Review

Neisseria gonorrhoeae molecular typing for understanding sexual networks and antimicrobial resistance transmission: A systematic review

Katy Town [a,b,*], Hikaru Bolt [c], Sara Croxford [c], Michelle Cole [d], Simon Harris [e], Nigel Field [b], Gwenda Hughes [a,c]

[a] National Institute for Health Research Health Protection Research Unit in Blood Borne and Sexually Transmitted Infections at University College London in partnership with Public Health England and in collaboration with the London School of Hygiene and Tropical Medicine, Mortimer Market Centre, Third Floor, Capper Street, London WC1E 6JB, UK
[b] Centre for Molecular Epidemiology and Translational Research, Institute for Global Health, University College London, Mortimer Market Centre, Capper Street, London WC1E 6JB, UK
[c] HIV/STI Department, National Infection Service, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK
[d] Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, National Infection Service, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK
[e] The Wellcome Trust Sanger Institute, Genome Campus, Cambridge CB10 1SA, UK

ARTICLE INFO

ABSTRACT

Objectives: *Neisseria gonorrhoeae* (NG) is a significant global public health concern due to rising diagnoses rates and antimicrobial resistance. Molecular combined with epidemiological data have been used to understand the distribution and spread of NG, as well as relationships between cases in sexual networks, but the public health value gained from these studies is unclear. We conducted a systematic review to examine how molecular epidemiological studies have informed understanding of sexual networks and NG transmission, and subsequent public health interventions.
Methods: Five research databases were systematically searched up to 31st March 2017 for studies that used sequence-based DNA typing methods, including whole genome sequencing, and linked molecular data to patient-level epidemiological data. Data were extracted and summarised to identify common themes.
Results: Of the 49 studies included, 82% used NG Multi-antigen Sequence Typing. Gender and sexual orientation were commonly used to characterise sexual networks that were inferred using molecular clusters; clusters predominantly of one patient group often contained a small number of isolates from other patient groups. Suggested public health applications included using these data to target interventions at specific populations, confirm outbreaks, and inform partner management, but these were mainly untested.
Conclusions: Combining molecular and epidemiological data has provided insight into sexual mixing patterns, and dissemination of NG, but few studies have applied these findings to design or evaluate public health interventions. Future studies should focus on the application of molecular epidemiology in public health practice to provide evidence for how to prevent and control NG.

© 2018 The Authors. Published by Elsevier Ltd on behalf of The British Infection Association.
This is an open access article under the CC BY license. (http://creativecommons.org/licenses/by/4.0/)
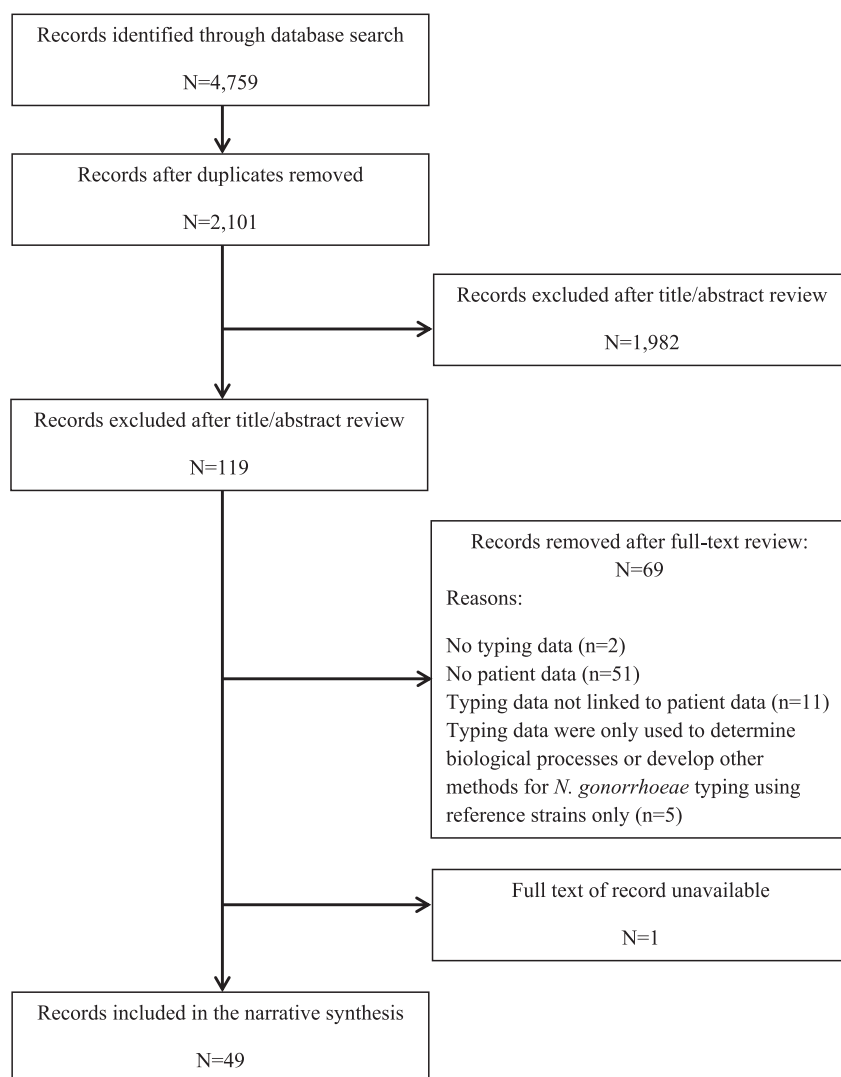
Introduction

Neisseria gonorrhoeae is a sexually transmitted pathogen of significant public health concern due to rising diagnosis rates, particularly in men who have sex with men (MSM), and the emergence of resistance to all classes of antimicrobials used for treatment.[1,2] It is important to better understand how and why *N. gonorrhoeae*

* Corresponding author at: National Institute for Health Research Health Protection Research Unit in Blood Borne and Sexually Transmitted Infections at University College London in partnership with Public Health England and in collaboration with the London School of Hygiene and Tropical Medicine, Mortimer Market Centre, Third Floor, Mortimer Market Centre, Capper Street, London WC1E 6JB, UK.
E-mail address: katy.town.15@ucl.ac.uk (K. Town).

Fig. 1. PRISMA flowchart indicating the systematic selection of journal articles for inclusion in this review
PRISMA flowchart for the conference abstract book is presented in the Supplementary material.

and resistant infections spread within sexual networks in order to design targeted and rational interventions to control transmission.

Traditional epidemiological methods using surveillance data and patient questionnaires of reported behaviour to understand and describe sexual networks have been used to improve our understanding of the distribution and transmission of *N. gonorrhoeae*, including the concentration of *N. gonorrhoeae* in specific groups at risk.[3,4] However, these methods are limited in their ability to determine whether infected individuals with the same epidemiological characteristics are part of the same transmission network. Establishing direct epidemiological links is challenging because gonorrhoea is frequently asymptomatic, especially in females, which may lead to missing (undiagnosed) cases in most datasets.

Molecular technologies can be used to group isolates according to similarities in their genetic data and infer relatedness between isolates.[5] By combining these molecular data with epidemiological data, hypotheses about the transmission of *N. gonorrhoeae* within and across different sexual networks can be tested. The use of molecular epidemiology in the analysis of *N. gonorrhoeae* populations is a rapidly evolving field but there has been no systematic assessment of its public health value.

In this systematic review, we aimed to use published literature to investigate how linked *N. gonorrhoeae* epidemiological and molecular typing data can enhance our understanding of sexual networks and pathogen transmission and how this information has been used within public health interventions to control gonorrhoea infections.

Methods

Search strategy and selection criteria

In this systematic review (reported according to the international prospective register of systematic reviews: PROSPERO 2016 CRD 42016037238),[6] studies were included if sequence based DNA typing methods were used (Multi-locus Sequence Typing (MLST), *N. gonorrhoeae* Multi-Antigen Sequence Typing (NG-MAST) and Whole Genome Sequencing (WGS)) (see Supplementary material for Glossary of Terms) and the typing data were linked to patient-level epidemiological data, including patient demographic data (e.g. gender, age, and ethnicity), sexual behaviour data (e.g. sexual orientation, sex work, condom use, number of partners, sex abroad) and/or clinical data (e.g. symptoms, site of infection, concurrent STIs, HIV status). We focused on the sequence-based DNA typing techniques described above as these are currently the most commonly used and recommended[7] techniques for molecular epi-