

Applying a Novel Approach to Scoping Review Incorporating Artificial Intelligence: Mapping the Natural History of Gonorrhoea

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Abstract

Background

This scoping review presents the results of three distinct search strategies combined to identify and map the range of conditions (clinical presentations, complications, coinfections and health problems) associated with gonorrhoea infection. We also report use of a novel artificial-intelligence-(AI)-assisted Medline search tool.

Methods

To fully characterize the range of health outcomes associated with gonorrhoea, we combined a structured preliminary search with a traditional systematic search, then supplemented with the output of a novel AI-assisted Medline search to identify eligible literature.

Results

We identified 189 health conditions associated with gonorrhoea infection from 107 unique references and 21 International Statistical Classification of Diseases and Related Health Problems Ninth and Tenth Revision (ICD 9/10) or Read codes. Pathogenic processes relating to these outcomes were also briefly summarized. The 189 identified health conditions were related to infection of the urogenital tract (n=86), anorectal tract (n=6) oropharyngeal tract (n=5) and the eye (n=14); and other conditions such as systemic (n=61) and neonatal conditions (n=7), psychosocial associations (n=3), and co-infections (n=7). The 107 unique references attained a Scottish Intercollegiate Guidelines Network (SIGN) score of $\geq 2++$ (n=2), 2+ (14 [13%]), 2- (30 [28%]) and 3 (45 [42%]), respectively. Remaining papers (n=16) were reviews.

Conclusions

Through AI screening of Medline, we captured – titles, abstracts, case reports and case series related to rare but serious health conditions. These outcomes might otherwise have been missed during a systematic search. The AI-assisted search provided a useful addition to traditional/manual literature searches especially when rapid results are required.

Background

Gonorrhoea is a sexually transmitted disease that has been persistently prevalent worldwide for millennia, despite serial attempts to control and treat it [1]. In 2016, 87 million incident cases were estimated in adults 14–49 years of age and the incidence may be growing [2]. The causative bacterium, *Neisseria gonorrhoeae* (*Ng*), has established resistance to all known antibiotics developed since the 1930s, and the World Health Organization (WHO) recently warned that the emergence of pan-drug resistant *Ng* is on the horizon [3]. In the US alone, almost half of the estimated 1.14 million cases occurring each year are resistant to antibiotics. If gonorrhoea becomes untreatable, its associated complications and health problems could result in an additional 1.2 million *Ng* infections and 579 gonorrhoea-attributable human immunodeficiency virus (HIV) infections within 10 years at a cost of \$378.2 million [4].

The course of gonorrhoea infection within an individual over time, known as the natural history, is highly complex and involves multiple anatomic sites of primary mucosal infection in men, women and neonates [1]. Anatomic sites include the urogenital, anorectal and pharyngeal tract, as well as the eye, particularly in neonates. Infection with *Ng* can directly result in a wide spectrum of clinical presentations and complications, and is indirectly associated with a range of other health problems in the short, medium and long-term [5]. Some complications and/or health problems are well described in the literature, such as pelvic inflammatory disease (PID) and infertility in women and epididymitis in men [1, 6]. However, the full range of conditions associated with gonorrhoea has not been systematically characterized in the literature in an accessible, evidence-based format. In this scoping review, we aim to identify and map the full range of clinical presentations, complications, coinfections and health problems that have been associated with gonorrhoea infection as identified in the published literature (**Figure 1**). Furthermore, we report on the first use of a novel artificial intelligence (AI)-assisted Medline search tool combined with a traditional systematic search methodology.

Methods

Due to the exploratory nature of the research question, we anticipated that the traditional ‘population, intervention, comparator and outcome’ (PICO) [7]-based formulation of the research question using systematic review methods alone would be either too restrictive (gonorrhoea-related conditions would have to be specified *a priori*, limiting the outcome), or alternatively, too imprecise, resulting in a high number of hits of low specificity. To address this, we used an established scoping review methodology [8] combining three complementary approaches to search the published literature. These included a structured preliminary search combined with a traditional systematic search, then supplemented with the output of a novel AI-assisted Medline search, which we report here for the first time.

The research question was based on the ‘patient, concept and context (PCC)[9] structure: ‘*Among persons infected with gonorrhoea, what is the range of clinical presentations, complications, coinfections and health outcomes that are associated with the infection?*’ ‘Association’ was assumed to imply that gonorrhoea infection could be a plausible component along the causal pathway to the health outcome, either directly or indirectly [10, 11]. Identified conditions were then contextualized according to known pathogenic processes, to be associated with primary urogenital, anorectal, oropharyngeal or conjunctival infection. To compile an initial list of key health problems associated with *Ng* infection, we first conducted a ‘high yield’ or ‘snowball’ search [12], accessing websites of major public health institutes in the United States (US), United Kingdom (UK), Germany and the Netherlands [13-17] to review current disease summaries and guidance on gonorrhoea (**Supplementary text 1.1, Additional file 1**). We pursued targeted Medline searches of key health problems based on the quoted references, knowledge of seminal authors and studies in the field, and the reference list of each paper (**Supplementary text 1.2, Additional file 1**). The resulting list of health problems was then compared against the existing compendia of clinical diagnoses related to gonorrhoea from the International Statistical Classification of Diseases and Related Health Problems Ninth and Tenth Revision (ICD9/10 [18, 19] and Read diagnostic codes [20]) (**Supplementary table 1–2, Additional file 1**). The list of health problems was supplemented with ICD codes (used to systematically classify diseases, disorders, injuries and other health conditions) where necessary.

We then conducted a traditional systematic Medline search applying the PICO methodology [7], posing the broad question “*In people exposed to Ng, what is the natural history of gonorrhoea infection?*” The search string was developed iteratively (**Additional file 2**), combining keywords and Medical Subject Headings (MeSH) terms identified from seminal references which in-turn resulted from the snowball search. Full-text articles were retrieved if the title and abstract specifically related aspects of the natural history or pathogenesis of *Ng* to clinical sequelae or health problems in humans. Only English language abstracts were included. No other limitations were applied. Reference lists were reviewed and full-text articles were accessed where relevant. The outcome of this search was used to provide a brief narrative summary of the key pathogenic processes associated with complications and health problems identified as well as to identify further health problems associated with *Ng*.

We supplemented the searches with Papyrus [21], a novel AI-assisted Medline search tool (**Supplementary text 3.1–3.3, Additional file 3**). A broad search query (‘gonorrhoea’) was run, identifying relevant literature with an English title and abstract. The AI tool used automatic natural language processing (NLP) methods and pre-processing using the Stanford Core NLP library [22] (see details in **Supplementary text 3.1, Additional file 3**) to extract identified ‘topic-words’ from all abstracts – typically nouns or expressions describing concepts related to gonorrhoea (e.g. ‘salpinx’). A vector space model was constructed and a ‘CoClus’ co-clustering algorithm [23](see details in **Supplementary text 3.2, Additional file 3**) was applied to partition the vocabulary and the document set into topics, so that each topic comprises semantically related ‘topic-words’ and their enclosing documents (e.g. an analogy in the press would be to discover automatically without prior knowledge a topic where some of the most important words are ‘covid19’, ‘lockdown’, ‘mask’, ‘PCR’, ‘vaccine’, ‘test’, ‘layoff’, ‘stimulus’, ‘bill’). Within each topic, associated ‘topic words’ are ranked by a score based on the frequency with which these words occur in abstracts, reflecting their importance with respect to the given topic (**Supplementary text 3.1, Additional file 3**). **Supplementary figure 1 (Additional file 1)** shows an example of the raw textual output of the words listed under a topic, as extracted by the tool. **Figure 2** shows the graphical user interface of Papyrus, which is composed of a topic map in the form of a mosaic of word clouds. It illustrates how each rectangle is a topic grouping a subset of abstracts (e.g., outcomes related to urogenital *Ng* infections) and their most representative topic-words (‘ectopic pregnancy’, ‘endometritis’, ‘epididymitis’ and ‘salpinx’). Details of the NLP methods are provided in **Supplementary text 3.1, Additional file 3**. As a first step, all ‘topic-words’ corresponding to each topic displayed in the

topic map were extracted and screened manually and independently by two reviewers (JW and EB) for relevance to clinical and psychosocial gonorrhoea-related health outcomes. The papers corresponding to the agreed topic-words were eligible for inclusion if they described a potential association between primary gonorrhoea infection at any anatomic site with any clinical or psychosocial health outcome in women, men or children. Abstracts and titles were then manually screened and full-text articles were only accessed if the inclusion criteria were met.

To map the list of health problems and outcomes associated with *Ng* infections, the three approaches were cross referenced, duplicate conditions and references were removed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) framework [24]. The retrieved reports were categorized by study design (e.g., cohort study/case control/literature review [**Additional file 4**]) and primary research papers were assigned a quality score according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria [25]. As some health outcomes are serious but rare (e.g., disseminated gonorrhoea infection [DGI]), categories of evidence considered included case reports, case series (SIGN score of 3) and higher levels of evidence. Health outcomes identified through secondary reporting in review papers only (and not in primary research) were also included as we considered that primary research from the pre-antibiotic era may not have been indexed on PubMed. Where associated conditions were derived from the clinical compendia of ICD 9/10 or Read codes (classification of clinical terms for describing the care and treatment of patients), these were categorized separately based on the causal pathogenic pathway. To summarize the results, health outcomes with the highest level of supporting evidence (SIGN score) were selected for inclusion in an illustrative figure. The full evidence table was reviewed by an independent expert (MA) for the plausibility of association with gonorrhoea. All identified conditions, associated references, study design and SIGN scores are provided in **Additional file 4**.

Results

In total, 53 health conditions were identified through the initial 'high yield' search, 99 health conditions through the systematic search and 124 health conditions (from 102 topic words) through the AI-assisted search. Details of the search are provided in Fig. 3. The removal of duplicate conditions ($n = 87$) resulted in 189 health conditions associated with primary gonorrhoea infection, supported by 107 unique references and 21 ICD 9/10 or Read codes (Fig. 3). Pathogenic processes relating to these outcomes were briefly summarized based on 14 out of 101 full-text articles retrieved during the systematic review (**Additional file 2** and legend, Fig. 4). We mapped the range of conditions identified for men, women and new-borns, based on the pathogenic pathways as described in Fig. 4. Each condition was attributed to the likely site of primary infection, and whether it was a primary clinical presentation/symptom, or a related complication, coinfection or long-term health outcome. Among the identified conditions, 86 were related to primary urogenital infection, 6 were related to the anorectal tract, 5 were related to oropharyngeal infection, 14 were infections in the eye, 3 were psychosocial and 7 were in neonates. In some cases ($n = 61$) the condition was systemic in nature and was not directly attributable to a single primary site of infection. Lastly, 7 conditions were classified as co-infections (e.g., HIV). Furthermore, studies related to these 189 conditions utilized various study designs, which included 132 primary research studies, 56 clinical/microbiological reviews, and the remainder were ICD 9/10 or Read codes. We identified a total of 107 supporting research papers, among which only 2 papers were SIGN $\geq 2++$; 14 (13%) of SIGN score 2+, 30 (28%) of SIGN score 2- and 45 (42%) of SIGN score of 3 were found. The remaining 16 papers were reviews. To illustrate our findings, a subset of conditions and the highest quality of related references were selected for inclusion in Fig. 4. The full list of conditions and sources is provided in **Additional file 4**. Of the references identified, 50% were published before 2004 and 25% before 1991.

Discussion

More than 580,000 gonorrhoea infections were notified in the US in 2018, the highest number reported since 1991 representing an increase of 83% since the historic low of 2009 [26]. As the range of effective antimicrobial therapies is depleted over time, the prospect of untreatable gonorrhoea is increasing [27]. Health outcomes that are rare or unseen in the contemporary industrialized world may again become commonplace [28], with serious implications for public health and healthcare costs [29]. To fully characterize the range of health outcomes associated with gonorrhoea, we combined traditional and novel literature searching methodologies. As we had anticipated, less than half of the conditions identified were captured through the 'high yield' and systematic searches combined, and the AI tool added substantial value in this regard. Through AI screening of

Medline titles and abstracts, case reports and case series (in particular) that related to rare but serious health conditions were captured. These outcomes might otherwise have been missed during a systematic search. Such non-analytic studies score low on objective quality scores but relate to conditions that may be important contributors to the total burden of gonorrhoea infection if gonorrhoea becomes untreatable in the future. For some outcomes, where primary research was not identified because it may have been conducted in the pre-PubMed era, we refer to review articles as secondary references. In the 1930s for example, 140 cases of gonococcal arthritis associated with 3 deaths were described over a 6-year period at Boston City Hospital [30, 31]. Such health outcomes, that commonly occurred in the pre-antibiotic and/or pre-PubMed era but are rare today in the industrialized world, may not otherwise have been identified.

There are limitations to our study. Similar to a manual systematic search, the AI tool returned topic words with a related abstract that required independent manual review and it is possible that some important health conditions were missed. We reviewed only English language abstracts and as such, health problems reported in the full-text articles may not have been mentioned in the abstract. It is also possible that the AI approach was overly sensitive, identifying health problems that are excessively rare (e.g., Adult respiratory distress syndrome) [32] and not likely to re-emerge, or for which a direct causal association may not be clearly established (e.g., prostate cancer) [33]. To our knowledge, this is the most comprehensive search, selection and synthesis of health conditions that has been related to gonorrhoea in the literature. Notably, the volume of high-quality research on the health outcomes of gonorrhoea was limited, and few controlled, observational studies with a low risk of confounding or bias that estimated a causal association were identified.

In conclusion, this scoping review using combined search methods proved to be a useful starting point from which to quickly but comprehensively identify relevant papers, inform future systematic literature searches, identify gaps in the existing literature and formulate new research questions. In our experience, AI-assisted Medline screening facilitated the exploratory nature of our research question and identified valuable supplementary material. Considering the exponential growth in the scientific literature [34], traditional/manual literature search methods will be limited in their future application as the time and resources required become prohibitive. The presented approach provides a viable adjunct, especially in situations where timely results of literature searches are of essence such as in the current situation with coronavirus disease (COVID-19) [35]. Pending further testing and validation, AI-assisted literature searching has the potential to become an important tool in the existing lexicon.

Abbreviations

AI – Artificial intelligence

COVID-19 – Coronavirus disease

DGI – Disseminated gonorrhoea infection

HIV – Human immunodeficiency virus

ICD 9/10 – International Statistical Classification of Diseases and Related Health Problems Ninth and Tenth Revision

MeSH – Medical Subject Headings

NLP – Natural language processing

Ng – *Neisseria gonorrhoeae*

PID – Pelvic inflammatory disease

PICO – Population, intervention, comparator and outcome

PCC – Patient, concept and context

PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses

SIGN – Scottish Intercollegiate Guidelines Network

TFI – Tubal factor infertility

US – United States

UK – United Kingdom

WHO – World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

JW and EB are employed by the GSK group of companies. JW and EB hold shares in the GSK group of companies. JW and EB declare no other financial and non-financial relationships and activities. MG, NM and MA declare no financial and non-financial relationships and activities and no conflicts of interest.

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Authors' contributions

JW and EB conceived the research. The incorporation of the AI search methods was proposed by EB to trial Papyrus and the study was designed and developed by all the authors (JW, MG, NM, MA) who actively contributed to data acquisition, interpretation, validation (overseen by MA), drafting, critical appraisal, revision of the manuscript and final approval. The analysis was conducted by JW and EB. All authors had full access to the data and gave final approval before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figures

Plain Language Summary

What is the context?

- Gonorrhoea is a sexually transmitted infection that can cause a range of health problems in men, women and new-borns.
- This scoping review aimed to answer the following research question: *Among persons infected with gonorrhoea, what is the range of clinical presentations, complications, coinfections and health outcomes that are associated with the infection?*

What is new?

- Using a novel artificial intelligence (AI)-assisted Medline search tool combined with a traditional systematic search methodology, we reviewed the published literature to identify and map the full range of clinical presentations, complications, coinfections and health problems associated with gonorrhoea infection.
- This review identified 189 health conditions associated with primary gonorrhoea infection, supported by 107 research papers and 21 codes related to the international standards for reporting disease (International Classification of Diseases [ICD] 9/10 version or Read codes). Pathogenic processes relating to these outcomes were briefly summarized and mapped for men, women and new-borns.

What is the impact?

- The AI-assisted screening captured rare but serious health conditions that were not otherwise identified through the traditional systematic literature search methodology.
- Thus, the AI-assisted approach provided a viable adjunct, especially when the time and resources required to conduct traditional/manual literature searches become prohibitive.

Figure 1

Plain Language Summary



Figure 2

Overview of the corpus in the Papyrus software ± Overview of the corpus in the Papyrus software. (1) The broad search query 'gonorrhoea' is entered in the search box. (2) Topics related to the search query 'gonorrhoea' are extracted automatically from the papyrus corpus and presented as a mosaic of rectangles on screen. In the present case, the map contains 37 distinct topics (rectangles) of inter-related words that were extracted by the tool. (3) A highlighted example is a topic related to antibiotics including topic words such as 'cephalosporins', 'ciprofloxacin', 'ceftriaxon'. By glancing over the combination of words shown in each rectangle, the user is able to infer whether the topic captures subject matter relevant to the search query (i.e., a subjective evaluation on behalf of the user). (4) When the user clicks on a topic of interest (e.g., 4a the rectangle containing 'ectopic pregnancy' [4a]) a ranked list of inter-related 'topic words' is displayed based on their relative importance to the topic at hand (e.g., 'endometritis', 'epididymitis' and 'salpinx' appear in the top 5 commonly occurring topic-words [inset, 4b]). (5) The chosen topic is then shown to comprise a total of 462 representative topic-specific words, presented according to their relative frequency of occurrence. (6) Abstracts from each of the topic words (in this case 591 abstracts) can then be displayed, with direct link to PubMed provided.

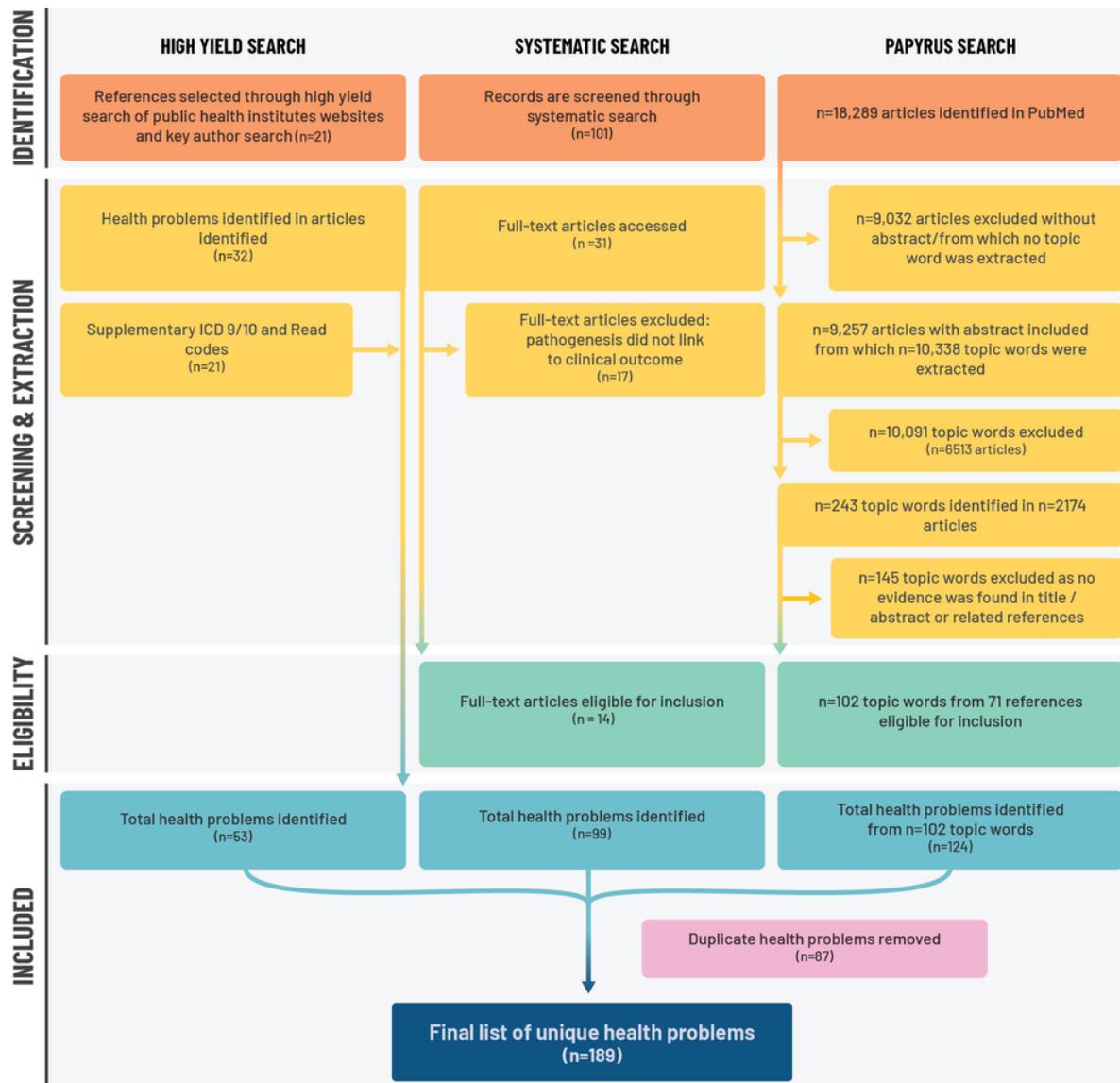


Figure 3

PRISMA flowchart ICD 9/10, International Statistical Classification of Diseases and Related Health Problems (Ninth or Tenth Revision); PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses

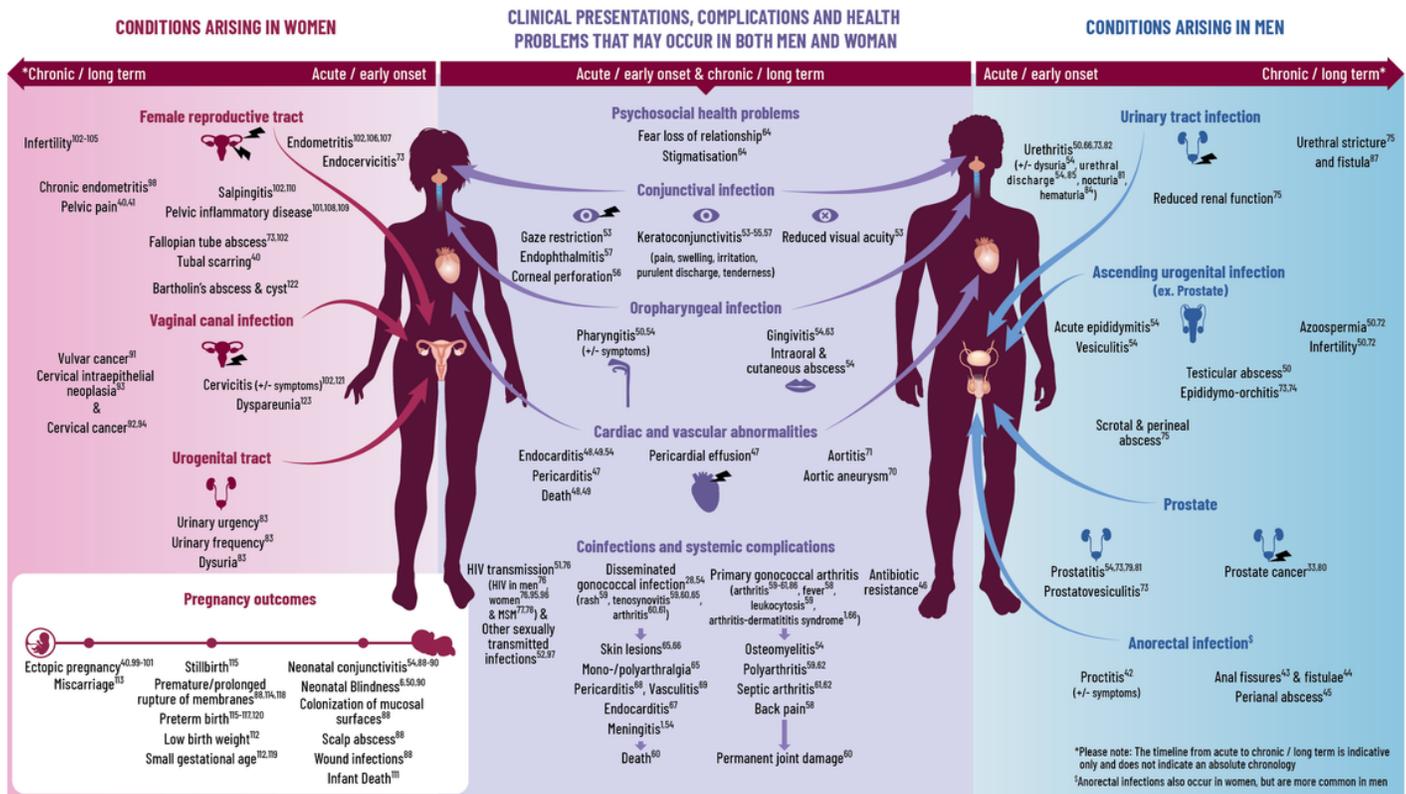


Figure 4

Gonorrhoea health map: Clinical presentations, complications and health problems that may occur in both men and women

Summary of the pathogenic processes related to observed health outcomes of gonorrhoea infection: From exposure to cellular invasion, ascending infection and dissemination. *Neisseria gonorrhoeae* (Ng) is transmitted person-to-person through sexual networks by direct contact between mucosal surfaces of the urogenital, anorectal or oropharyngeal tracts, and sometimes via the eye. In men, it attaches to the sperm and is transmitted via the ejaculate to their partners (50–73% probability, independent of number of exposures) [1]. In women, enzymes in the cervicovaginal flora facilitate transfer to and uptake of Ng by the male urethra (20–35% probability with one exposure) [1]. Up to one third of exposures will not result in infection and the bacterium is spontaneously cleared. In the remainder, the incubation period is 1–6 days [36]. In both men and women, the first step in the pathogenesis is adherence to the epithelium of the human mucosal surface. In the urogenital tract, Ng enters male and female epithelial cells through different receptors, leading to different clinical disease presentations (i.e., cervicitis in women, urethritis in men) [1]. The Ng bacterium evades the innate immune response and manipulates the adaptive immune response to promote continued inflammation [37]. If sustained, this facilitates sub-epithelial penetration and is associated with increased susceptibility to human immunodeficiency virus (HIV) type 1 [1]. Without treatment, Ng can ascend the urogenital tract. Intense neutrophilic activity in the upper tract directly damages epithelial cells [37] and leads to the death of cells lining the upper tract. Subsequently this may cause scarring and occlusion (e.g., causing tubal factor infertility (TFI), ectopic pregnancy in women and urethral stricture in men) [38]. If Ng enters the bloodstream and disseminates, interacting with other host cell types (e.g., blood vessel endothelial dendritic cells, macrophages), it may cause skin and/or joint/tendon infection, and more rarely endocarditis or meningitis and other systemic sequelae [39]. Pregnant women can transmit Ng to their newborns during delivery, which may result in neonatal conjunctivitis and/or rarely, disseminated infection. A comprehensive depiction of clinical presentations, complications and health outcomes can be seen in the accompanying figure [40-121].

Supplementary Files

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