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Global epidemiology of *Neisseria gonorrhoeae* in infertile populations: systematic review, meta-analysis and metaregression

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ABSTRACT

Objective To provide an in-depth systematic assessment of the global epidemiology of gonorrhoea infection in infertile populations.

Methods A systematic literature review was conducted up to 29 April 2019 on international databases and WHO regional databases, and reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All prevalence measures of gonorrhoea infection among infertile populations, based on primary data, qualified for inclusion. Infertile populations were broadly defined to encompass women/men undergoing infertility evaluation or treatment (infertility clinic attendees and partners). Pooled mean prevalence by relevant strata was estimated using random-effects meta-analysis. Associations with prevalence and sources of heterogeneity were explored using metaregression. Risk of bias was assessed using four quality domains.

Findings A total of 147 gonorrhoea prevalence studies were identified from 56 countries. The pooled mean prevalence of current gonorrhoea infection was estimated globally at 2.2% (95% CI 1.3% to 3.2%), with the highest prevalence in Africa at 5.0% (95% CI 1.9% to 9.3%). The mean prevalence was higher for populations with tubal factor infertility (3.6%, 95% CI 0.9%–7.7%) and mixed cause and unexplained infertility (3.6%, 95% CI 0.0% to 11.6%) compared with other diagnoses, such as ovarian and non-tubal infertility (0.1%, 95% CI 0.0% to 0.8%), and for secondary (2.5%, 95% CI 0.2% to 6.5%) compared with primary (0.5%, 95% CI 0.0% to 1.7%) infertility. Metaregression identified evidence of variations in prevalence by region and by infertility diagnosis, higher prevalence in women than men and a small-study effect. There was a trend of declining prevalence by about 3% per year over the last four decades (OR=0.97, 95% CI 0.95 to 0.99).

Conclusions Gonorrhoea prevalence in infertile populations is several folds higher than that in the general population, with even higher prevalence in women with tubal factor infertility and in individuals with secondary infertility. These findings support the potential role of gonorrhoea in infertility and suggest that some infertility is possibly preventable by controlling gonorrhoea transmission.

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INTRODUCTION

Infertility, 'a disease characterised by failure to establish clinical pregnancy after 12 months of regular, unprotected sexual intercourse',[1 2] affects ~2% of reproductive-age women with no prior live birth and >10% of those with an earlier successful delivery.[3] While infertility in men remains poorly quantified,[4] available estimates by world region suggest a range of 2.5%–12.0%.[5]

A potential contributor to infertility, for both women and men, is a common STI caused by the bacterium *Neisseria gonorrhoeae*,[6] in addition to *Chlamydia trachomatis* (CT).[7–10] In 2016, the WHO estimated that nearly 87 million individuals acquired this infection globally, with incidence rates estimated at 20 per 1000 women and 26 per 1000 men.[11] In women, gonorrhoea is often asymptomatic, complicating early detection and treatment and increasing their risk of cervicitis and pelvic inflammatory disease,[12 13] while in men, it has been associated with epididymitis, epididymo-orchitis and chronic prostatitis.[14–17] Untreated, these conditions may lead to subfertility/infertility.[12 14 15 18]

Despite their health, social and economic implications,[19 20] STIs and infertility have long been a low priority on national policy agendas. Recently, the WHO formulated the 'Global Health Sector Strategy on STIs, 2016–2021', with the goal of ending STI epidemics as a public health concern by 2030.[21] A key target is achieving by 2030 a 90% reduction in *N. gonorrhoeae* incidence.[21] The urgency in addressing gonorrhoea is compounded by its recent classification as a 'superbug',[22] given the widespread antimicrobial resistance, even to infection's last-line treatment.[23–26] Consequently, the WHO launched a global action plan to control gonorrhoea transmission and sequelae,[27 28] including building a business case for the global public health value of gonococcal vaccines.[29 30] Achieving WHO set targets entails fulfilment of five strategic directions/actions; the first is to understand the STI epidemic and burden, including subfertility/infertility, as a basis for advocacy, political commitment, national planning, resource mobilisation and allocation, implementation and programme improvement.[21]

This study was motivated by our recent work assessing CT prevalence levels in different at-risk populations in the Middle East and North Africa,

where we identified an association between CT prevalence and infertility, with prevalence among infertile populations being three-fold higher than that among the general population.[10] The present study aimed to characterise the global epidemiology of gonorrhoea infection in infertile populations by (1) systematically reviewing and synthesising evidence of infection prevalence, (2) estimating the pooled mean prevalence, stratified by WHO region among other key factors, and (3) exploring population-level associations with prevalence and sources of between-study heterogeneity.

Longitudinal studies examining gonorrhoea's adverse health outcomes (a curable infection) are difficult/unethical to conduct. A recent study attempted to overcome this challenge through linking national testing databases to hospital records, but identified too few cases to reach conclusive evidence about gonorrhoea's role in infertility.[31] In the absence of direct evidence, our study aimed to provide *indirect evidence* for a *link* between gonorrhoea and infertility but strictly did not aim to nor can it establish causality. The underlying hypothesis is that current infection is of unknown duration and persistence to establish a causal link with infertility, but is often predictive of past exposure.[32–34] This assertion is supported by several lines of evidence. It is established through tens of studies of different designs that gonorrhoea as well as chlamydia, being curable infections, carry a high risk of reinfection because of re-exposure to the same sexual partner or to other high-risk partners.[33 35–37] As such, it can be assumed that a current gonorrhoea infection is strongly indicative of a previous gonorrhoea infection[33 38 39]; indeed studies have shown that the strongest predictor of current gonorrhoea infection is a history of gonorrhoea infection.[32 40] For example, in the UK, a history of gonorrhoea infection was found to be the strongest predictor of current gonorrhoea infection even after controlling for other demographic and behavioural factors (adjusted OR 4.36, 95% CI 1.78 to 10.71).[32]

It is also established that there are strong correlations between exposure and the prevalence of different STIs, such as gonorrhoea and chlamydia,[41 42] herpes simplex virus type 2 (HSV-2) and HIV[43–45] (beyond the debated biological synergy[46]), even though these STIs could be acquired at different time frames. As such, exposure to an STI is a predictor of exposure to another STI. For instance, HSV-2 is often used as a proxy biomarker for HIV exposure and epidemic potential.[43–45] Just as STI exposures acquired at different time points are correlated with each other, it is reasonable to expect that measures of gonorrhoea prevalence assessed at different times in the same population are also correlated.[32 40] This is because, fundamentally, the driving factor of STI exposure is sexual risk behaviour[47]; current gonorrhoea infection in a population/person can be seen as a proxy of the past and present sexual risk behaviour of that population/person or person's sexual partners.[48 49] Studies also show that people tend to be consistent in their sexual risk behaviour over at least a few years' duration.[50–52]

METHODS

Detailed methodology has been previously published as a study protocol.[53] A brief description is provided as follows.

Search strategy and selection criteria

A systematic review of gonorrhoea prevalence in infertile populations was conducted following Cochrane Collaboration guidelines,[54] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[55] (checklist in online supplementary table 1).

Literature was searched, up to 29 April 2019 on PubMed and Embase, and up to 5 February 2019 on the WHO Index Medicus regional databases, using broad terms with no language or year restrictions (online supplementary box 1). Duplicate citations were excluded using a reference manager, EndNote (Thomson Reuters, USA). Title and abstract screening and full-text screening of relevant/potentially relevant citations were performed by HC and AM. Reference lists of reviews and relevant articles were further hand-searched.

Any article reporting prevalence of current urogenital infection or serological markers of gonorrhoea in infertile populations, based on primary data, qualified for inclusion. Infertile populations were broadly defined to include women/men undergoing infertility evaluation or treatment (infertility clinic attendees and partners). Studies in voluntarily sterile populations, based on the infection's self-report, including <10 participants, or assessing gonorrhoea in tissue samples from the upper genital tract, were excluded.

Data extraction and synthesis

Data were extracted by HC and AM and double extracted by FA (extraction list in online supplementary box 2). In addition to the overall gonorrhoea measure, stratified measures were extracted whenever a stratum included ≥10 participants.

Studies assessing gonorrhoea using different assay types (nucleic acid amplification test (NAAT), culture, Gram stain and Ig among others) were extracted separately for different analyses. Studies applying the same assay to different biological specimens were included once based on a predefined order prioritising, for women, gonorrhoea detection in endocervical swabs, followed by vaginal and urine samples; and for men, detection in urethral swabs, followed by urine and semen samples.

Risk of bias and precision assessments

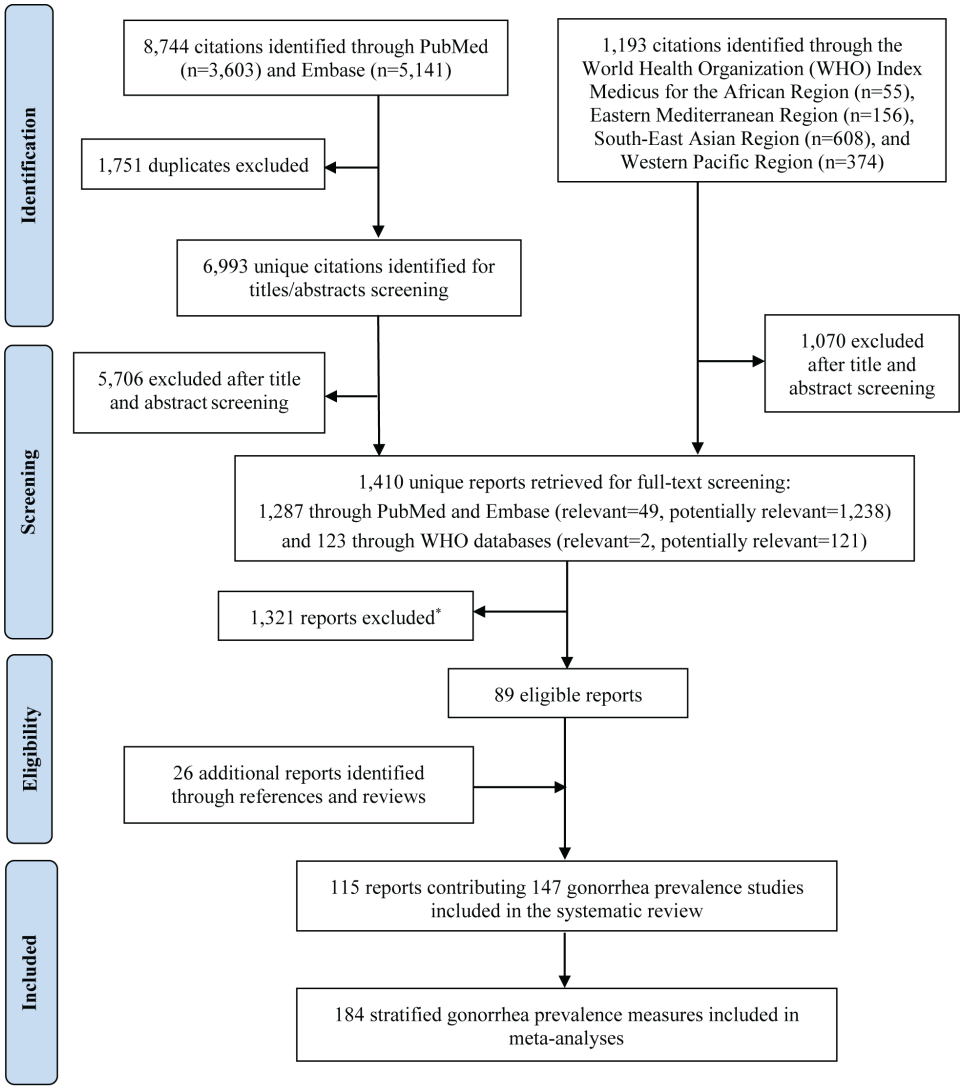
Informed by the Cochrane approach[54] and existing literature,[56–59] each study was rated as having 'low' versus 'high' risk of bias on four quality domains: (1) validity of infertility definition (follows WHO definition vs otherwise), (2) lack of exposure to antimicrobials for ≥1 week prior to collection of biological samples (ascertained vs otherwise), (3) consistency in assay used for infection ascertainment (same assay used to test all participants vs otherwise) and (4) response rate (≥80% vs <80%). A study with missing information for a specific domain was considered as having 'unclear' risk of bias for that domain. A study was deemed of 'higher' precision if its original sample tested ≥100 participants.

Meta-analysis

Pooled mean gonorrhoea prevalence and 95% CIs were estimated using random-effects meta-analysis. Here, overall prevalence was replaced by strata, whenever possible. For each study, only one final stratification was considered, based on a predefined priority order: country, sex, infertility diagnosis, infertility type, age and year of data collection. Stratified meta-analyses by relevant factors were further performed, and heterogeneity assessment was conducted.[60 61]

Metaregression

Metaregression analyses were conducted to explore sources of between-study heterogeneity and to examine associations with prevalence for the following predefined factors: WHO region (African region (AFRO), Americas (AMRO), Eastern Mediterranean (EMRO), European (EURO), Southeast Asia (SEARO),



*Reasons for exclusion:

- Eligibility criteria not met (number of reports=144)
- Full-text did not include data on relevant outcomes (number of reports=1,051)
- Full-text could not be retrieved and abstract does not have data on relevant outcomes (number of reports=58)
- Conference abstract did not include data on relevant outcomes (n=46)
- Abstract and full-text could not be retrieved (number of reports=8)
- Duplicate of another study included in the review (number of reports=14)

Figure 1 Flowchart of the study selection process for the global systematic review of *Neisseria gonorrhoeae* infection prevalence in infertile populations, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[55]

Western Pacific (WPRO)), sex, infertility type, infertility diagnosis, presence of urogenital signs and symptoms, assay type, median year of data collection, sample size/precision (to assess small-study effect) and risk of bias domains. Variables' details/subgroupings are in online supplementary box 2 and online supplementary table 2.

Strength of evidence for an association with prevalence was deemed 'good' at 0.05<p value≤0.10 and 'strong' at p value≤0.05. Sensitivity analysis focusing on studies assessing current infection was performed.

RESULTS

Search results and scope of evidence

Figure 1 shows the study selection process. Search identified 9937 citations: 3603 through PubMed, 5141 through Embase and 1193 through the WHO Index Medicus databases. After excluding duplicates and screening titles and abstracts, 1410 unique reports underwent full-text screening. Of these, 89 were eligible for inclusion. The rest were excluded for reasons outlined in figure 1. Twenty-six additional reports were identified through reference list hand-searching. In sum, 115 reports contributing 147 gonorrhoea prevalence studies were included in the review. These yielded 184 stratified measures for meta-analyses.

There were 27 264 gonorrhoea test results from 56 countries. EURO contributed 44.2% of studies (n=65), AMRO 16.3% (n=24), AFRO 13.6% (n=20), SEARO 8.2% (n=12), WPRO and EMRO 7.5% (n=11) each, and multicentre/multiregional studies 2.7% (n=4). Most studies (n=107, 72.8%) assessed current infection, of which 26.2% were NAAT-based; 67.3% were culture-based; and 6.5%were Gram stain/gonozyme/

fluorescent antibody-based. The rest either reported ever infection using IgG (n=20, 13.6%) or IgA (n=3, 2.0%), or were based on unclear assays (n=17, 11.6%). Studies are detailed in online supplementary tables 3-8.

Prevalence overview

Reported current infection prevalence across regions ranged from 0% to 53.0% (online supplementary tables 3-8). The median was 0%, as 57 out of 107 studies reported zero prevalence; it is difficult to identify a positive case for a low-prevalence infection in a study of a small sample size. The highest median current infection prevalence was for AFRO at 3.3%. Ever infection prevalence (IgG) ranged from 1.3% to 65.0%, with a median of 25.0%; the median per region ranged from 2.5% in EMRO to 39.1% in AFRO (online supplementary tables 3-8).

Risk of bias and precision assessments

Online supplementary tables 9 and 10 show the summarised and study-specific precision and risk of bias assessments. Briefly, 50.3% of studies were of higher precision (≥100 participants). Over a third (34.7%) followed WHO infertility definition; 1.3% included infertile participants for <12 months, while the rest (64.0%) did not report an infertility definition. Only 14.3% of studies excluded infertile participants exposed to antimicrobials in the week prior to sample collection; 6.1% may have included such participants; and information was missing for the rest of studies (79.6%). Almost all studies (96.6%) demonstrated consistency in gonorrhoea testing across infertile participants. Response rate was mostly unavailable (97.3%); studies were almost entirely facility/clinic-based or retrospective charts were review-based.

Studies were overall of reasonable quality (online supplementary table 9). Nearly all (98.6%) had low risk of bias in ≥1 quality domain and 41.5% had low risk of bias in ≥2 domains. Meanwhile, only 8.8% had high risk of bias in ≥1 quality domain and <1% had high risk of bias in ≥2 domains. Over 90% of studies had unclear risk of bias in ≥2 domains.

Summary estimates of pooled mean gonorrhea prevalence

Forest plots showing meta-analysis results for studies reporting current infection prevalence, by relevant strata, are in figure 2 and online supplementary figures 1-14.

Pooled mean prevalence of current gonorrhoea infection was globally at 2.2% (95% CI 1.3% to 3.2%), and regionally at 5.0% (95% CI 1.9% to 9.3%) in AFRO, 2.7% (95% CI 0.6% to 5.8%) in EMRO, 2.5% (95% CI 0.4% to 5.7%) in WPRO, 2.4% (95% CI 0.8% to 4.5%) in EURO, 1.0% (95% CI 0.0% to 3.4%) in AMRO and 0.0% (95% CI 0.0% to 0.06%) in SEARO (table 1). Meanwhile, mean ever infection prevalence was globally at 21.0% (95% CI 13.2% to 30.0%) and varied regionally from 5.4% (95% CI 1.2% to 12.0%) in AMRO to 46.6% (95% CI 28.4% to 65.3%) in AFRO (table 1).

Estimates varied by infertility diagnosis (table 1). Mean current infection prevalence was 3.6% (95% CI 0.9% to 7.7%) for tubal factor infertility (TFI), 3.6% (95% CI 0.0% to 11.6%) for mixed (samples combining different diagnoses) and unexplained infertility, 2.6% (95% CI 1.1% to 4.5%) for general/unspecified infertility, 1.4% (95% CI 0.2% to 3.3%) for male factor infertility and 0.06% (95% CI 0.0% to 0.8%) for ovarian and non-TFI infertility. This measure was also 2.5% for secondary infertility (95% CI 0.2% to 6.5%) and 0.5% for primary infertility (95% CI 0.0% to 1.7%).

Mean current infection prevalence varied by assay type: 0.7% (95% CI 0.08% to 1.6%) using NAAT, 2.7% (95% CI 1.4% to 4.3%) using culture, 3.8% (95% CI 0.0% to 24.4%) using other assays assessing current infection and 8.7% (95% CI 0.0% to 31.3%) using Gram stain (table 1).

Mean current infection prevalence was 2.5% in women (95% CI 1.2% to 4.1%) vs 1.5% in men (95% CI 0.5% to 3.0%), 3.0% in studies before 2005 (95% CI 1.5% to 4.8%) vs 1.1% in those after 2005 (95% CI 0.4% to 2.0%), 4.1% in samples including <100 participants (95% CI 1.8% to 6.9%) vs 1.0% in those including ≥100 participants (95% CI 0.3% to 1.9%) and 16.2% in symptomatic individuals (95% CI 7.1% to 27.7%) vs 1.0% in asymptomatic ones (95% CI 0.3% to 2.0%) (table 1).

Mean ever infection prevalence showed similar results, although at much higher prevalence levels (table 1).

There was evidence for heterogeneity in prevalence across studies. Most meta-analyses showed a p value of <0.001 for Cochran's Q statistic, wide prediction intervals indicating high heterogeneity and $I^2 \geq 70\%$, affirming most variability as due to true differences in prevalence across studies rather than chance (table 1).

Associations with prevalence and sources of between-study heterogeneity

Univariable metaregression results are in table 2. There was 'strong' evidence for an association with prevalence (p value of ≤0.05) for WHO region, sex, infertility diagnosis, presence of urogenital signs and symptoms, assay type, year of data collection, sample size and exposure to antimicrobials prior to sample collection; 'good' evidence for infertility type (0.05<p value≤0.10), but no evidence for validity of infertility definition, consistency in assay used for infection ascertainment and response rate.

Compared with AMRO, AFRO showed four-fold higher odds of gonorrhoea infection (OR=4.0, 95% CI 1.5 to 10.1), while no significant differences were found for the other regions. Women had twice higher odds of infection than men (OR=2.0, 95% CI 1.1 to 3.7). Individuals with secondary infertility also had twice higher odds of infection (OR=2.1, 95% CI 0.9 to 5.2) than those with primary infertility. Odds were 2.4-fold (95% CI 1.2 to 4.6) and 2.0-fold (95% CI 0.8 to 5.0) higher for women with TFI and for individuals with mixed cause and unexplained infertility, respectively, compared with those with general/unspecified infertility. Symptomatic individuals had six-fold higher odds of infection compared with asymptomatic ones (OR=5.9, 95% CI 2.6 to 13.5).

Culture and other assays detecting current infection showed 2.5-fold (95% CI 1.3 to 4.8) and 4.1-fold (95% CI 1.1 to 15.3) higher odds, respectively, compared with NAAT, while assays detecting IgG showed 22.1-fold higher odds (95% CI 9.5 to 51.2). There was evidence for declining prevalence at ~3% per year over the last four decades (OR=0.97, 95% CI 0.95 to 0.99) and for small-study effect, with studies including ≥100 participants showing lower prevalence (OR=0.5, 95% CI 0.3 to 0.9).

Sensitivity analysis using only studies assessing current gonorrhoea infection affirmed the aforementioned results, although some associations failed to reach statistical significance because of the smaller number of studies (online supplementary table 11).

Full multivariable metaregression analysis could not be performed due to lack of statistical power.[62] However, backward variable selection yielded a final multivariable model including four predictors: region, presence of urogenital signs and

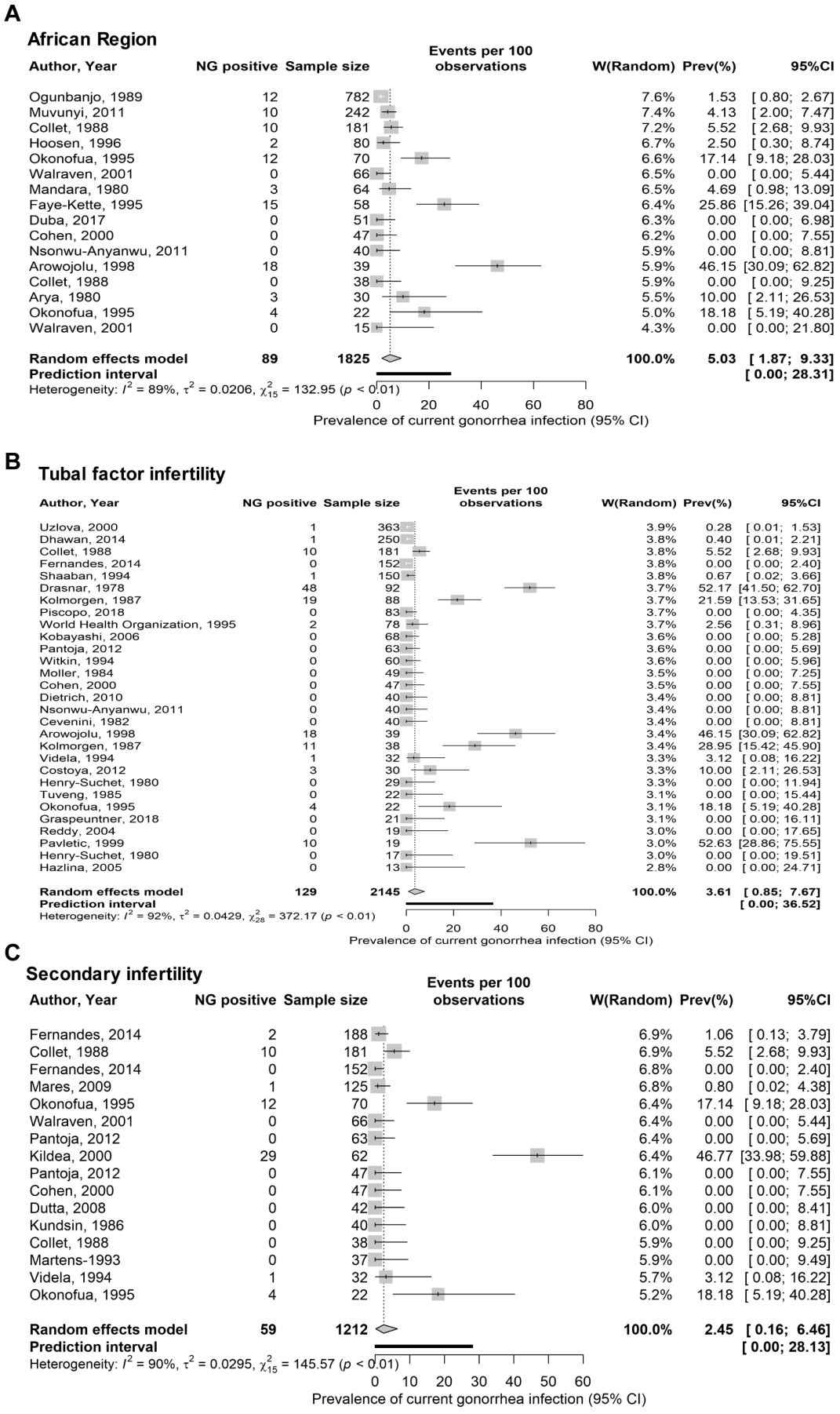


Figure 2 Forest plots showing key results of the meta-analysis on studies reporting the prevalence of current NG infection in infertile populations for (A) the WHO -African Region, (B) tubal factor infertility and (C) secondary infertility. NG, *Neisseria gonorrhoeae*.

Table 1 Results of meta-analyses of studies reporting the prevalence of NG infection in infertile populations stratified by relevant indicators

	Studies/strata	Sample		NG prevalence (%)				Heterogeneity measures		
	Total N	Tested*	NG positive	Median†	Range‡	Pooled mean	95% CI	Q‡ (P value)	I^2§ (%, 95% CI)	Prediction interval¶ (95% CI)
WHO region										
AFRO										
Current infection	16	1825	89	3.3	0–46.2	5.0	1.9 to 9.3	133.0 (p<0.0001)	88.7 (83.3 to 92.4)	0.0 to 28.3
Ever infection (IgG)	5	324	132	50.0	25.0–92.0	46.6	28.4 to 65.3	38.3 (p<0.0001)	89.6 (78.4 to 94.9)	0.0 to 99.3
IgA and unclear	3	132	1	0.0	0–2.0	0.1	0.0 to 2.4	1.4 (p=0.5046)	0.0 (0.0 to 84.8)	0.0 to 37.2
AMRO										
Current infection	24	7204	79	0.0	0–53.0	1.0	0.0 to 3.4	312.7 (p<0.0001)	92.6 (90.3 to 94.4)	0.0 to 20.7
Ever infection (IgG)	3	260	17	5.6	1.3–10.4	5.4	1.2 to 12.0	6.9 (p=0.0324)	70.9 (0.8 to 91.4)	0.0 to 100.0
IgA and unclear	6	496	22	3.7	0–9.8	3.1	0.4 to 7.5	21.8 (p=0.0006)	77.0 (48.8 to 89.7)	0.0 to 23.4
EMRO										
Current infection	13	1471	36	1.0	0–50.0	2.7	0.6 to 5.8	77.0 (p<0.0001)	84.4 (74.8 to 90.3)	0.0 to 19.0
Ever infection (IgG)	1	79	2	3.0		–**	–	–	–	–
IgA and unclear	–	–	–	–	–	–	–	–	–	–
EURO										
Current infection	54	6398	361	0.0	0–52.2	2.4	0.8 to 4.5	917.9 (p<0.0001)	94.2 (93.1 to 95.1)	0.0 to 27.7
Ever infection (IgG)	7	359	48	11.7	0–60.6	12.2	2.8 to 26.3	65.0 (p<0.0001)	90.8 (83.6 to 94.8)	0.0 to 69.9
IgA and unclear	12	2230	223	5.2	0–31.0	6.3	1.9 to 12.6	245.3 (p<0.0001)	95.5 (93.7 to 96.8)	0.0 to 38.9
SEARO										
Current infection	8	843	1	0.0	0–0.4	0.0	0.0 to 0.06	2.0 (p=0.9578)	0.0 (0.0 to 0.0)	0.0 to 0.1
Ever infection (IgG)	5	307	48	8.6	4.9–36.4	14.7	4.6 to 28.8	36.6 (p<0.0001)	89.1 (77.2 to 94.8)	0.0 to 75.0
IgA and unclear	2	57	0	0.0	0–0	--**	--	--	--	--
WPRO										
Current infection	17	4760	78	0.0	0–47.0	2.5	0.4 to 5.7	269.2 (p<0.0001)	94.1 (91.9 to 95.7)	0.0 to 21.1
Ever infection (IgG)	--	--	--	--	--	--	--	--	--	--
IgA and unclear	2	145	10	3.8	0–7.5	--**	--	--	--	--
Multicentre										
Current infection	2	233	2	1.5	0–3.0	--**	--	--	--	--
Ever infection (IgG)	5	141	64	39.5	31.8–62.2	44.2	30.6 to 58.3	7.7 (p=0.0521)	61.2 (0.0 to 87.0)	1.7 to 93.3
IgA and unclear	--	--	--	--	--	--	--	--	--	--
Global										
Current infection	134	22 734	646	0.0	0–53.0	2.2	1.3 to 3.2	2002.6 (p<0.0001)	93.4 (92.6 to 94.1)	0.0 to 20.1
Ever infection	25	1470	311	25.0	0–92.0	21.0	13.2 to 30.0	363.4 (p<0.0001)	93.4 (91.4 to 94.9)	0.0 to 71.6
IgA and unclear	25	3060	256	2.0	0–31.0	3.8	1.3 to 7.0	302.1 (p<0.0001)	92.1 (89.5 to 94.0)	0.0 to 26.9
Assay type										
NAAT (current infection)	33	12 594	118	0.0	0–32.9	0.7	0.08 to 1.6	395.1 (p<0.0001)	91.9 (89.7 to 93.7)	0.0 to 9.0
Culture (current infection)	94	9682	482	0.0	0–53.0	2.7	1.4 to 4.3	1212.9 (p<0.0001)	92.3 (91.2 to 93.3)	0.0 to 25.7
Other†† (current infection)	3	221	15	0.0	0–23.8	3.8	0.0 to 24.4	38.7 (p<0.0001)	94.8 (88.2 to 97.7)	0.0 to 100.0
Gram stain (current infection)	4	237	31	13.0	0–29.6	8.7	0.0 to 31.3	58.9 (p<0.0001)	94.9 (90.0 to 97.4)	0.0 to 100.0

Continued

Table 1 Continued

	Studies/strata	Sample		NG prevalence (%)				Heterogeneity measures		
	Total N	Tested*	NG positive	Median†	Range‡	Pooled mean	95% CI	Q‡ (P value)	I^2§ (%, 95% CI)	Prediction interval¶ (95% CI)
IgG (ever infection)	25	1470	311	25.0	0–92.0	21.0	13.2 to 30.0	363.4 (p<0.0001)	93.4 (91.4 to 94.9)	0.0 to 71.6
IgA	3	260	21	7.8	6.7–9.8	8.0	4.9 to 11.7	0.5 (p=0.7937)	0.0 (0.0 to 55.0)	0.0 to 40.3
Unclear	22	2800	235	0.3	0–31.0	3.2	0.8 to 6.8	300.2 (p<0.0001)	93.0 (90.7 to 94.8)	0.0 to 27.8
Sex										
Women										
Current infection	100	8038	407	0.0	0–53.0	2.5	1.2 to 4.1	1151.4 (p<0.0001)	91.4 (90.1 to 92.5)	0.0 to 27.0
Ever infection (IgG)	22	1283	285	25.0	0–92.0	22.4	13.8 to 32.3	321.3 (p<0.0001)	93.5 (91.3 to 95.1)	0.0 to 74.2
IgA and unclear	19	1383	127	0.0	0–31.0	2.7	0.3 to 6.7	166.0 (p<0.0001)	89.2 (84.6 to 92.4)	0.0 to 28.5
Men										
Current infection	34	14696	239	0.2	0–29.6	1.5	0.5 to 3.0	712.6 (p<0.0001)	95.4 (94.3 to 96.2)	0.0 to 14.1
Ever infection (IgG)	3	187	26	8.6	1.3–36.4	12.2	0.03 to 37.2	33.4 (p<0.0001)	94.0 (85.9 to 97.5)	0.0 to 100.0
IgA and unclear	6	1677	129	7.1	0–28.5	6.9	1.7 to 15.0	134.9 (p<0.0001)	96.3 (94.0 to 97.7)	0.0 to 46.1
Infertility type										
Primary/majority primary										
Current infection	35	7858	162	0.0	0–39.0	0.5	0.0 to 1.7	442.7 (p<0.0001)	92.3 (90.3 to 93.9)	0.0 to 12.1
Ever infection (IgG)	12	519	105	27.1	0–92.0	22.0	8.9 to 38.6	177.1 (p<0.0001)	93.8 (90.9 to 95.8)	0.0 to 87.3
IgA and unclear	5	953	79	6.3	0–14.8	5.1	1.4 to 10.6	26.1 (p<0.0001)	84.7 (65.8 to 93.1)	0.0 to 30.8
Secondary/majority secondary										
Current infection	16	1212	59	0.0	0–47.0	2.5	0.2 to 6.5	145.6 (p<0.0001)	89.7 (84.9 to 93.0)	0.0 to 28.1
Ever infection (IgG)	6	420	151	38.4	14.5–60.6	36.4	22.1 to 52.0	48.6 (p<0.0001)	89.7 (80.3 to 94.6)	0.3 to 87.5
IgA and unclear	2	124	8	5.6	4.2–7.0	--**	--	--	--	--
Not specified/not applicable										
Current infection	83	13664	425	0.0	0–53.0	3.1	1.7 to 4.8	1390.9 (p<0.0001)	94.1 (93.2 to 94.9)	0.0 to 26.1
Ever infection (IgG)	7	531	55	8.6	1.3–36.4	9.6	4.0 to 17.0	37.9 (p<0.0001)	84.2 (69.0 to 91.9)	0.0 to 40.6
IgA and unclear	18	1983	169	0.3	0–31.0	3.2	0.4 to 7.8	272.4 (p<0.0001)	93.8 (91.5 to 95.4)	0.0 to 33.6
Infertility diagnosis										
Tubal factor infertility										
Current infection	29	2145	129	0.0	0–53.0	3.6	0.9 to 7.7	372.2 (p<0.0001)	92.5 (90.3 to 94.2)	0.0 to 36.5
Ever infection (IgG)	12	678	194	34.6	2.0–92.0	31.1	16.6 to 47.8	207.4 (p<0.0001)	94.7 (92.4 to 96.3)	0.0 to 1.6
IgA and unclear	9	415	16	0.0	0–9.8	1.7	0.1 to 4.8	17.4 (p=0.0266)	53.9 (2.2 to 78.3)	0.0 to 13.2
Ovarian and non-tubal infertility										
Current infection	17	1709	15	0.0	0–17.1	0.06	0.0 to 0.8	42.1 (p=0.0004)	62.0 (35.7 to 77.5)	0.0 to 4.4
Ever infection (IgG)	6	392	47	7.8	0–31.8	9.6	2.6 to 19.7	36.3 (p<0.0001)	86.2 (72.2 to 93.2)	0.0 to 52.5
IgA and unclear	3	154	9	0.0	0–7.8	2.5	0.0 to 9.7	3.8 (p=0.1472)	47.8 (0.0 to 84.7)	0.0 to 100.0
Male factor infertility										
Current infection	19	7208	162	0.7	0–29.6	1.4	0.2 to 3.3	361.7 (p<0.0001)	95.0 (93.4 to 96.2)	0.0 to 14.6
Ever infection (IgG)	1	74	1	1.3	--	--**	--	--	--	--
IgA and unclear	4	981	55	7.1	0–7.5	4.3	0.4 to 11.4	44.3 (p<0.0001)	93.2 (85.9 to 96.8)	0.0 to 56.2

Continued

Table 1 Continued

	Studies/strata	Sample		NG prevalence (%)				Heterogeneity measures		
	Total N	Tested*	NG positive	Median†	Range‡	Pooled mean	95% CI	Q‡ (P value)	I^2§ (%, 95% CI)	Prediction interval¶ (95% CI)
Mixed and unexplained infertility										
Current infection	14	536	50	0.0	0–47.0	3.6	0.0 to 11.6	141.5 (p<0.0001)	90.8 (86.4 to 93.8)	0.0 to 51.6
Ever infection (IgG)	3	153	28	25.0	3.0–38.9	18.9	0.3 to 52.1	33.9 (p<0.0001)	94.1 (86.2 to 97.5)	0.0 to 100.0
IgA and unclear	3	378	39	6.3	0–14.8	6.0	0.5 to 16.0	16.7 (p=0.0002)	88.0 (66.5 to 95.7)	0.0 to 100.0
General infertility and partners										
Current infection	55	11 363	290	0.0	0–50.0	2.6	1.1 to 4.5	991.6 (p<0.0001)	94.6 (93.6 to 95.4)	0.0 to 24.7
Ever infection (IgG)	3	173	41	26.7	8.6–36.4	22.7	8.4 to 41.2	14.0 (p=0.0009)	85.7 (58.2 to 95.1)	0.0 to 100.0
IgA and unclear	6	1132	137	2.1	0–31.0	6.7	0.2 to 19.7	190.7 (p<0.0001)	97.4 (96.0 to 98.3)	0.0 to 69.5
Median year of data collection										
<2005										
Current infection	85	8352	482	0.0	0–53.0	3.0	1.5 to 4.8	1185.9 (p<0.0001)	92.9 (91.8 to 93.9)	0.0 to 28.7
Ever infection (IgG)	25	1470	311	25.0	0–92.0	21.0	13.2 to 30.0	363.4 (p<0.0001)	93.4 (91.4 to 94.9)	0.0 to 71.6
IgA and unclear	22	2419	229	1.3	0–31.0	3.8	1.1 to 7.6	289.1 (p<0.0001)	92.7 (90.3 to 94.6)	0.0 to 30.6
≥2005										
Current infection	49	14 382	164	0.0	0–50.0	1.1	0.4 to 2.0	542.7 (p<0.0001)	91.2 (89.1 to 92.8)	0.0 to 10.6
Ever infection (IgG)	--	--	--	--	--	--	--	--	--	--
IgA and unclear	3	641	27	3.4	0–7.5	3.5	0.9 to 7.3	4.0 (p=0.1341)	50.2 (0.0 to 85.6)	0.0 to 70.8
Sample size										
<100 participants										
Current infection	65	3175	273	0.0	0–53.0	4.1	1.8 to 6.9	662.0 (p<0.0001)	90.3 (88.4 to 91.9)	0.0 to 38.2
Ever infection (IgG)	8	387	80	25.9	3.0–92.0	29.4	12.1 to 50.3	114.7 (p<0.0001)	93.9 (90.2 to 96.2)	0.0 to 95.6
IgA and unclear	8	241	2	0.0	0–4.2	0.1	0.0 to 1.6	3.2 (p=0.8710)	0.0 (0.0 to 27.9)	0.0 to 2.2
≥100 participants										
Current infection	69	19 559	373	0.0	0–50.0	1.0	0.3 to 1.9	1111.1 (p<0.0001)	93.9 (92.9 to 94.8)	0.0 to 12.9
Ever infection (IgG)	17	1083	231	14.5	0–62.2	17.7	9.3 to 27.9	248.6 (p<0.0001)	93.6 (91.1 to 95.3)	0.0 to 68.3
IgA and unclear	17	2819	254	6.7	0–31.0	5.7	2.4 to 10.1	278.5 (p<0.0001)	94.3 (92.2 to 95.8)	0.0 to 32.0
Urogenital symptoms										
Asymptomatic										
Current infection	53	15 567	233	0.0	0–33.3	1.0	0.3 to 2.0	694.0 (p<0.0001)	92.5 (91.0 to 93.8)	0.0 to 11.5
Ever infection (IgG)	7	322	84	31.8	0–62.2	25.0	10.1 to 43.4	69.1 (p<0.0001)	91.3 (84.7 to 95.1)	0.0 to 88.0
IgA and unclear	4	595	17	0.0	0–3.42	1.2	0.02 to 3.4	3.8 (p=0.2898)	20.0 (0.0 to 87.7)	0.0 to 10.6
Symptomatic‡‡										
Current infection	19	863	183	18.2	0–53.0	16.2	7.1 to 27.7	282.9 (p<0.0001)	93.6 (91.4 to 95.3)	0.0 to 75.7
Ever infection (IgG)	1	60	16	26.7	--	--**	--	--	--	--
IgA and unclear	4	485	32	2.1	0–14.8	2.8	0.0 to 17.4	60.2 (p<0.0001)	95.0 (90.2 to 97.5)	0.0 to 95.0
Not specified										
Current infection	62	6304	230	0.0	0–50.0	1.2	0.3 to 2.5	610.0 (p<0.0001)	90.0 (87.9 to 91.7)	0.0 to 18.1
Ever infection (IgG)	17	1088	211	10.4	1.3–92.0	19.2	10.0 to 30.4	282.5 (p<0.0001)	94.3 (92.3 to 95.8)	0.0 to 73.6

Continued

Table 1 Continued

	Studies/strata	Sample		NG prevalence (%)				Heterogeneity measures		
	Total N	Tested*	NG positive	Median†	Range‡	Pooled mean	95% CI	Q‡ (P value)	I^2§ (%, 95% CI)	Prediction interval¶ (95% CI)
IgA and unclear	17	1980	207	6.3	0–31.0	5.0	1.7 to 9.4	199.7 (p<0.0001)	92.0 (88.7 to 94.3)	0.0–31.3

*The same population may have contributed different measures for current NG infection and ever infection with NG.
†Median and range of stratified gonorrhoea prevalence measures included in meta-analyses.
‡Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in effect size (here, NG prevalence) across studies.
§I^2: a measure assessing the magnitude of between-study variation that is due to differences in effect size (here, NG prevalence) across studies rather than chance.
¶Prediction interval: a measure estimating the 95% interval of the distribution of true effect sizes (here, NG prevalence measures).
**A minimum of three studies was necessary to conduct a meta-analysis.
††Other assays assessing current infection such as gonozyme and fluorescent antibody tests.
‡‡Across studies, commonly reported diagnosis and clinical manifestations in infertile women included abnormal/mucopurulent cervical and vaginal discharge, pelvic inflammatory disease, cervicitis, salpingitis, and genital tuberculosis; and in infertile men, dysuria, urethritis, orchitis, epididymitis, prostatitis, vesiculitis, isolated funiculitis, varicocele and testicular trauma.
AFRO, African Region; AMRO, Region of the Americas; EMRO, Eastern Mediterranean Region; EURO, European region; NAAT, nucleic acid amplification test; NG, *Neisseria gonorrhoeae;* SEARO, South-East Asia Region; WPRO, Western Pacific Region.

symptoms, sample size and assay type (p value of ≤0.1, online supplementary table 12). The analysis confirmed the univariable metaregression results.

DISCUSSION

We provided, to our knowledge, the first systematic review of gonorrhoea infection in infertile populations. Current infection prevalence was several folds higher than that in the general population; the global estimate in infertile populations was 2.2%, compared with only 0.8% in the general population (per WHO 2016 estimates).[11] Regional estimates followed a similar pattern. Current infection prevalence rates in infertile versus the general population were 5.0% vs 1.8%[11] in AFRO, 2.7% vs 0.7%[11] in EMRO, 2.5% vs 0.8%[11] in WPRO, and 2.4% vs 0.3%[11] in EURO, respectively. These findings should be seen against the expectation that infertile populations should be prone to a lower prevalence than the general population; there is higher frequency of STI testing among them, and therefore earlier detection and higher treatment coverage relative to the general population. Infertile populations may also undergo prophylactic antibiotic administration, not necessarily with testing, prior to procedures such as in vitro fertilisation/embryo transfer.[63 64]

Higher prevalence was also associated with conditions conventionally considered as sequelae of gonorrhoea infection,[12] such as TFI and secondary infertility. TFI was associated with twofold higher odds of gonorrhoea infection. The biological plausibility behind this association has been repeatedly described, with evidence showing that untreated gonococcal infection can lead to pathogen ascension to the upper genital tract, causing pelvic inflammatory disease, tubal scarring, oviduct occlusion and internal tissue adhesion.[12 18 65] Higher prevalence was also found in individuals with mixed and unexplained infertility diagnoses. However, samples comprising mixed infertility diagnoses often included individuals with TFI, while more studies are needed to elucidate the association with unexplained infertility. Prevalence was further higher in individuals with secondary infertility, possibly because secondary infertility is more likely to be caused by 'preventable/acquired factors', such as recurrent exposure to STIs, as opposed to primary infertility, which is more likely to be caused by non-preventable genetic/congenital abnormalities.[3 66 67]

These findings attest to the potential role of gonorrhoea, and/or possibly other STIs associated with gonorrhoea, such as chlamydia, in infertility. Since early detection and treatment of gonococcal infections have been challenged by infection's asymptomatic nature,[68 69] and growing antimicrobial resistance,[22–26] these findings support the global public health value of developing gonococcal vaccines[29 30] as a fundamental solution to gonorrhoea's adverse implications.[70] These findings also support the timeliness of a comprehensive prevention approach promoting sexual health to control *N. gonorrhoeae* and other STIs, mitigate antimicrobial resistance and achieve WHO global health sector strategy targets.[21] Such an approach would focus on the simultaneous implementation of biomedical (rolling-out testing and vaccination), behavioural (promoting healthier sexual lives) and structural prevention interventions (improving access to testing, treatment and care services). Indeed, successful and sustainable implementation of biomedical interventions cannot be achieved without adequate levels of public awareness, access to/uptake of services, and adherence/retention in prevention and treatment cascades.

Interestingly, there was evidence of declining prevalence by ~3% per year over the last four decades, possibly mirroring

Table 2 Results of univariable metregression analyses for the prevalence of NG infection in infertile populations

			Studies/strata	Samples	Univariable analyses		Variance explained
	Predictors		Total N	Total N	OR (95% CI)	P value*	R^2 (%)
Population characteristics	WHO region	AMRO	33	7960	1.00		5.1
		AFRO	24	2281	3.95 (1.54 to 10.09)	0.004	
		EMRO	14	1550	1.37 (0.45 to 4.19)	0.576	
		EURO	73	8987	1.32 (0.64 to 2.76)	0.452	
		SEARO	15	1207	1.24 (0.42 to 3.70)	0.692	
		WPRO	19	4905	1.23 (0.45 to 3.37)	0.686	
		Multicenter	6	374	8.96 (1.90 to 42.29)	0.006	
	Sex	Men	43	16560	1.00		2.0
		Women	141	10704	1.98 (1.06 to 3.67)	0.031	
	Infertility type	Primary/majority primary	52	9330	1.00		0.7
		Secondary/majority secondary	24	1756	2.14 (0.88 to 5.17)	0.091	
		Not specified/not applicable	108	16178	1.06 (0.58 to 1.95)	0.840	
	Infertility diagnosis	General infertility/not specified	64	12441	1.00		4.7
		Tubal factor infertility	50	3238	2.39 (1.23 to 4.63)	0.010	
		Male factor infertility	24	8263	0.72 (0.31 to 1.67)	0.442	
		Ovarian and non-tubal infertility	26	2255	0.80 (0.36 to 1.81)	0.595	
		Mixed and unexplained infertility	20	1067	2.03 (0.83 to 4.98)	0.122	
	Presence of urogenital signs and symptoms	Asymptomatic	64	16484	1.00		8.2
		Symptomatic	24	1408	5.94 (2.61 to 13.54)	<0.001	
		Not specified	96	9372	1.67 (0.96 to 2.91)	0.070	
Study methodology characteristics	Assay type	NAAT (current infection)	33	12594	1.00		22.0
		Culture (current infection)	94	9682	2.54 (1.34 to 4.83)	0.005	
		Other† (current infection)	7	458	4.08 (1.09 to 15.27)	0.037	
		IgG (ever infection)	25	1470	22.10 (9.53 to 51.20)	<0.001	
		IgA/unclear	25	3060	3.74 (1.61 to 8.67)	0.002	
	Year of data collection‡		184	27264	0.97 (0.95 to 0.99)	0.001	5.5
	Sample size	<100 participants	81	3803	1.00		3.0
		≥100 participants	103	23461	0.51 (0.30 to 0.86)	0.011	
Risk of bias domains	Infertility definition	Follows WHO definition	70	11293	1.00		0
		Otherwise/unclear	114	15971	0.85 (0.49 to 1.46)	0.549	
	Exposure to antimicrobials	Lack of exposure last week	25	2037	1.00		2.2
		Exposure in last week	9	1503	0.91 (0.23 to 3.61)	0.890	
		Unclear	150	23724	2.27 (1.06 to 4.90)	0.036	
	Infection ascertainment	Consistency in assay used	179	26612	1.00		0
		Otherwise/Unclear	5	652	1.30 (0.25 to 6.66)	0.750	
	Response rate	≥80%	2	70	1.00		0
		<80%/unclear	182	27194	0.78 (0.06 to 10.10)	0.849	

*Strength of evidence for an association with prevalence was deemed 'good' at 0.05<p value≤0.10, and 'strong' at p value≤0.05.
†Includes Gram stain, gonozyme and fluorescent antibody assays.
‡Missing values for year of data collection were imputed using data for year of publication adjusted by the median difference between year of publication and year of data collection (for studies with complete information).
AFRO, African Region; AMRO, Region of the Americas; EMRO, Eastern Mediterranean Region; EURO, European Region; NAAT, nucleic acid amplification test; NG, *Neisseria gonorrhoeae*; SEARO, South-East Asia Region; WPRO, Western Pacific Region.

declines in prevalence in the population at large,[71 72] or growing STI testing and treatment coverage, and use of improved diagnostics in infertility workup.[73] There was also evidence of regional variability in prevalence, with AFRO being most affected. This may reflect variability in background prevalence: AFRO has the highest gonorrhoea prevalence in the general population.[11]

The higher infection levels in infertile women compared with men, possibly reflect larger contribution of gonorrhoea to infertility in women (online supplementary figure 14),[74] higher susceptibility to gonorrhoea acquisition in women[75] or persistence for longer durations, as this infection is largely asymptomatic in women.[68 69] As signs and symptoms are indicative of infection sequelae,[76] gonorrhoea prevalence was higher in symptomatic compared with asymptomatic individuals.

There were differences in prevalence by assay type, a result difficult to interpret given differences in sensitivity and specificity,[73] and recent and differential use of NAAT in resource-rich versus resource-limited settings.[73] Of note, the variation in the use of assays across settings and time is not likely to differentially affect one population, such as infertile populations, as opposed to another, such as the general population. While ever infection prevalence was much higher than current infection prevalence, this finding has probably limited epidemiological relevance,

Key messages

- Current gonorrhoea infection prevalence in infertile populations varied across regions but was several folds higher than that for the general population across world regions.
- Twice higher odds of gonorrhoea infection were found in women with tubal factor infertility and secondary infertility.
- A fraction of observed infertility is possibly preventable by controlling *Neisseria gonorrhoeae* transmission.

given cross-reaction with other pathogens, such as *Staphylococcus aureus*.[73 77 78]

Our study has unavoidable limitations. Data quantity and quality varied across regions and sometimes limited our ability to produce representative summary estimates; there were only six studies assessing current infection in SEARO, all from India. It was not possible to conduct full multivariable metaregression to adjust for potential confounders, with the large number of predictors relative to that of studies. Prevalence estimates by infertility diagnosis may have been affected by unavoidable overlap across categories; samples with mixed infertility often included TFI, and those with non-TFI may have included other infertility diagnoses. An analysis by age could not be performed, given the low number of studies reporting patients' age. There was evidence for small-study effect in metaregression (table 2 and online supplementary table 12), suggesting publication bias; studies with small sample size reported higher prevalence. Conversely, differential access to quality STI testing and treatment in infertility clinics, in settings with better versus limited access to STI services, may have biassed such studies towards lower prevalence.[10 79–81] Risk of bias assessment was limited by studies with missing information. Gonorrhoea prevalence was often reported as a secondary outcome, with no 'gonorrhoea' term listed in title/abstract, thereby complicating study identification.

In conclusion, gonorrhoea prevalence in infertile populations is several folds higher than that in the general population. This finding, along with even higher prevalence in women with TFI and individuals with secondary infertility, attests to the potential role of *N. gonorrhoeae* in infertility and suggests that a fraction of infertility is possibly preventable by controlling *N. gonorrhoeae* transmission. Expansion of *N. gonorrhoeae* surveillance and monitoring in infertile populations is warranted as gaps in evidence persist. A multifaceted response should be considered to ensure progress towards WHO global health sector strategy targets.[21]

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