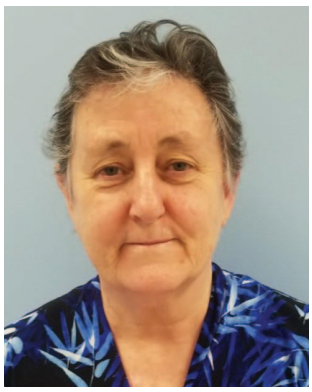
Gonorrhoea: past, present and future




Evgeny A Semchenko[A], *Xiaofan Chen*[A], *Caroline Thng*[B], *Maree O'Sullivan*[B] *and Kate L Seib*[A,C]

[A]Institute for Glycomics, Griffith University, Southport, Qld 4215, Australia

[B]Gold Coast Sexual Health, Southport Community Health Precinct, Southport, Qld 4215, Australia

[C]Tel: +61 7 555 27453, Email: k.seib@griffith.edu.au

Abstract. The sexually transmitted infection (STI) gonorrhoea is an ancient human disease caused by the Gram-negative bacterial pathogen *Neisseria gonorrhoeae*. Despite decades of research focused on preventing, diagnosing, and treating gonorrhoea, it remains a major global health concern due to its high prevalence, high rates of asymptomatic cases, the severe sequelae that can result from untreated infections, and the increasing difficulty in treating infections caused by multi-drug resistant strains of *N. gonorrhoeae*. It is estimated that there are more than 87 million cases of gonorrhoea worldwide each year, and the WHO, CDC and Australian National Antimicrobial Resistance (AMR) Strategy have prioritised *N. gonorrhoeae* as an urgent public health threat for which new therapeutics and a vaccine are needed.

Where did it all begin? The long history of gonorrhoea

Gonorrhoea is an ancient disease of humans, with symptoms resembling gonorrhoea reportedly described in ancient Chinese and Middle Eastern records dating as far back as 3500 BC[1]. There is also reference to urethral discharge, believed to be gonorrhoea, in the book of Leviticus in the Old Testament of the Bible (Leviticus 15:1-3). The name gonorrhoea is credited to Greek physician Galen (AD 130-200), which means the flow of semen, derived from the Greek words 'gonos' (semen) and 'rhoia' (to flow)[1]. In the 16th century, as STIs were recognised as being more common in prostitutes, gonorrhoea became known as 'the clap,' likely in reference to the old Le Clapiers district of Paris where prostitutes were housed. It was not until 1879, however, that the bacteria responsible for gonorrhoea was identified and named *Neisseria gonorrhoeae* after Albert Neisser the German microbiologist who first isolated the bacteria (Figure 1). Over time, gonorrhoea has been described extensively in scientific literature, as well as in essays such as 'Boswell's Clap' that describe James Boswell's nineteen episodes of gonococcal urethritis between 1760–1790 based on his detailed diary accounts[2], and news articles describing its antibiotic resistance status, including 'Man has 'world's worst' super-gonorrhoea' (BBC News, UK, 28 March 2018).

Where are we now? Current clinical aspects of gonorrhoea

The WHO estimates that more than 1 million STIs occur every day[3]. There are an estimated 87 million gonorrhoea

infections occurring each year[3] and *N. gonorrhoeae* has been prioritised as an urgent public health threat by the WHO[4], CDC[5] and Australian National AMR Strategy[6]. STI surveillance systems vary widely within and across WHO regions, which means that current figures likely underestimate the burden of gonorrhoea due to limitations in diagnosis and reporting. Several systems currently exist in Australia for the surveillance of *N. gonorrhoeae* infections, including state-level reporting via the Notification of Communicable Diseases, as well as the Australian Gonococcal Surveillance Programme (AGSP) conducted by the National Neisseria Network (NNN). These systems provide incidence, demographic, and antimicrobial resistance data to inform clinical and public health responses to continue towards gonorrhoea control. Rates of gonorrhoea have continued to increase in Australia over the last 10 years, with an 80% increase between 2013 to 2017[7]. Rates of gonorrhoea are particularly high in gay and bisexual men (GBM), Australia's First Peoples and younger populations (19–29 years) and there has been a recent resurgence of gonorrhoea in urban heterosexuals[7]. In 2019 there were 34 265 gonococcal infections notified in Australia[8].

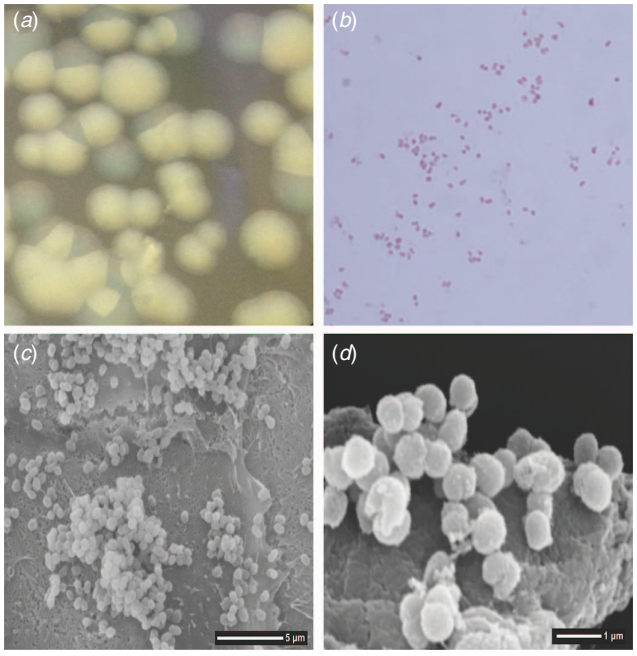


Figure 1. *Neisseria gonorrhoeae* (Ng) under the microscope. (A) Light microscope image of Ng colonies on an agar plate (×4 magnification). Opaque and translucent colonies are seen due to phase variation of opacity (Opa) proteins. (B) Light microscope image of Gram-stained Ng (×100 magnification). Scanning electron micrograph of Ng microcolonies on the surface of urethral epithelial cells, acquired at (C) ×5000 magnification (scale bar represents 5 µm) and (D) ×17 000 magnification (scale bar represents 1 µm).

The gold standard for *N. gonorrhoeae* diagnosis remains culture due to its high specificity and the ability to perform antibiotic sensitivity tests to guide treatment. However, culture yields are highly dependent on bacterial loads, storage and transport of specimens. This impacts extragenital site sampling where culture rates could be as low as 64% in pharyngeal infections[9]. In addition, the intimate and invasive nature of obtaining urethral and cervical samples limit its utility for widespread screening and testing programmes. Since 2002 nucleic acid amplification tests (NAATs) have been preferred as the screening tool for *N. gonorrhoeae* infection. NAATs have demonstrated superior detection rates with 97–99% sensitivity, and outperform culture by up to 2-fold for rectal and 5-fold for pharyngeal gonorrhoea infections[10]. NAATs have also been pivotal in improving access and uptake of gonorrhoea screening programmes, with a high level of acceptability and effectiveness for detecting gonorrhoea infection[11]. Multiplex NAATs testing are also being developed, so that samples can be tested for up to nine different pathogens including *Chlamydia trachomatis*, *Trichomonas vaginalis* and *Mycoplasma genitalium*[12]. Concomitant infection of *N. gonorrhoeae* with these infections occur in up to 30% of cases. Finally, NAAT tests have the ability to deliver a result in a matter of hours. A study in the UK demonstrated that the rapid

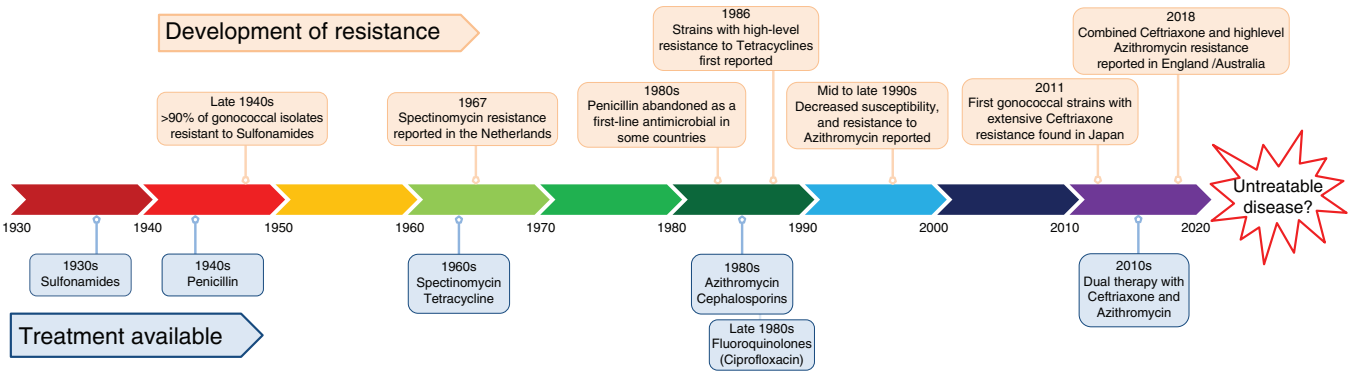


Figure 2. Timeline of *Neisseria gonorrhoeae* antibiotic treatments and antibiotic resistance. The recommended antimicrobials for treatment of *N. gonorrhoeae* since the 1930s are shown below the timeline. The evolution of resistance in *N. gonorrhoeae* is shown above the timeline. Adapted from Unemo and Shafer[15].

turnaround of results would reduce time to diagnosis by more than 8 days leading to potential reduction in transmission[13].

The outcome of *N. gonorrhoeae* infection varies by site of infection and by sex[14]. Symptomatic infections predominantly affect the genito-urinary tract with 90% of penile infections presenting with purulent discharge or dysuria, whilst approximately 50% of cervical infections present with changes in vaginal discharge, intermenstrual or post coital bleeding. Complications of *N. gonorrhoeae* can occur leading to epididymo-orchitis and pelvic inflammatory disease subsequently leading to an increased risk of infertility and ectopic pregnancy. Rarely, haematogenous spread can occur causing skin lesions, arthritis and tenosynovitis (disseminated gonococcal infection). Extragenital *N. gonorrhoeae* infections also occur leading to pharyngitis, proctitis and uveitis, though asymptomatic pharyngeal and rectal infections are common. Though gonorrhoea remains a curable infection, treatments have changed rapidly over time to

Table 1. Antimicrobials and vaccines under development for *Neisseria gonorrhoeae* (Ng).

Name	Description	Mode of action/function	Stage	Reference
Antimicrobials				
Lefamulin	Antibiotic	Protein synthesis inhibitor	Clinical trial	18
Gepotidacin	Novel antibiotic	DNA replication/topoisomerase inhibitor	Clinical trial	
Zoliflodacin	Novel antibiotic	DNA replication/topoisomerase inhibitor	Clinical trial	
SMT-571	Novel antibiotic	Disrupts cell division	Preclinical	24
DIS-73285	Novel antibiotic	Electron chain protein disruption	Preclinical	25
Fenamic acids	Repurposed drug	Anthranilic acid derivatives/NSAIDs, mode of action against Ng unknown	Preclinical	26
Methyldopa	Repurposed drug	Hypertension medication, adherence blocking	Preclinical	27
Carbamazepine	Repurposed drug	Anticonvulsant medication, adherence blocking	Preclinical	27
LL37	Host-derived cationic peptide	Disrupts bacterial membrane	Preclinical	28
Self-inhibitory peptides	Engineered synthetic peptides	Destabilizes target protein function/activity	Preclinical	29
Mannosides	Class of small drugs that contain sugar – mannose	Adherence blocking	Preclinical	30
Vaccines/candidate vaccine antigens				
4CMenB	Licensed meningococcal serogroup B vaccine: MeNZB OMV, NadA, NHBA-GNA1030, fHBP-GNA2091	Induces antibodies to Ng, OMV component calculated to have 31% effectiveness against gonorrhoeae in a retrospective study of MeNZB	Clinical trial	21,23
2C7	Peptide mimic of Ng LOS epitope 2C7	Bactericidal antibodies	Preclinical	14
AniA	Nitrite reductase	Function blocking and bactericidal antibodies	Preclinical	
BamA	Outer membrane protein assembly factor	Bactericidal antibodies	Preclinical	
MetQ	Methionine-binding protein of ABC transporter	Adherence blocking and bactericidal antibodies	Preclinical	
MsrA/B	Methionine sulfoxide reductase	Function blocking and bactericidal antibodies	Preclinical	
MtrE	Outer membrane channel protein of MtrCDE efflux pump	Bactericidal antibodies	Preclinical	
NHBA	Neisseria Heparin Binding Antigen	Function inhibiting, adherence blocking and bactericidal antibodies	Preclinical	
OMV	Naturally secreted outer membrane vesicles	Contain repertoire of Ng outer membrane proteins	Preclinical	
PilQ	Type IV pilus biogenesis and competence protein	Bactericidal antibodies	Preclinical	
TbpA/B	Transferrin binding proteins A and B	Bactericidal and growth inhibitory antibodies	Preclinical	
TdfH	TonB-dependent transporter H	Function blocking antibodies	Preclinical	

overcome emerging drug-resistant *N. gonorrhoeae* (Figure 2). The future effectiveness of antibiotic treatment has been significantly compromised by the fact that *N. gonorrhoeae* has developed resistance to all classes of antibiotics used to treat it[15]. Worldwide, penicillin, ciprofloxacin and cefixime are no longer recommended first-line treatments. Instead dual antibiotic combination of ceftriaxone and azithromycin are preferred, though there is increasing concern of azithromycin resistance. In 2018, 'Super gonorrhoea' resistant to all routine antibiotics, including the recommended dual therapy of intramuscular ceftriaxone/oral azithromycin, was reported in the UK[16] and Australia[17].

Where to next? Future therapeutic and vaccine development for gonorrhoea

This century, scientists have made significant advances in understanding gonococcal biology, as well as its mechanisms for causing disease and evading the immune system. Most importantly, they have also discovered new approaches to prevent and treat the infection, many of which are in final stages of development. Currently there are three new antibiotics in clinical trials and there are also several other novel drugs or treatment methods in development or preclinical settings (Table 1)[18]. Novel diagnostics and genotyping technologies are also being developed for rapid detection of mutations to guide antibiotic therapy[19].

It is widely considered that vaccination will be the best long-term solution to gonorrhoea. However, gonococcal vaccine development is challenging. *N. gonorrhoeae* infection does not protect against subsequent infection, therefore there are no correlates of protection from natural immunity to guide vaccine development[14]. Four gonococcal vaccine candidates have been tested in human clinical trials (all pre-2000) but none provided any protection against *N. gonorrhoeae* infection[14]. However, several new vaccine antigens are currently in preclinical development (Table 1)[14,20]. Considerable funding from the US National Institute of Health (NIH) was recently allocated for creation of large collaborative research groups, aiming to deliver a gonococcal vaccine into clinical trials within 5 years.

The feasibility of a gonococcal vaccine was supported by recent findings from a retrospective study that showed decreased *N. gonorrhoeae* rates following vaccination with an outer membrane vesicle (OMV)-based vaccine (MeNZB) licenced to protect against the closely related bacteria *Neisseria meningitidis*[21]. MeNZB was estimated to have a vaccine effectiveness of 31% against *N. gonorrhoeae*[21]. Mathematical modelling has indicated that a gonococcal vaccine with 30% efficacy would be expected to halve gonorrhoea prevalence within 20 years[22]. The MeNZB vaccine was succeeded by a multicomponent meningococcal serogroup B vaccine – 4CMenB (tradename Bexsero), that in addition to the MeNZB OMVs, contains additional recombinant antigens. 4CMenB has been shown to induce cross-reactive antibodies to *N. gonorrhoeae* in humans[23], and is now in clinical trials to investigate its efficacy against gonorrhoea. One of these studies is underway in a population at high risk of contracting *N. gonorrhoeae* in Australia (MenGO; ANZCTR Identifier: 12619001478101). Two additional efficacy studies will commence shortly in Australia (GoGoVax; ClinicalTrials.gov Identifier: NCT04415424) and United States (NCT04350138), with estimated completions dates in 2023.

Conclusions

The discovery of antibiotics ushered a new age in medicine, allowing treatment of many bacterial infections that plagued mankind, including millennia old gonorrhoea. However, the gonococcus was able to acquire resistance to new antibiotics as quickly as they were developed and we have reached the point where strains resistant to 'last line of defence' antibiotics have emerged, prompting urgent action. Currently there are several new antibiotics and vaccine antigens being investigated at all stages of the clinical development pipeline, which will hopefully deliver new treatments and a cure for the clap.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This research did not receive any specific funding.

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Biographies

Evgeny Semchenko is a Postdoctoral Researcher at the Institute for Glycomics at Griffith University. He is a microbiologist and an expert in the field of pathogenic Neisseria, working on investigating interactions between bacteria and host glycans, identifying and characterising bacterial glycan-binding proteins and applying this knowledge to the development of new vaccines and treatment options.

Xiaofan Chen is a student at the Institute for Glycomics at Griffith University. She just finished her honours degree and continues to focus on pathogenic Neisseria during her PhD, investigating new ways to treat gonorrhoea.

Caroline Thng is a Sexual Health and HIV physician at Gold Coast Sexual Health. She has worked as a specialist in both the UK and Australia, and is an expert in complex STI and HIV management. She has delivered clinical trials, observational cohort studies, social research, and epidemiological research both locally and in collaborative projects. She is the co-PI in the first Australian trial using Meningococcal B vaccine as a potential prevention strategy against gonorrhoea infection.

Maree O'Sullivan is the Clinical Director at the Gold Coast Sexual Health Service. She has clinical trials experience over 20 years, including multinational drug trials predominately in the HIV and vaccine sectors. She has also undertaken self -initiated, and collaborative, qualitative and quantitative clinical research in HIV and Chlamydia.

Kate Seib is a Research Leader and the Associate Director (Research) at the Institute for Glycomics at Griffith University. Her expertise is in the field of molecular microbiology, with a focus on understanding virulence mechanisms and characterising vaccine antigens of human mucosal pathogens (e.g. *Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella catarrhalis, Haemophilus influenzae*).