progress towards set targets; the first is to understand the STI epidemic and STI burden including infertility as a basis for advocacy, political commitment, national planning, resource mobilisation and allocation, implementation and programme improvement.[11]

Against this background, our proposed systematic review aims to characterise comprehensively the global epidemiology of gonorrhoea infection in infertile populations defined broadly to also include partners/infertility clinic attendees. Our specific objectives are (1) to conduct a global systematic review and synthesis of evidence of gonorrhoea infection prevalence in infertile populations, (2) to generate estimates for the pooled mean prevalence of gonorrhoea in infertile populations globally, as well as stratified by WHO region, type of assay, sex, infertility type and infertility diagnosis among other relevant key factors and (3) to identify sources of between-study heterogeneity and quantify their contribution to the variability in gonorrhoea prevalence.

Strictly speaking, this study does not aim to investigate the causal link between gonorrhoea infection and infertility. Investigating such direct causal link has proved difficult, as prospective studies are not possible, for ethical reasons, given that gonorrhoea is a curable infection. Our study thus provides only indirect suggestive evidence for a potential link between gonorrhoea infection and infertility. However, current gonorrhoea infection is often predictive of past exposure to the infection and vice versa.[12–14] Most these exposures are asymptomatic and thus of unknown duration and persistence.

METHODS

The development of this protocol was informed by the Cochrane Collaboration guidelines,[15] with section items reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidelines.[16] The checklist for PRISMA-P can be found in table 1. The timeline for conducting the review of the literature is from the 26th of March 2018 to the 28th of July 2019.

Review questions

The research questions are: What is the scope of evidence for gonorrhoea infection among infertile populations? What are the pooled mean gonorrhoea infection levels among infertile populations globally, and do these estimates vary by WHO region, assay type, sex, infertility type and infertility diagnosis among other relevant factors? What sources contribute to the heterogeneity in gonorrhoea prevalence among infertile populations?

Data sources and search strategy

We will search the global literature by surveying PubMed, Embase and WHO Index Medicus databases using broad index terms, that is MeSH/Emtree terms exploded to cover all subheadings, as well as relevant free text terms for 'gonorrhoea', 'neisseria gonorrhoeae', 'pelvic inflammatory disease', 'gonococcus', 'gonococci', 'gonococcal', 'epididymitis', 'orchitis', 'seminal vesicle disease' and 'seminal vasculitis' matched with 'infertility', 'fertility' and 'assisted reproductive techniques/infertility therapy', with no language or year restriction. Our search strategy was drafted to capture any study among infertile populations that could include gonorrhoea as a primary or secondary outcome. Epidemiology terms restricting the search to outcomes of interest such as 'incidence' or 'prevalence' were not used to ensure the search comprehensiveness. Our detailed search strategy can be found in box 1. This initial search was conducted on the 8th of May 2018 and will be updated prior to manuscript publication.

The bibliography lists of all articles included in the review and all relevant reviews of literature will be further hand searched to avoid missing any articles with relevant information.

Eligibility criteria

Any document reporting a measure of gonorrhoea prevalence in infertile populations based on primary data will be eligible for inclusion in the review. Our definition of infertile populations is broad and includes men and/or women undergoing any infertility evaluation or treatment, that is, infertility clinic attendees and their partners. No restrictions based on study setting, time frame or language will be applied. Our exclusion criteria cover case reports, case series, editorials, commentaries, qualitative studies, literature reviews whose bibliography lists will still be hand searched for any additional articles that can be potentially relevant, studies in populations exposed to voluntary sterilisation, studies based on self-reported exposure to gonorrhoea, studies assessing gonorrhoea in samples of less than 10 participants as these have too small of a sample to provide a meaningful measure of prevalence and studies assessing the infection in tissue samples from the upper genital tract given our interest in current urogenital infection with gonorrhoea.

Study outcomes and prioritisation

Our outcome of interest includes any gonorrhoea prevalence measure that is the number of existing current urogenital gonorrhoea infections or gonococcal antibodies identified among an infertile population.

Table 1 Preferred reporting items for systematic review and meta-analysis protocols checklist[16]

Section and topic	Item no	Checklist item	Addressed in page
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, 12
Authors			
Contact	3a	Provide name, institutional affiliation, email 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	1, 15
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	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
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	6–7
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	6
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	6 & box 1
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)	8
Data collection process	11 c	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	8–9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any preplanned data assumptions and simplifications	8–9

Continued

Table 1 Continued

Section and topic	Item no	Checklist item	Addressed in page
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	7
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	9–10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	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)	10–11
	15 c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, metaregression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Metabias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	9–10

NA, not applicable; PICO, participants, interventions, comparators and outcomes; PROSPERO, International Prospective Register of Systematic Reviews.

Box 1 Search strategy used to identify studies describing gonorrhoea epidemiology in infertile populations

PubMed
("Neisseria gonorrhoeae"[Mesh] OR "Gonorrhea"[Mesh] OR "Pelvic Inflammatory Disease"[Mesh] OR "Epididymitis"[Mesh] OR "Orchitis"[Mesh] OR "Seminal vesicle disease"[Mesh] OR "Neisseria gonorrhoeae"[Text] OR "Gonorrhoeae"[Text] OR "Gonorrhea"[Text] OR "Gonococcus"[Text] OR "Gonococci"[Text] OR "Gonococcal"[Text] OR "Gonococcal infection"[Text] OR "Pelvic inflammatory disease"[Text] OR "Gonococcal epididymitis"[Text] OR "Orchi-epididymitis"[Text] OR "Orchiepididymitis"[Text] OR "seminal disease"[Text] OR "seminal vesicle disease"[Text] OR "Seminal vasculitis"[Text]) AND ("Infertility" [Mesh] OR "Fertility"[Mesh] OR "Reproductive Techniques, Assisted"[Mesh] OR "Infertility"[Text] OR "Infertile"[Text] OR "Fertility"[Text] OR "Reproductive"[Text] OR "Subfertility"[Text] OR "Subfertile"[Text] OR "Sub-fertility"[Text] OR "Sub-fertile"[Text])
Embase
(exp gonorrhea/or exp neisseria gonorrhoeae/or exp epididymitis/or exp orchitis/or exp pelvic inflammatory disease/or gonorrhea.mp. or neisseria gonorrhoeae.mp. or gonorrhoeae.mp. or gonococcus.mp. or gonococci.mp. or gonococcal.mp. or gonococcal infection.mp. or pelvic inflammatory disease.mp. or gonococcal epididymitis.mp. or orchi-epididymitis.mp. or orchiepididymitis.mp. or seminal vesicle disease.mp. or seminal disease.mp. or seminal vasculitis.mp.) AND (exp infertility/or exp fertility/or exp infertility therapy/or exp reproductive procedure/or reproductive.mp. or infertility.mp. or infertile.mp. or fertility.mp. or subfertility.mp. or subfertile.mp. or sub-fertility.mp. or sub-fertile.mp.)
WHO African Index Medicus
Gonorrhea, gonorrhoeae, gonococcus, gonococci, gonococcal
WHO Index Medicus for the Eastern Mediterranean Region
Gonorrhea, gonorrhoeae, gonococcus, gonococci, gonococcal
WHO Index Medicus for the South-East Asia Region
Gonorrhea, gonorrhoeae, gonococcus, gonococci, gonococcal
WHO Index Medicus for the Western Pacific Region
Gonorrhea, gonorrhoeae, gonococcus, gonococci, gonococcal

Multiple gonorrhoea prevalence measures ascertained using different assay types (eg, polymerase chain reaction (PCR), culture, gram stain, immunoglobulin among others) will be extracted as separate studies to be used for different analyses. Assays applied to different biological specimen types will be considered based on a predefined sequential order that prioritises, for men, urogenital gonorrhoea infection detected in urethral swabs, followed by urine and then semen samples, and for women, urogenital infection detected in endocervical swabs, followed by vaginal and then urine samples. All serological measures of gonorrhoea, if any, will be also extracted.

Study selection

The search results identified through electronic databases will be imported into a reference manager, endnote. Here, screening for duplicate citations will be performed using eight different search combinations including one or more of the 'author', 'year', 'title' and 'journal' fields. After excluding duplicates, we will export the references of remaining citations to Excel where the screening of titles and abstracts will be performed by HC. During this

first screening stage, articles will be coded 1 'relevant' if an outcome of interest is reported in the abstract, 2 'potentially relevant' if an outcome of interest is not reported in the abstract but could be included in the full-text and 0 'not relevant' if otherwise. Double screening for a fraction of the articles (25%) will be performed by another coauthor (MH), and discrepancies will be discussed among authors. Full texts of articles identified as 'relevant' or 'potentially relevant' will be retrieved for further screening. For this systematic review, the term 'report' will be used to refer to a research document/article that includes one or more outcome measures of interest (here, gonorrhoea incidence or prevalence), while the term 'study' will be used to refer to details related to a specific outcome measure in a specific population. Duplicate study findings will be considered only once; however, all reports of a study will be retained during screening, and eventually the most complete data for each outcome will be extracted from wherever it is most completely reported.

Data extraction and management

Data from articles identified as relevant during the full-text screening stage will be extracted by HC into a statistical software program. The following information will be extracted: author(s), publication year, full citation, country, WHO region, year of data collection start and end, study site, study design, sampling methodology, biological specimen type, sample size, study population and its characteristics (sex, age, infertility type, infertility diagnosis, presence of urogenital signs and symptoms), sample size of tested population, number of participants positive for gonorrhoea infection and type of assay used for gonorrhoea infection ascertainment. In addition to the overall gonorrhoea measure, reported stratified measures will be extracted whenever 10 or more individuals have been included per stratum. Double extraction will be performed by MH, and discrepancies will be settled by consensus or by contacting the authors. Data extraction for articles in foreign languages will be performed by native speakers as available.

Risk of bias assessment

A risk of bias assessment (ROB) for each gonorrhoea study included in the review will be conducted and informed by the Cochrane approach[15] and existing studies.[17–20] Each study will be rated as having 'low' versus 'high' ROB on four quality domains assessing (1) the validity of the infertility definition (follows WHO definition that is failure to conceive after at least 1 year of regular unprotected intercourse vs otherwise), (2) the lack of exposure to antimicrobials for at least 1 week prior to the collection of biological samples (ascertained vs otherwise), (3) consistency in the assay used for infection ascertainment (same assay used for testing all participants vs otherwise) and (4) the response rate (≥80% vs <80%). Studies with missing information for any of the domains will be considered as having 'unclear' ROB for that specific domain. The precision of measures will be determined based on the sample size of the population tested. A study will be considered of 'high' precision if its original sample included a minimum of 100 tests for gonorrhoea infection.

In addition to reporting findings of the ROB assessment for individual studies, confidence in the body of evidence will be assessed by reporting the fraction of studies with low (or high) ROB in, respectively, at least one, two, three or all four quality domain(s).

The impact of ROB and precision domains on observed prevalence will be investigated through forest plots, meta-analyses and meta-regressions. Results for the ROB and precision assessments will be carefully considered in the interpretation of review findings.

Data synthesis and analysis

Gonorrhoea studies based on the overall sample will be reported in a table format along with key information pertaining to each study. The scope of evidence will be described by conducting descriptive analyses (ranges and medians) on the extracted data. Forest plots will be also produced to visualise prevalence measures and their 95% CIs stratified by key study and population characteristics (WHO region, assay type, sex, infertility type, infertility diagnosis, median year of data collection, sample size/precision, presence of urogenital signs and symptoms and ROB domains).

The global and regional pooled estimates for the mean gonorrhoea prevalence and their associated 95% confidence intervals (CIs) will be then calculated using meta-analysis. Here, the prevalence measure for the overall study sample (for example, gonorrhoea prevalence in women) will be replaced by stratified measures (for example, gonorrhoea prevalence in women by infertility diagnosis), whenever possible. For each study, only one stratification will be selected based on the following order of priority: country, sex, infertility diagnosis, infertility type, age and year of data collection. The variances of selected studies will be stabilised using a Freeman–Tukey double arcsine square-root transformation.[21 22] Studies then will be weighted using the inverse variance method[22 23] and will be subsequently pooled into a summary estimate for the mean using a Dersimonian–Laird random-effects model.[24] Additional meta-analyses will be implemented to estimate the pooled mean gonorrhoea prevalence stratified by assay type, sex, infertility type and infertility diagnosis among other factors (such as ROB and precision domains).

Heterogeneity across studies will be described by reporting, for each meta-analysis: the Cochran's Q statistic, a measure that assesses the existence of heterogeneity across studies; I^2 a measure that quantifies the magnitude of between-study variation due to true differences in effect size across studies and the prediction interval, a measure that estimates the 95% interval of the distribution of true effect sizes.[15 25]

Metaregression analyses will be conducted to explore potential sources of between-study heterogeneity. Univariable analyses will be first implemented to examine the association of key a priori predictors (WHO region, assay type, sex, infertility type, infertility diagnosis, median year of data collection, sample size/precision (small-study effect), presence of urogenital signs and symptoms and ROB domains) with gonorrhoea prevalence. Any association with p value ≤0.1 in univariable analyses will be eligible for inclusion in the multivariable model. Here, predictors with a p value ≤0.05 will be retained in the final model. Adjusted odds ratios and 95% CIs will be reported.

Sensitivity analyses will be considered based on preliminary results.

Patient and public involvement

By design, no patients and/or public are involved in the proposed study.

DISCUSSION

The proposed systematic review is, to our knowledge, the first to characterise comprehensively the epidemiology of gonorrhoea infection in infertile populations. Our study is timely and will inform efforts attending to the WHO 'Global Health Sector Strategy on STIs, 2016–2021', particularly to the key target of reducing gonorrhoea incidence globally by 90% by 2030.[11] Our study will also shed light on the role of STI epidemiology in infertility, a condition with severe social and economic implications[8 9] that has been for long a largely neglected area of reproductive health. The ultimate aim of this work is to provide the evidence necessary to inform public health research, policy and the adequate resource allocation and prioritisation.

Contributors The proposed study was conceived by LJA-R and designed by HC and LJA-R. HC developed the search strategy with input from LJA-R, IT, KB, JK and TCM. Literature searches and duplicate screening was conducted by HC. Strategies for the conduct of data screening, data extraction, quality risk assessment, data synthesis and statistical analyses were developed by HC and LJA-R. HC wrote the first draft of this protocol and of the PROSPERO registration form. All authors contributed to discussion of the study process and to the writing of the manuscript. All authors have read and approved the final manuscript.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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