UK Health Security Agency

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.

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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.

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. brasiliensis, N. dumasiana*, *N. oralis*, *N. shayeganii, N. wadsworthii and N. skkuensis* (1).

Characteristics

Neisseria species are Gram negative cocci, 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 37ºC with 5 to 10% CO_2 (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% CO_2 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% CO_2 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 form 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.

Species	Colonies	Additional comments
Neisseria gonorrhoeae	Diplococci with concave adjacent sides. Smooth, round, moist, uniform grey/brown with a greenish colour underneath	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.
Neisseria meningitidis	Diplococci. Similar to *N. gonorrhoeae*	Non-haemolytic on blood agar. No pigmentation. Autolysis with prolonged growth.
Neisseria lactamica	Diplococci. Colonies less moist and smaller than *N. gonorrhoeae* and *N. meningitidis*	Haemolytic on horse blood agar*. Yellow pigmentation
Neisseria cinerea	Diplococci/scattered clusters. Small, greyish white with entire edges, and slightly granular	Non-haemolytic. Yellow pigmentation*
Neisseria elongata	Small slender rods that occur in chains. Small, greyish white, shiny opaque colonies, low-hemispherical with an entire edge	Non-haemolytic with some pitting of the agar. Yellow pigmentation*
Neisseria elongata sub. *elongata*	Flat colonies	Non-haemolytic
Neisseria elongata subsp. *glycolytica*	Similar to *N. elongata* colonies.	Haemolysis varies. Yellow pigmentation*. Relatively large grey, opaque, moderately raised with flat top and smooth with a soft homogenous consistency on blood agar.
Neisseria elongata subsp. *nitroreducens*	Similar to *N. elongata* colonies.	
Neisseria sicca	Cocci occuring in pairs and tetrads. small round colonies, having a smooth surface and an entire edge	Hameolytic*. Yellow pigmentation*. Colonies increase in size, and appear raised, rough, and black after 24 hrs. Very firm to the medium.
Neisseria mucosa	Diplococci. Large, mucoid, and often adherent	No haemolysis*. No pigmentation or greyish to buff yellow.

Neisseria canis	Diplococci/rarely in tetrads. Smooth, butyrous with a light-yellow tinge	No haemolysis. No pigmentation.
Neisseria flava	Diplococci. Discrete, opaque, pale-yellow, slightly flatter than *N. meningitidis* colonies.	Yellow pigmentation*
Neisseria subflava	Cocci occuring in pairs and tetrads. Smooth, transparent, or opaque, often adherent	No haemolysis. Yellow pigmentation. They tend to resist Gram decolourisation
Neisseria bacilliformis	Small rods. Round, smooth, glistening, light grey	
Neisseria weaveri	Broad, plump, medium-to-large, straight rods of varying length in chains or longer rods. Smooth, flat, somewhat glistering with an entire border.	Haemolytic. Colonies are variable in size and increase after 24hrs
Neisseria flavescens	Cocci occuring in pairs or tetrads. Smooth and opaque.	Non-haemolytic. Golden/yellow pigmentation.
Neisseria oralis	Cocci occuring in chains. Small, circular, entire, raised, moist, and yellow.	Weakly haemolytic.
Neisseria shayeganii	Rod-shaped and long. Small, circular, entire, convex, moist, light yellow/grey.	Non-haemolytic
Neisseria wadsworthii	Diplococci in chains. Small, circular, entire, convex, moist, light yellow/orange	Non-hameolytic
Neisseria zoodegmatis	Coccoid rods. Circular, convex, entire, opaque, shiny, and smooth	Hameolytic. No pigmentation
Neisseria animaloris	Coccoid rods. Colonies are circular, convex, entire, opaque, shiny, and smooth	Haemolytic. No pigmentation.
Neisseria dumasiana	Coccoid to coccobacilli, may be present in pairs. Grey, moist, circular, convex, entire	Non-haemolytic. Grey pigmentation
Niesseria brasiliensis	Diplococci, brownish colonies	
Niesseria Skkuensis	Small, round, and light grey	
Neisseria polysaccharea	Cocci arranged in pairs or tetrads. Relatively small (2mm) yellowish colonies	Non-haemolytic. Large amounts of polysaccharides produced

*Neissria caviae**	Diplococci with adjacent sides flattened. Small (2mm), circular, convex with entire edge, and a smooth glistening surface. butyrous becoming viscid.	Weakly haemolytic*. Light caramel-light brown pigmentation
*Neisseria cuniculi**	Oval cocci, small, and smooth	Haemolytic
*Neisseria ovis**	Diplococci. Grey, opaque, convex	Haemolytic
* 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). This is essential to increase specificity for *N. meningitidis* (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. meningitidi*s 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 -70ºC

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

- 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

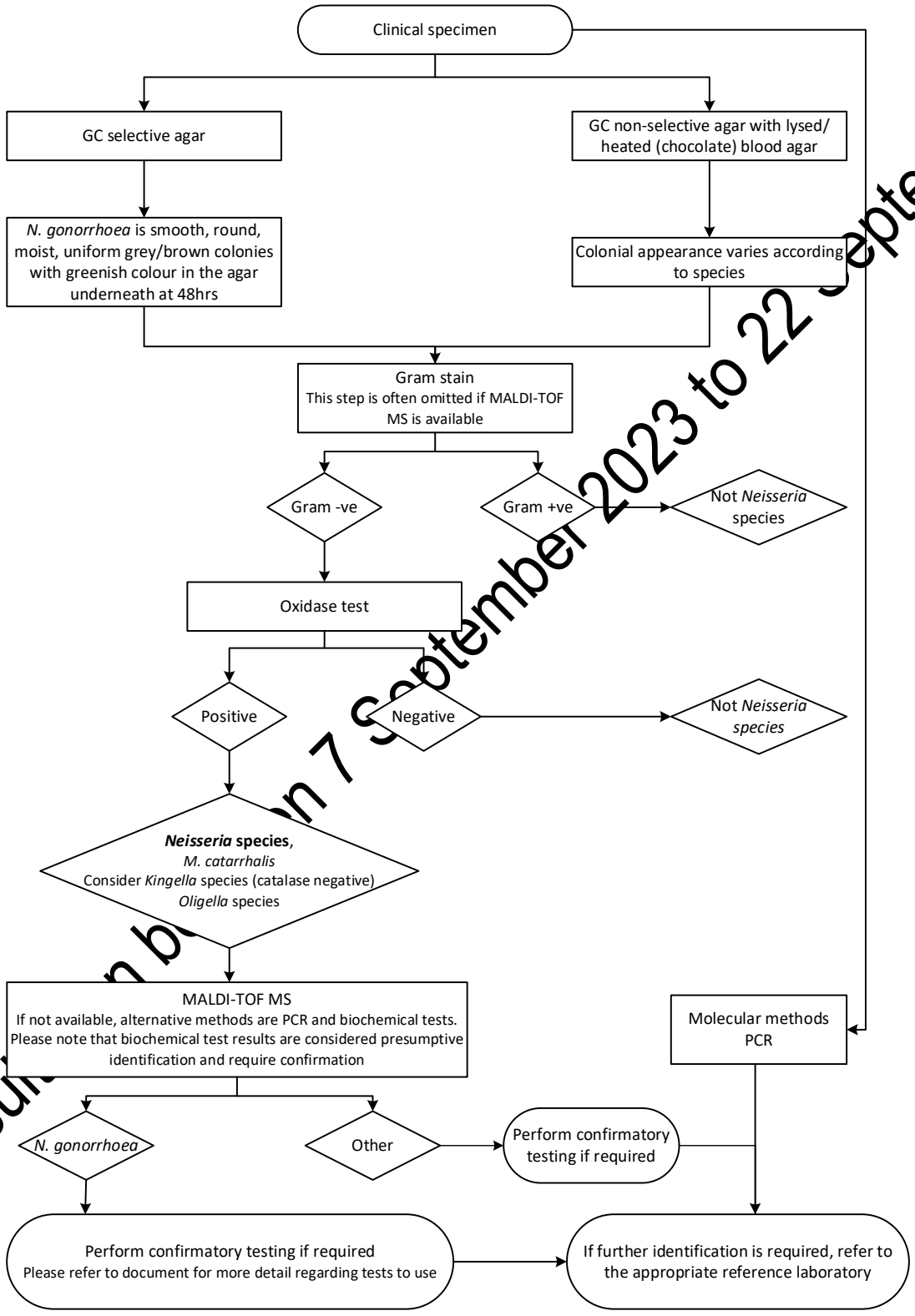
Scotland

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*

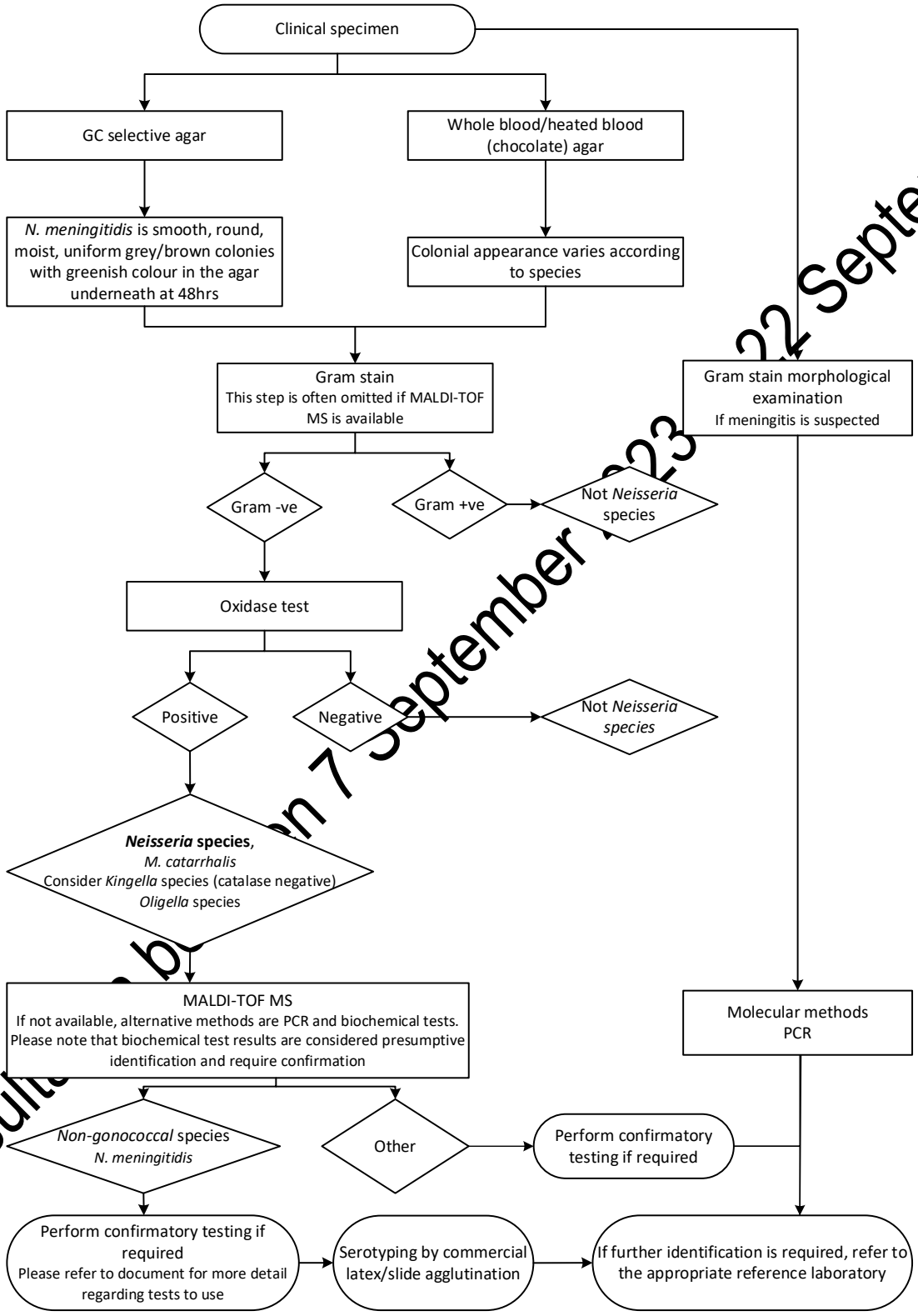
An accessible text description of this flowchart is provided with this document



The flowchart is for guidance only.

Algorithm 2: Identification of non-gonococcal *Neisseria* species

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



The flowchart is for guidance only.

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

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