UK Standards for Microbiology Investigations

Identification of *Neisseria* species

National Institute for Health and Care Excellence (NICE) has renewed accreditation of the process used by the UK Health Security Agency to produce UK Standards for Microbiology Investigations (UK SMIs). The renewed accreditation is valid until 30 June 2026 and applies to guidance produced using the processes described in 'UK Standards for Microbiology Investigations Development Process' (2021). The original accreditation term began on 1 July 2011.
Acknowledgments

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The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the medical editors for editing the medical content.

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*Note: The Anticipated next review date is an estimate and may be subject to change.*
Identification of *Neisseria* species

1 General information

View general information related to UK SMIs.

2 Scientific information

View scientific information related to UK SMIs.

3 Scope of document

This UK Standards for Microbiology Investigations (UK SMI) document describes the identification of *Neisseria* species and includes routine culture, microscopy, oxidase test and MALDI-TOF MS for identification. It also covers biochemical tests and molecular methods for confirmation.

This document describes the differentiation of pathogenic *Neisseria* species from non-pathogenic *Neisseria* species and the related genera of *Moraxella* and *Kingella*. The identification of these genera is covered in ID 11 - Identification of *Moraxella* species and morphologically similar organisms and ID 12 – Identification of *Haemophilus* species and the HACEK group of organisms.

This document does not focus on the screening of *Neisseria gonorrhoea* and *Neisseria meningitidis* or antimicrobial susceptibility testing of *Neisseria* species. The screening of *N. meningitidis* is covered in B 51 - Screening for *Neisseria meningitidis*.

Some of the *Neisseria* species have been reclassified, and the updated nomenclature of these species have been included in this document for reference.

This UK SMI should be used in conjunction with other UK SMIs.

4 Introduction

4.1 Taxonomy and characteristics

The genus *Neisseria* comprises gram-negative bacteria belonging to the family *Neisseriaceae*, order *Neisseriales* within the phylum β-Proteobacteria (1-4). There are currently more than 30 *Neisseria* species and 3 subspecies of which may be isolated from humans and animals (1,2). The following species: *Neisseria ovis*, *Neisseria cuniculi* and *Neisseria caviae* have been reclassified to *Moraxella ovis*, *Moraxella cuniculi* and *Moraxella caviae*, respectively (1).

The clinically important species are *Neisseria gonorrhoeae* (*N. gonorrhoeae*), and *Neisseria meningitidis* (*N. meningitidis*). The respective species are closely related but cause entirely different diseases with distinct clinical pathologies. *N. gonorrhoeae* is an obligate pathogen that causes the sexually transmitted infection gonorrhea.
Identification of Neisseria species

*N. meningitidis* is an opportunistic pathogen that colonises the nasopharyngeal mucosa and has the potential to cause meningococcal disease which includes meningitis and septicemia.

The other *Neisseria* species such as *Neisseria lactamica* and *Neisseria cinerea* are generally considered commensals, but have been implicated as causes of infection in patients who are immunocompromised (5). More recent *Neisseria* species implicated in human disease include *N. brasiiliensis, N. dumasiana, N. oralis, N. shayeganii, N. wadsworthii and N. skkuensis* (1).

**Characteristics**

*Neisseria* species are Gram negative coci, 0.6 to 1.0µm in diameter, occurring singly but more often in pairs with adjacent sides flattened; except *Neisseria elongata, Neisseria weaver, Neisseria bacilliformis* and *Neisseria shayeganii* that consist of rods, 0.5µm wide, often arranged as diplococci or in short chains (6-9). They are non-motile (10). Some species produce a greenish-yellow carotenoid pigment, and some may be nutritionally fastidious and haemolytic. Some species are saccharolytic. The optimum growth temperature is 35 to 37°C. *Neisseria* are oxidase positive and catalase positive (except *Neisseria elongata*).

**5 Technical information and limitations**

The advancement in molecular typing revealed that *Neisseria* species are larger and more diverse than previously thought (1,10). This led to the discovery of many novel species and the reclassification and nomenclature changes of others (1).

The changes made in the taxonomy of the *Neisseria* genus need to be reflected in the databases of the identification tools used in laboratories, this is particularly important for species that are closely related to *N. gonorrhea* and *N. meningitidis* as a lack of match of these closely related species to the database and subsequent identification can lead to uncertainty and misidentification resulting in serious consequences (11-13).

Note: The social consequences to the patient and the organization of an incorrect diagnosis of gonorrhea disease as a result of misidentification should not be underestimated.

**6 Safety considerations**

The section covers specific safety considerations (14-35) related to this UK SMI, and should be read in conjunction with the general safety considerations on GOV.UK. *N. meningitidis* is a Hazard group 2 organism, the processing of diagnostic samples should be carried out at Containment Level 2.
Due to the severity of the disease and the risks associated with generating aerosols, any manipulation of suspected isolates of *N. meningitidis* should always be undertaken in a microbiological safety cabinet until *N. meningitidis* has been ruled out (as must any laboratory procedure giving rise to infectious aerosols) (31).

*N. meningitidis* causes severe and sometimes fatal disease. Laboratory acquired infections have been reported (36,37). The organism infects primarily by the respiratory route. An effective vaccine is available for most meningococcal groups. Vaccination is required for laboratory staff routinely working with the organism.

*N. gonorrhoeae* is also a Hazard group 2 organism which is responsible for the sexually transmitted infection, gonorrhoea and can also cause eye or throat infection - which is the most likely risk to laboratory workers through either vertical transmission, poor laboratory practice or inhalation of aerosols.

Refer to current guidance on the safe handling of all organisms documented in this UK SMI.

The above guidance should be supplemented with local COSHH and risk assessments.

Compliance with postal and transport regulations is essential.

### 7 Target organisms

Please refer to Table 1 for *Neisseria* species that have been associated with human disease (1).

Other organisms which may be misidentified as *Neisseria* species are *Moraxella catarrhalis* and *Kingella denitrificans* (38,39).

### 8 Identification

Culture-based methods remain the gold standard for identification, with the integration of faster identification techniques such as MALDI-TOF MS improving the accuracy of identification. There is also a growing shift towards molecular methods for identification. However, these techniques require specialised laboratories, trained staff and expensive reagents which may not be available to all routine laboratories.

#### 8.1 Culture methods

Culture methods provide presumptive identification of *Neisseria* species based on colony morphology (in some cases - Gram stain) and oxidase followed by identification via MALDI-TOF MS. Additional confirmation can be performed using biochemical or molecular tests.

In cases where confirmation is not possible and further identification is required, isolates should be referred to the appropriate reference laboratory.
8.1.1 Bacterial growth media

Some *Neisseria* species including *N. gonorrhoeae* and *N. meningitidis* are fastidious and require enriched media for growth. They grow best in aerobic conditions at temperatures of 35 to 37°C with 5 to 10% CO₂ (40). Colonies usually appear within 18 to 48 hours of incubation and vary in morphological appearance.

8.1.1.1 Primary agar

Whole blood agar or heated blood (chocolate) incubated for 18 to 48 hours in 5 to 10% CO₂ at 35 to 37°C (12). The media usually consist of Columbia agar base supplemented with 5% horse blood or chocolatised horse blood.

**Note:** *N. gonorrhoeae* grows poorly on blood agar, so a non-selective GC agar with lysed or chocolatised horse blood should be used instead (41).

8.1.1.2 Selective agar

GC selective agar incubated for >40 hours in 5 to 10% CO₂ at 35 to 37°C. This selective agar is primarily used for the selective isolation of *N. gonorrhoeae* but can also be used for the isolation of *N. meningitidis*.

**Note:** *Neisseria* species except *Neisseria lactamica* generally do not grow well on Thayer-Martin based GC selective agar and can be differentiated from *N. gonorrhoeae* and *N. meningitidis* using methods such as MALDI-TOF MS or biochemical tests.

8.1.2 Colonial appearance

*Neisseria* species are usually pigmented and opaque. However, both *N. gonorrhoeae* and *N. meningitidis* form smooth, round, moist, uniform grey/brown colonies with a greenish colour underneath on primary isolation medium. Table 3 details the colony morphology of *Neisseria* species.

8.2 Microscopic appearance

8.1.2.1 Gram stain

Please refer to TP 39 – Staining procedures

*Neisseria* species

Gram-negative cocci arranged in pairs with long axes parallel or gram-negative rods that are arranged in chains or as diplococci, table 3 details the microscopic appearance of *Neisseria* species in Gram’s stain.

**Note:** Gram-stain is often omitted from the identification process if isolates are going to be identified using MALDI-TOF MS.
### Table 1. Microscopic and colonial morphology of *Neisseria* species (1)

Please note that the information in this table provides general characteristics of colony appearance and can vary among different strains and culture conditions.

<table>
<thead>
<tr>
<th>Species</th>
<th>Colonies</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Diplococci with concave adjacent sides. Smooth, round, moist, uniform grey/brown with a greenish colour underneath</td>
<td>Non-haemolytic. No pigmentation. Poor growth on blood agar when the medium is very fresh, or the number of bacteria present in the sample is especially high. Autolysis and sticky colonies with prolonged growth.</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Diplococci. Similar to <em>N. gonorrhoeae</em></td>
<td>Non-haemolytic on blood agar. No pigmentation. Autolysis with prolonged growth.</td>
</tr>
<tr>
<td><em>Neisseria lactamica</em></td>
<td>Diplococci. Colonies less moist and smaller than <em>N. gonorrhoeae</em> and <em>N. meningitidis</em></td>
<td>Haemolytic on horse blood agar*. Yellow pigmentation</td>
</tr>
<tr>
<td><em>Neisseria cinerea</em></td>
<td>Diplococci/scattered clusters. Small, greyish white with entire edges, and slightly granular</td>
<td>Non-haemolytic. Yellow pigmentation*</td>
</tr>
<tr>
<td><em>Neisseria elongata</em></td>
<td>Small slender rods that occur in chains. Small, greyish white, shiny opaque colonies, low-hemispherical with entire edge</td>
<td>Non-haemolytic with some pitting of the agar. Yellow pigmentation*</td>
</tr>
<tr>
<td><em>Neisseria elongata</em> sub. elongata</td>
<td>Flat colonies</td>
<td>Non-haemolytic</td>
</tr>
<tr>
<td><em>Neisseria elongata</em> subsp. glycolytica</td>
<td>Similar to <em>N. elongata</em> colonies.</td>
<td>Haemolysis varies. Yellow pigmentation*. Relatively large grey, opaque, moderately raised with flat top and smooth with a soft homogenous consistency on blood agar.</td>
</tr>
<tr>
<td><em>Neisseria elongata</em> subsp. nitroreducens</td>
<td>Similar to <em>N. elongata</em> colonies.</td>
<td></td>
</tr>
<tr>
<td><em>Neisseria sicca</em></td>
<td>Cocci occurring in pairs and tetrads. small round colonies, having a smooth surface and an entire edge</td>
<td>Haemolytic*. Yellow pigmentation*. Colonies increase in size, and appear raised, rough, and black after 24 hrs. Very firm to the medium.</td>
</tr>
<tr>
<td><em>Neisseria mucosa</em></td>
<td>Diplococci. Large, mucoid, and often adherent</td>
<td>No haemolysis*. No pigmentation or greyish to buff yellow.</td>
</tr>
<tr>
<td><strong>Neisseria canis</strong></td>
<td>Diplococci/rarely in tetrads. Smooth, butyrous with a light-yellow tinge</td>
<td>No haemolysis. No pigmentation.</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Neisseria flava</strong></td>
<td>Diplococci. Discrete, opaque, pale-yellow, slightly flatter than <em>N. meningitidis</em> colonies.</td>
<td>Yellow pigmentation*</td>
</tr>
<tr>
<td><strong>Neisseria subflava</strong></td>
<td>Cocci occurring in pairs and tetrads. Smooth, transparent, or opaque, often adherent.</td>
<td>No haemolysis. Yellow pigmentation. They tend to resist Gram decolourisation.</td>
</tr>
<tr>
<td><strong>Neisseria bacilliformis</strong></td>
<td>Small rods. Round, smooth, glistening, light grey</td>
<td></td>
</tr>
<tr>
<td><strong>Neisseria weaveri</strong></td>
<td>Broad, plump, medium-to-large, straight rods of varying length in chains or longer rods. Smooth, flat, somewhat glistening with an entire border.</td>
<td>Haemolytic. Colonies are variable in size and increase after 24hrs.</td>
</tr>
<tr>
<td><strong>Neisseria flavescens</strong></td>
<td>Cocci occurring in pairs or tetrads. Smooth and opaque.</td>
<td>Non-haemolytic. Golden/yellow pigmentation.</td>
</tr>
<tr>
<td><strong>Neisseria oralis</strong></td>
<td>Cocci occurring in chains. Small, circular, entire, flat and moist, and yellow.</td>
<td>Weakly haemolytic.</td>
</tr>
<tr>
<td><strong>Neisseria shayegani</strong></td>
<td>Rod-shaped and long. Small, circular, entire, convex, moist, light yellow/grey.</td>
<td>Non-haemolytic</td>
</tr>
<tr>
<td><strong>Neisseria wadsworthii</strong></td>
<td>Diplococci in chains. Small, circular, entire, convex, moist, light yellow/orange</td>
<td>Non-haemolytic</td>
</tr>
<tr>
<td><strong>Neisseria zoodegmatis</strong></td>
<td>Coccoid rods. Circular, convex, entire, opaque, shiny, and smooth</td>
<td>Haemolytic. No pigmentation.</td>
</tr>
<tr>
<td><strong>Neisseria animaloris</strong></td>
<td>Coccoid rods. Colonies are circular, convex, entire, opaque, shiny, and smooth.</td>
<td>Haemolytic. No pigmentation.</td>
</tr>
<tr>
<td><strong>Neisseria dumasiana</strong></td>
<td>Coccoid to coccobacilli, may be present in pairs. Grey, moist, circular, convex, entire.</td>
<td>Non-haemolytic. Grey pigmentation</td>
</tr>
<tr>
<td><strong>Neisseria brasiliensis</strong></td>
<td>Diplococci, brownish colonies</td>
<td></td>
</tr>
<tr>
<td><strong>Neisseria Skkuensis</strong></td>
<td>Small, round, and light grey</td>
<td></td>
</tr>
<tr>
<td><strong>Neisseria polysaccharea</strong></td>
<td>Cocci arranged in pairs or tetrads. Relatively small (2mm) yellowish colonies</td>
<td>Non-haemolytic. Large amounts of polysaccharides produced</td>
</tr>
</tbody>
</table>
Identification of *Neisseria* species

<table>
<thead>
<tr>
<th><em>Neisseria caviae</em></th>
<th>Diplococci with adjacent sides flattened. Small (2mm), circular, convex with entire edge, and a smooth glistening surface, butyrous becoming viscid.</th>
<th>Weakly haemolytic*. Light caramel-light brown pigmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria cuniculi</em></td>
<td>Oval cocci, small, and smooth</td>
<td>Haemolytic</td>
</tr>
<tr>
<td><em>Neisseria ovis</em></td>
<td>Diplococci. Grey, opaque, convex</td>
<td>Haemolytic</td>
</tr>
</tbody>
</table>

* Reclassified

### 8.3 Oxidase test

Please refer to [TP 26 – Oxidase test](#). *Neisseria* species are oxidase positive.

**Note:** *Kingella* species and *M. catarrhalis* are also oxidase positive and can be misidentified as *Neisseria* (38,39).

### 8.4 Matrix-assisted laser desorption/ionisation - time of flight mass spectrometry (MALDI-TOF MS)

MALDI-TOF MS is currently used as the primary method for the identification of *Neisseria* species, while biochemical tests and molecular methods serve as an alternative identification approach for centres without MALDI-TOF MS or are employed as a confirmatory method (41).

Although the problem of the *Neisseria* genus study is complex, MALDI-TOF MS has been developed and validated to differentiate the clinically important species, *N. gonorrhoeae* and *N. meningitidis*.

MALDI-TOF MS has excellent performance for *N. gonorrhoeae* identification (12,42) and is highly accurate for the identification of *N. meningitidis* however closely related *Neisseria* species such as *Neisseria polysaccharea* and *Neisseria cinerea* may be misidentified as *N. meningitidis* (11,12,43). While the identification of non-pathogenic *Neisseria* to species level is generally not required, the misidentification of commensal strains as *N. meningitidis* can have serious health and social consequences. Therefore, confirmatory testing with biochemical tests or molecular methods may be required if a consistent identification is not achieved by MALDI-TOF MS (43).

Continual improvement of MALDI-TOF MS requires enriching its database with spectra from closely related and poorly represented *Neisseria* species (11). The ongoing efforts to expand...
and refine the database will ultimately improve reliability and accuracy of MALDI-TOF MS for identification.

8.5 Further identification

8.5.1 Biochemical tests and commercial identification systems

Biochemical tests including commercial identification kits provide basic biochemical information that can aid in the identification of *Neisseria* species. However, relying solely on these tests is insufficient for accurate identification of *Neisseria* species. Therefore, these tests are not considered reliable for the primary identification of *Neisseria* species.

Refer to manufacture’s guidance or the Manual of Clinical Microbiology for the biochemical properties of *Neisseria* species (44).

Commercially available kits can be used for confirmation of MALDI-TOF MS results. The accuracy of these kits has not been fully determined for species other than *N. gonorrhoeae* and *N. meningitidis* therefore, all results obtained should be interpreted with caution.

Laboratories should follow manufacturers’ instructions and rapid tests and kits should be validated and be shown to be fit for purpose prior to use.

Currently, there are limited immunological kits available for the identification of *Neisseria* species. However, biochemical kits can be used as an alternative. Many of the biochemical kits allow for the combined detection of preformed enzymes and carbohydrate utilisation.

In addition, commercial latex or slide agglutination kits can be used for further characterisation of *N. meningitidis* to serogroup level (45,46). The latex agglutination kits are designed for direct use on CSF or serum but will also work for cultures. Slide agglutinating sera are for use on cultures only. Heated clinical samples or formalin treated suspensions of cultures should be processed within microbiological safety cabinets to reduce aerosols.

8.5.2 Molecular methods

Molecular techniques have made identification of many species more rapid and precise than is possible with phenotypic techniques. The routine implementation of molecular methods can be challenging, as not all clinical laboratories have access to the different molecular methods. Therefore, in such cases significant isolates identified by MALDI-TOF MS should be sent to appropriate reference laboratories for further testing and confirmation of results if required.

8.3.2.1 Polymerase Chain Reaction (PCR)

PCR is mainly used as complementary or confirmatory testing method for the identification of *Neisseria* species following MALDI-TOF MS results (47). Laboratories that are unable to perform PCR for confirmation of MALDI-TOF MS results can carry
out immunological or biochemical testing using available commercial kits and/or send isolates to reference laboratories for further testing as required.

8.3.2.2 Next generation sequencing (NGS)

With the increased availability of NGS technologies, there may be a shift towards their utilisation for the identification of Neisseria species alongside other target pathogens in the future. However currently these technologies are largely restricted to reference units.

Whole genome sequencing (WGS) is routinely used by UKHSA and has greatly improved surveillance capabilities and monitoring trends in antimicrobial resistance. WGS has replaced traditional phenotypic and polymerase chain reaction (PCR) methods for routine surveillance. It also has high discriminatory power and can provide in-depth genetic analysis and identification (10). Therefore, it has the potential to be an alternative to techniques like MALDI-TOF MS for the identification of Neisseria including unknown Neisseria species (10).

8.4 Storage and referral

Short term storage – isolates should be kept in a viable state on heated blood (chocolate) agar slopes.

Long term storage – isolates should be frozen at -20°C to -80°C in glycerol based medium or cryo-beads (41).

Note: N. gonorrhoeae storage is recommended at -70°C

9 Reporting

9.1 Infection Specialist

Inform the infection specialist of all confirmed N. meningitidis isolates, and of all Neisseria species isolated from normally sterile sites, or in cases of invasive infection.

The infection specialist should also be informed if the request bears relevant information, for example:

- cases of meningitis, septicaemia (especially with purpuric rash)
- investigation of N. meningitidis outbreak, or of the carrier state

Inform the infection specialist of all confirmed N. gonorrhoeae isolates, and of all Neisseria species from:

- minors
- cases of sexual assault, rape, or abuse
Identification of *Neisseria* species

- cases of *N. gonorrhoeae* isolated from normally sterile sites or from invasive infection – also send to the appropriate reference laboratory
- Multi-drug resistant isolates of GC from all sites.

Follow local protocols for reporting to clinician.

9.2 Presumptive identification

It is not recommended that presumptive identifications for *Neisseria meningitidis* or *Neisseria gonorrhoea* are reported due to the risk associated with mis-diagnosing both infections before full identification are obtained by MALDI-TOF MS or PCR. For centres where these tests are not available a presumptive identification can be made using 2 or 3 biochemical and immunological tests or commercial kits but should be confirmed by accurate methods.

9.3 Confirmation of identification

Any one of the approaches listed below can be taken to confirm the identity of the *Neisseria* species following identification processes as outlined in this document and/or Reference Laboratory report:

1. MALDI-TOF MS confirmation
2. Molecular confirmation using PCR

**Note:** Commercial latex kit or slide agglutination reagent is an additional step for further confirmation and characterisation of *N. meningitidis* to serogroup

For confirmation and identification refer to section 10.

9.4 Health Protection Team (HPT)

Refer to local agreements in devolved administrations.

9.5 UK Health Security Agency

Refer to current guidelines on Second Generation Surveillance System (SGSS) reporting (30).

9.6 Infection prevention and control team

Inform the infection prevention and control team of presumptive and confirmed isolates of *N. meningitidis*. 
10 Referral to reference laboratories

For information on the tests offered, turnaround times, transport procedure and the other requirements of the reference laboratory see user manuals and request forms.

Contact appropriate reference laboratory for information on the tests available, turnaround times, transport procedure and any other requirements for sample submission:

- England
- Wales
- Scotland
- Northern Ireland

**Note:** In case of sending away to laboratories for processing, ensure that specimen is placed in appropriate package and transported accordingly.
Algorithm 1: Identification of *Neisseria gonorrhoea*

An accessible text description of this flowchart is provided with this document.

The flowchart is for guidance only.

Identification | Issue number: dg+ | Issue date: dd.mm.yy | Page: 16 of 21

UK Standards for Microbiology Investigations | Issued by the Standards Unit, UK Health Security Agency
Algorithm 2: Identification of non-gonococcal *Neisseria* species

An accessible text description of this flowchart is provided with this document.

Clinical specimen

- GC selective agar
  - *N. meningitidis* is smooth, round, moist, uniform grey/brown colonies with greenish colour in the agar underneath at 48hrs
  
  Gram stain
  - This step is often omitted if MALDI-TOF MS is available
    - Gram -ve
    - Gram +ve
      - Oxidase test
        - Positive
        - Negative
          - Not *Neisseria* species

  - Whole blood/heated blood (chocolate) agar
  
  Colonial appearance varies according to species
  
  Gram stain morphological examination
  - If meningitis is suspected
    - Not *Neisseria* species

- Oxidase test
  - Positive
    - *Neisseria* species, *M. catarrhalis*
    - Consider *Kingella* species (catalase negative)
    - *Oligella* species
  
  - Negative
    - Not *Neisseria* species

- MALDI-TOF MS
  - If not available, alternative methods are PCR and biochemical tests.
    - Please note that biochemical test results are considered presumptive identification and require confirmation
    
    Non-gonococcal species
    - *N. meningitidis* (performed confirmatory testing if required, please refer to document for more detail regarding tests to use)
    
    Other
    - Serotyping by commercial latex/slide agglutination
      
      If further identification is required, refer to the appropriate reference laboratory

- Molecular methods
  - PCR
    
    Perform confirmatory testing if required

The flowchart is for guidance only.
References

An explanation of the reference assessment used is available in the scientific information section on the UK SMI website.

1. Parte AC and others. 'List of Prokaryotic names with Standing in Nomenclature (LPSN) moves to the DSMZ'. International Journal of Systematic and Evolutionary Microbiology 2020: volume 70, issue 11, pages 5607-12. https://doi.org/10.1099/ijsem.0.004332


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11. Hong E and others. 'Identification of Neisseria meningitidis by MALDI-TOF MS may not be reliable'. Clinical Microbiology and Infection 2019: volume 25, issue 6, pages 717-22. 10.1016/j.cmi.2018.09.015
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