PHLN
Public Health Laboratory Network

Gonococcal infection | *Neisseria gonorrhoeae*

Laboratory case definition

The Public Health Laboratory Network (PHLN) has developed standard case definitions to inform the diagnosis of key diseases in Australia. This document contains the laboratory case definition (LCD) for gonorrhoea.

Version	Status	Authorisation	Consensus Date
1.1	Update to new template and content to ensure gold standards of practice has been incorporated.	PHLN	11 December 2023
1.0	Initial PHLN Laboratory Case Definition	PHLN	25 July 2002

1 PHLN summary laboratory definition

1.1. Condition

Gonococcal infection

1.1.1. Definitive criteria

- Isolation of *Neisseria gonorrhoeae* by culture; or
- Detection of *Neisseria gonorrhoeae* by nucleic acid amplification testing (NAAT).

Note: The identification of *N. gonorrhoeae* from any anatomical site constitutes a case of gonococcal disease for public health purposes.

1.1.2. Point Of Care Tests (POCT)

The use of POCT as they relate to this case definition are for the purposes of surveillance. This includes point-of-care tests for detecting *N. gonorrhoeae* which are listed on the Australian Register of Therapeutic Goods and administered by appropriately trained persons in-line with the Requirements for POCT. It is acknowledged that point of care tests may be used outside of a quality management governance environment or an accredited pathology laboratory, however the laboratory case definition does not apply to tests performed in these settings.

The CDNA case definition may have been updated since the publication of this LCD. Please check the current case definitions webpage on the Australian Government Department of Health's website: www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm for the latest version.

1.1.3. Links to related documents and websites

- https://www1.health.gov.au/internet/main/publishing.nsf/Content/063E816933017261CA2583F300074085/$File/Gonococcal-Infection.pdf
- https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_gono.htm
- http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea
- https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-annlrpt-gonoanrep.htm
- https://kirby.unsw.edu.au/report-type/annual-reports
- https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3901-pdf-cnt.htm/$FILE/cdi3901f.pdf

2 Introduction

Neisseria gonorrhoeae is an exclusively human pathogen. Sexual transmission occurs most commonly. Primary infection can occur in the mucus membranes of the reproductive tract (cervix, fallopian tubes and uterus), the urethra, rectum, pharynx and conjunctiva. Infection may be symptomatic or asymptomatic and confined to local infections, local complicated infections or systemic dissemination. Infection is highly contagious, and usually transmitted by direct inoculation of infected secretions from one mucous membrane to another [1].

Infection can also be transmitted vertically during childbirth resulting in *ophthalmia neonatorum* [2]. Gonococcal conjunctivitis is a sight threatening infection at any age and a medical emergency requiring urgent treatment [5,6]. More rarely gonococcal infections can be transmitted via non-sexual mechanisms [3].

Disseminated gonococcal infection (DGI) is estimated to occur in 0.5 to 3% of patients infected with *N. gonorrhoeae* [7] and can lead to a range of clinical presentations including septic arthritis, arthritis-dermatitis syndrome (arthralgias, tenosynovitis, skin lesions), bacteraemia, fever, endocarditis and meningitis [8,9]. The complications of gonorrhoea disproportionally affect women and include pelvic inflammatory disease, ectopic pregnancy, and infertility. There is an increased risk of HIV acquisition in both women and men [10-12].

Up to 80% of females and 10-15% of males with urogenital gonococcal infection are asymptomatic [4]. Additionally, rectal and pharyngeal infections are usually asymptomatic both in males and females [1]. For pharyngeal, rectal or cervical infection, test of cure (TOC) by Nucleic Acid Amplification Test (NAAT) should be performed 2 weeks after treatment is completed [4]. Gonococcal infections may be coincident with other infections causing symptomatology, such as *Chlamydia trachomatis, Trichomonas vaginalis* and *Candida albicans* [1].

In Australia, between 2012 and 2019 the gonorrhoea notification rate increased 127% (62.3 to 141.4 per 100 000), then decreased 23% between 2019 and 2021 (109.4 per 100 000 in 2021). In 2023, notification rates have exceeded pre-pandemic levels [13, 14].

A recent Australian jurisdictional epidemiological and genomic analysis of 2,186 *N. gonorrhoeae* isolates demonstrated widespread transmission within and between population groups, with distinct transmission clusters associated with men who have sex with men and heterosexuals. Men who have sex with men and women were identified as potential bridging population between these groups. The study also identified transmission of *N. gonorrhoeae*

between HIV-positive and HIV-negative individuals receiving pre-exposure prophylaxis (PrEP) [15].

Globally, disease control strategies for gonorrhoea rely on effective antimicrobial therapy; and antimicrobial resistance (AMR) poses a substantial threat as, over time, *N. gonorrhoeae* has progressively developed resistance to all drugs used for empirical first-line treatment [16]. Currently ceftriaxone is the mainstay of therapy however, raised minimum inhibitory concentration (MIC) values or resistance to ceftriaxone, and treatment failures have been reported [16]. In recent years the international spread of ceftriaxone-resistant gonococcal strains has been confirmed [17] and the first gonococcal clone with resistance to ceftriaxone combined with high-level resistance to azithromycin was isolated in the UK and Australia in 2018 [18]. Due to gaps in AMR surveillance, the extent of gonococcal antimicrobial resistance and treatment failure rates is not well understood globally, especially in low-resource settings with high disease prevalence [16]. However, infections acquired in, or from, the Asia-Pacific represent most of the verified ceftriaxone treatment failures [16]. Since 2022, reports of ceftriaxone resistant and extensively drug resistant isolates in Australia, the United Kingdom and Europe have increased [19-21] The importation of MDR and XDR *N. gonorrhoeae* remains an ongoing threat to Australia [22-23].

The Australian Gonococcal Surveillance Programme (AGSP) has continuously monitored gonococcal AMR since 1981. The emergence of gonococcal AMR in Australia has been driven by importation of resistant strains and recent findings heighten concerns for the future of treatment and disease control.

The WHO Global Action Plan on AMR identifies key priorities including detection and prompt treatment of patients and their sexual partners, good compliance with recommended treatment regimen, patient education, and strengthening surveillance and research [24, 25].

3 Laboratory diagnosis

Reporting: Gonorrhoea is a notifiable disease in Australia. Only confirmed cases should be notified.

https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_gono.htm

Laboratory diagnosis of gonorrhoea is by bacterial culture and/or nucleic acid amplification testing (NAAT). NAAT has the advantage over culture of having greater diagnostic sensitivity, generally lower result turnaround time and the ability to detect other sexually transmitted

infections (e.g. *Chlamydia trachomatis*), so is the mainstay of diagnosis. However, where possible, all patients with probable gonococcal infection clinically, or who have tested positive by NAAT, should have a swab collected for culture and susceptibility testing, prior to antibiotic treatment. This is increasingly important with the emergence of AMR.

Rapid (~90 minute) NAAT tests for gonococcal infection and chlamydia are available, greatly reducing the time to treatment. These tests may be performed within laboratories or based at the clinician-patient interface as point-of care tests (POCTs). Within Australia, POCTs may be supervised within the scope of practice and accreditation quality framework of a NATA accredited laboratory; or performed independently of a supervising laboratory such as in a clinic setting. Positive results from POCTs performed independently of a supervising laboratory should be confirmed by a NATA accredited laboratory. Those that are not confirmed with conventional laboratory testing should be notified to the relevant state/territory health authority by the person performing the test. Rapid lateral flow tests for gonococcal infection are not currently recommended due to poor performance.

3.1. Microscopy

N. gonorrhoeae appears as Gram-negative diplococci on Gram's staining, with either extracellular placement, or intracellular placement in polymorphonuclear leukocytes. Direct microscopy of a Gram-stained smear is suitable in defined settings for the rapid presumptive diagnosis of symptomatic *N. gonorrhoea* from male patients, with >95% sensitivity and specificity. Given poor sensitivity and specificity, microscopy is not recommended for cervical, vaginal, rectal and throat infections. [26]. Diagnosis is confirmed by culture or NAAT.

3.2. Culture

Bacterial culture is sensitive and highly specific but this varies by sample. For urethral and cervical specimens, sensitivity approaches 85–95% under optimal conditions [27, 28] and specificity up to 100%. Culture remains necessary for comprehensive antimicrobial susceptibility testing. For optimal results, swabs should be immediately inoculated onto specific enriched media for growth, and selective media for isolation from mucosal sites with commensal flora and incubated in 4-6% CO2 at 35-37C with 70-80% humidity for 24 hours. Macroscopically *N. gonorrhoeae* appear as small, shiny grey colonies; however, variation is possible.

3.2.1. Confirmation of Identification

Historically, confirmation of isolate identity relied on various tests, including Gram's staining and microscopy, positive cytochrome oxidase reaction, biochemical tests, immunological, spectrometric, and molecular tests [29]. Mass spectrometry technology is now widely used for identification of bacteria. For *N. gonorrhoeae*, this technology has a positive predictive value exceeding 99%. Gonococcal typing and genome sequencing is performed for scientific, epidemiological, and public health investigations.

3.2.2. Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing should be part of the diagnostic and public health process and determined from MIC values using agar dilution methodology or Etest® gradient diffusion strips. Disc diffusion testing is not recommended except in resource constrained settings. [29] The Australian National Neisseria Network jurisdictional reference laboratories perform MIC testing for a panel of antibiotics including penicillin, ciprofloxacin, ceftriaxone and azithromycin on *N. gonorrhoeae* for clinical management, and the Australian Gonococcal Surveillance Programme (AGSP). Both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical Laboratory Standards Institute (CLSI) provide interpretive criteria for gonococcal antimicrobial susceptibility testing. The 2016 WHO *N. gonorrhoeae* reference strains are recommended for quality control in MIC testing [30]. The Communicable Diseases Intelligence publishes quarterly and annual AGSP reports [31].

3.3. Nucleic Acid Amplification Tests

The majority of infections are diagnosed by NAATS. Advantages of NAATs versus culture include faster turnaround, higher sensitivity, simultaneous detection via multiplex targets, and efficiency gains by adopting batch testing [32, 33, 34, 35].

NAATs have proved of benefit in extra-genital sites where organism loads are typically lower, [33, 36] However, frequent mutations and gene transfer between commensal *Neisseria spp*. and *N. gonorrhoeae* require a confirmatory assay from extra-genital sites. [36,37]

Whilst some commercial NAATs are available for detection of *N. gonorrhoeae* AMR markers, these are typically targeted to a single antibiotic and/or resistance mechanism. Consequently, culture remains the definitive method for characterising AMR.

4 SNOMED CT concepts

SNOMED CT code	Concept name	Description
68704007	Organism	*Neisseria gonorrhoeae*
15628003	Disorder	Gonorrhoea
122266004	Procedure	Neisseria gonorrhoeae culture
398381009	Procedure	*Neisseria gonorrhoeae* nucleic acid detection
399143002	Procedure	Polymerase chain reaction test for *Neisseria gonorrhoeae*

5 References

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6 Glossary

Ag/Ab – Antigen/Antibody

AMR – Antimicrobial resistance

ARTG – Australian Register of Therapeutic Goods

BA – Blood agar

Biotype – Strain distinguished from other microorganisms of the same species by its physiological properties or a group of organisms with the same genotype

CCNA – Cell cytotoxicity neutralisation assay

(US) CDC – Centers for Disease Control and Prevention

CDNA – Communicable Diseases Network Australia

CDS – Calibrated dichotomous susceptibility

CIA – Chemiluminescent immunoassay

Clade – Group of organisms composed of a common ancestor and all its lineal descendants

CLSI – Clinical and Laboratory Standards Institute

CSF – Cerebrospinal fluid

Ct – Cycle threshold

DFA – Direct fluorescent antibody

DNA – Deoxyribonucleic acid

EDTA – Ethylenediaminetetraacetic acid

EIA – Enzyme immunoassay

ELISA – Enzyme linked immunosorbent assay

EUCAST – European Committee on Antimicrobial Susceptibility Testing

HI – Haemagglutination inhibition

ICT – Immunochromatographic test

IFA – Immunofluorescent antibody

IgA – Immunoglobulin A

IgG – Immunoglobulin G

IgM – Immunoglobulin M

IVD (device) – In vitro diagnostic medical device

In vitro – performed in a test tube, culture dish, or elsewhere outside a living organism

In vivo – performed or taking place in a living organism

ITS – Inter-genic spacer region

LAMP – Loop-mediated isothermal amplification

LPS – Lipopolysaccharide

MALDI-TOF – Matrix-assisted laser desorption ionization-time of flight

MAT – Microscopic agglutination test

MDST – Molecular drug susceptibility testing

MDR – Multidrug resistant

MIA – Microsphere immunoassay

MLST – Multilocus sequence typing

NAAT – Nucleic acid amplification test/ing

NATA - National Association of Testing Authorities, Australia

NGS – Next generation sequencing

NPAAC – National Pathology Accreditation Advisory Council

NRL – National Serology Reference Laboratory

PCR – Polymerase chain reaction

PC2 laboratory – Physical containment level 2 laboratory

PC3 laboratory – Physical containment level 3 laboratory

PC4 laboratory – Physical containment level 4 laboratory

PFGE – Pulsed field gel electrophoresis

POC – Point-of-care

QAP – Quality assurance program

QC – Quality control

RAPD – Random amplified polymorphic DNA

RCPA – Royal College of Pathologists of Australasia

RFLP – Restriction fragment length polymorphism

RNA – Ribonucleic acid

RT – Reverse transcriptase

RT-PCR – Reverse transcription polymerase chain reaction

SBT – Sequence based typing

Serotype – Pathogens of the same species that are antigenically different

SNT – Serum neutralisation

SSBA – Security sensitive biological agent

STI – Sexually transmitted infection

Strain – Variant that possesses unique and stable phenotypic characteristics

SQAP – Serology quality assurance program

Test sensitivity – Ability of a test to correctly identify patients with a disease

Test specificity – Ability of a test to correctly identify people without the disease

TGA – Therapeutic Goods Administration

UTM – Universal transport medium

VTM – Viral transport media

WGS – Whole genome sequencing

WHO – World Health Organization

WHO CC – WHO Collaborating Centre

XDR – Extensively drug resistant