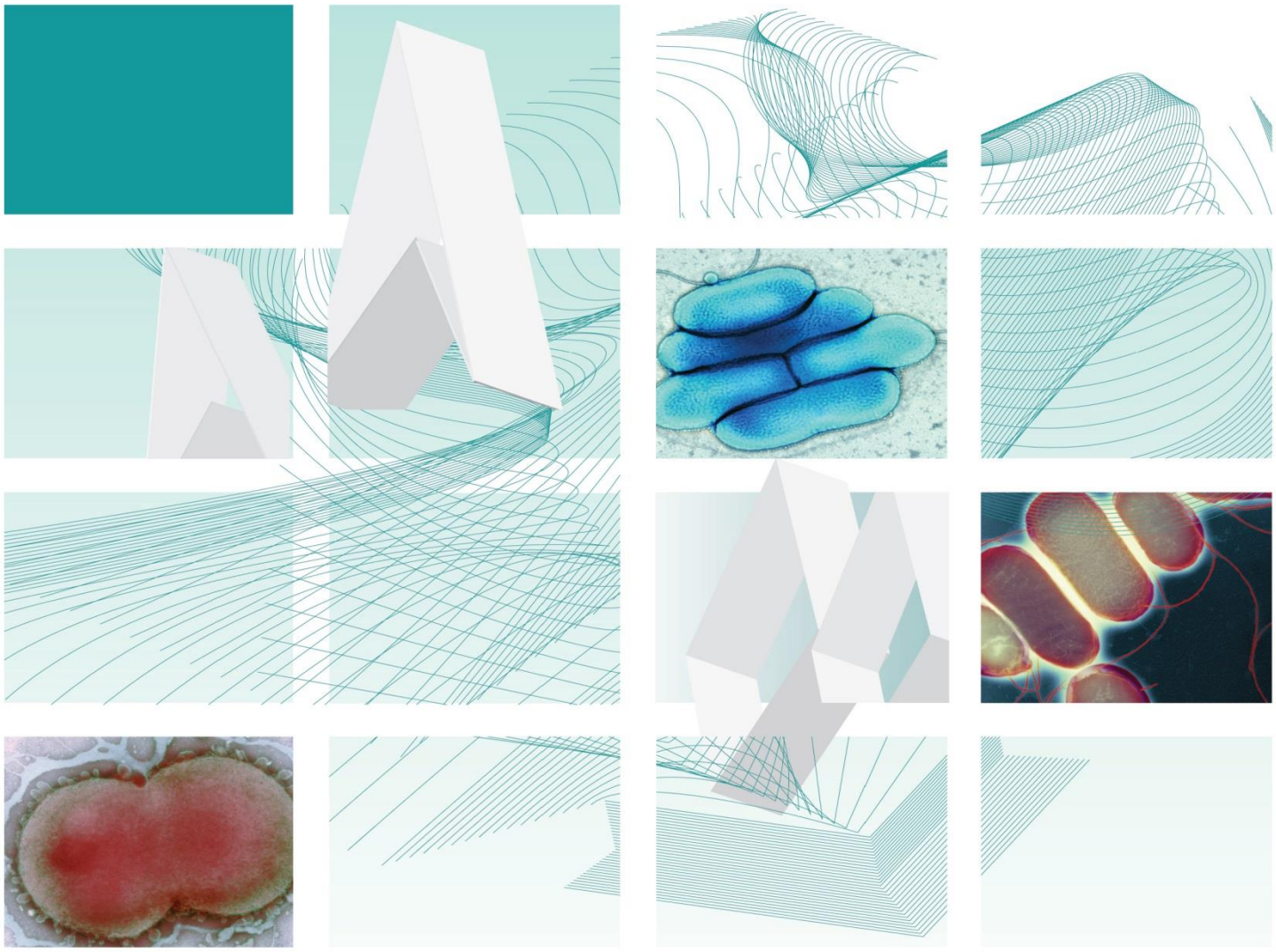
UK Standards for Microbiology Investigations

Investigation of specimens for screening for MRSA



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Bacteriology | B 29 | Issue no: 7 | Issue date: 26.05.20 | Page: 1 of 18

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Contents

Amendment table

Each UK SMI method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@phe.gov.uk.

New or revised documents should be controlled within the laboratory in accordance with the local quality management system.

Amendment No/Date.	8/03.04.14
Issue no. discarded.	5.2
Insert Issue no.	6
Section(s) involved	**Amendment**
Whole document.	Document has been transferred to a new template to reflect the Health Protection Agency's transition to Public Health England. Front page has been redesigned. Status page has been renamed as Scope and Purpose and updated as appropriate. Professional body logos have been reviewed and updated. Standard safety and notification references have been reviewed and updated.
Introduction.	Introduction has been restructured to aid flow. Livestock MRSA has been inserted. Strength of enrichment broth recommended changed from 7% to 2.5%.
Appendix.	Old Appendix 1 deleted. Old Appendix 2 has become Appendix 1 with a link replacing the table. Old Appendix 3 has become Appendix 2.
References.	References reviewed and updated.

Amendment number/date	9/26.05.20
Issue number discarded	6
Insert issue number	7
Anticipated next review date*	26.05.23

Section(s) involved	Amendment
Whole document	Document written in new template Introduction, background information and references updated Information on sample collection added

*Reviews can be extended up to five years subject to resources available.

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 Standard for Microbiology Investigation (UK SMI) describes the processing of screening human specimens to detect meticillin-resistant *Staphylococcus aureus* (MRSA).

Guidelines for the control of MRSA in healthcare facilities have been produced by a working party of the Healthcare Infection Society (HIS), the British Society for Antimicrobial Chemotherapy (BSAC) and the Infection Control Nurses Association (ICNA)[1]. These guidelines recommend a risk assessment approach and advise Infection Control Committees to adapt them locally when designing infection control policies. Other recommendations and epidemiological data have been published by the Scottish Infection Standards and Strategy Group (SISSG)[2], the Department of Health (DH)[3] and Public Health England (PHE).

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

4 Background

Meticillin was the first penicillinase resistant penicillin and has been widely used in testing susceptibility of *S. aureus* to penicillinase resistant β-lactam agents. Hence, despite the fact that meticillin is no longer available and oxacillin and cefoxitin have replaced it for susceptibility testing, resistant strains are commonly known as MRSA.

MRSA strains are a continuing problem in healthcare settings, with transmissions and outbreaks now occurring in the community. Screening for MRSA provides a means of identifying patients and staff who may be at risk of infection and/or involved in transmission of the organism.

In order to achieve the most effective use of finite hospital resources and to minimise morbidity due to these organisms it is usual to have a policy of planned screening to guide control measures to protect patients from MRSA colonisation and infection. Precisely what patient and staff screening is performed will depend on the endemicity of the problem and the case mix of the unit. If MRSA is highly endemic, with constant challenges to the provider units, then a risk assessment process is recommended. One approach is to concentrate on patients at greatest risk. Screening may also be appropriate in areas with low patient risk, particularly so where there is extensive interaction and transfer of patients with MRSA among wards or to acute care wards.

Infection risks

Studies have shown that the majority of patients from whom MRSA is isolated are colonised rather than infected with the organism[4]. Factors predisposing to colonisation

include procedures involving “hands on” care especially in acute surgical, renal dialysis and critical care units[5]. The risk of colonisation resulting in infection is increased in the presence of any breach in the skin, such as surgical wounds and devices penetrating the skin, for example prostheses and catheters. These breaches provide a portal of entry for bacteria[5]. Eradication of nasal carriage of *S. aureus* may be beneficial in certain clinical conditions such as recurrent furunculosis.

Mechanisms of resistance

Intrinsic resistance to β-lactams in clinical strains of *S. aureus* is often heterogeneous[6]. High-level resistance is expressed by a minority of cells on ordinary media at 37°C but more uniformly in hypertonic media or at 30°C[7,8]. Although most MRSA produce a β-lactamase, this is not responsible for their resistance to meticillin. Classical MRSA contain the *mecA* gene and this is the essential determinant of meticillin resistance. *MecA* is a 2,130 base pair segment of DNA coding for a penicillin-binding protein (PBP2’ or PBP2a) characterised by a low affinity for most β-lactams, and which is thought to take over the functions of all other PBPs when they are saturated by meticillin or other β-lactam antibiotics. Methicillin-sensitive Staphylococcus aureus (MSSA) do not produce this protein and their DNA will not hybridise with a probe specific for the *mecA or mecC* gene. The genetic determinant of PBP2a and PBP2c is transcribed in all MRSA cells and all phenotypic classes of MRSA, but additional factors affect the expression of meticillin resistance.

The *mecA* gene is part of a mobile genetic element, the SCC*mec*, which is incorporated in the chromosome[9]. Twelve distinct types of SCC*mec*, designated I to XI have been described to date[10-13]. Most healthcare associated (HA-MRSA) harbour types I, II or III whereas most community-associated (CA-MRSA) harbour types IV or V, although EMRSA-15 encode type IV[14].

More recently, a *mec*A homologue which shows only 69% homology with *mec*A has been described. The gene is now known as *mec*C and is carried in a mobile element known as SCC*mec*XI which has been identified in MRSA from humans and animals including wildlife and livestock.

The presence of the *mecA* and *mecC* genes and oxacillin, meticillin or cefoxitin MIC above breakpoints recommended by national and international validated methods are accepted criteria for methicillin resistance.

Borderline resistance

Some strains of *Staphylococcus aureus* may be encountered which are *mecA* and *mecC* negative but which exhibit a borderline resistance. This may be due to hyperproduction of β-lactamase (particularly obvious when testing oxacillin susceptibility) or alteration of PBPs[15]. There is some evidence from animal models that hyperproduction of β-lactamase is not clinically significant, but further data on virulence and effectiveness of therapy of patients infected with borderline resistant strains are needed to determine whether control measures are warranted[16,17].

Multiple drug resistance

The most prevalent epidemic MRSA strains in the UK remain susceptible to several antibiotics including the glycopeptides vancomycin and teicoplanin. However, MRSA strains showing reduced susceptibility to vancomycin have been described[18]. This eventuality should be considered in any patient with MRSA in whom there is an

apparent treatment failure with a glycopeptide antibiotic[19]. Some strains now demonstrate resistance to as many as 20 antimicrobial compounds, including antiseptics and disinfectants and this trend in acquisition of extra resistances appears to be increasing[6]. Despite this there are several agents that are appropriate for the treatment of MRSA infections and new agents are being developed and introduced[19].

Antibiotic susceptibility

Detection of a presumptive MRSA strain should be followed by its full identification as *S. aureus,* confirmation of meticillin resistance and testing susceptibility to other antimicrobial agents. Conventional oxacillin susceptibility tests are markedly affected by test conditions and the use of cefoxitin in disc diffusion tests has been shown to be less affected by test conditions and to be more reliable than tests with oxacillin[20,21]. Both disc diffusion and breakpoint methods are widely used.

Recommended screening methods

Routine screening by direct plating:

A chromogenic selective MRSA agar has the benefit of providing a rapid result (preliminary results after overnight incubation) although is less sensitive than other methods.

Screening by molecular methods:

Use of a commercial method applied directly to screening swabs may be considered if very rapid results are required.

Screening by enrichment:

In particular circumstances (for example checking patients for clearance of MRSA) screening by an enrichment method may be used. Several swabs from different sites from the same patient can be combined in the same 2.5% NaCl nutrient broth. This is a cost-effective method where the aim is to determine the presence, rather than the site, of MRSA carriage.

Both direct plating and enrichment methods may be used. Enrichment delays reporting of results by 24hr but negative results with a more sensitive technique (enrichment) may be required before MRSA control measures are discontinued for the patient[22].

Screening by selective broth:

Culture of MRSA screening swabs in selective broth can increase the sensitivity of the test, provided that the selective medium is not inhibitory to the MRSA strain involved. A range of commercially available selective broth can be used. These generally contain cefoxitin which is principally aimed at inducing the expression of meticillin resistance and inhibiting the growth of MSSA[23].

5 Safety considerations

Containment Level 2.

Refer to current guidance on the safe handling of all organisms documented in the safety considerations section of the UK SMI scientific information (see section 2).

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

6 Diagnostic tests/investigation

6.1 MRSA laboratory screening

6.1.1 Specimen type

Recommended MRSA screening specimens (a combination of three swabs from different body sites): nose, throat, axilla, groin (or perineum) and rectum[24].

In addition, if a patient has a long-term catheter a catheter urine specimen must be taken.

6.1.2 Pre-laboratory processes

Specimen collection, transport and storage[25,26,27]

Unless otherwise stated, swabs for MRSA culture should be placed in appropriate transport medium[28-32].

Self-collected samples should follow manufacturer recommendations.

Collect specimens other than swabs into appropriate CE marked leak proof containers and place in sealed plastic bags.

Specimens for molecular methods should follow manufacturer's instructions.

Specimens should be transported and processed as soon as possible[27].

Swabs may be placed directly in enrichment broth on the ward. Swabs in enrichment broths should not be refrigerated. If ward staff are involved they should be adequately trained.

Swabbing

Use of correct swabbing technique has been shown to improve bacterial recovery rate[33]. Pooled swabs may be used.

Procedure

Swabs should be taken from the following sites:

- nose: carefully place swab into nasal vestibule (not the middle nor back of the nose) and rotate around 5 times (5 seconds). One swab can be used for both nostrils
- groin: in the fold between the perineum and the thigh, swab should be rolled around several times

- any skin lesions / PEG (percutaneous endoscopic gastrostomy) sites / catheter sites/ drain sites
- consider the throat, especially in suspicion of prolonged carriage

A combination of 3 sites (nose plus another 2 sites: axilla, throat, groin, perineum or rectum) should be used[24].

Note: if the patient is catheterised a catheter urine specimen should be taken

6.1.3 Laboratory processes (analytical stage)

Culture

Ideally, a screening method should allow the growth of all MRSA, inhibit or differentiate other organisms, and allow direct identification tests to be performed on colonies. Unfortunately, some of these requirements conflict and a compromise is necessary.

Conventional methods used for screening should detect strains of MRSA by inhibiting contaminants and selecting *S. aureus* strains which are meticillin resistant. Direct plating on selective medium has the advantage that results may be available within 24hr, but most studies indicate that direct plating is less sensitive than broth enrichment followed by plating on solid media[34]. Whether this is the case with more recently developed chromogenic media remains to be determined. Sodium chloride, antibiotics and other selective agents may be added to the media to reduce contamination, although they might inhibit *S aureus* and the other antibiotics such as oxacillin or cefoxitin that are normally added to select methicillin resistant strains[35,36].

Enrichment broth containing 7% NaCl may inhibit the growth of some isolates of MRSA if present in small numbers[37]. For this reason 2.5% NaCl is recommended as it has been shown to work well when sub culturing to chromogenic agar[38].

Mannitol Salt Agar (MSA) and variations of MSA have been widely used but have the disadvantage that direct agglutination tests for identification of *S. aureus* on MSA are unreliable or growth of MRSA is slow. The HIS/BSAC/ICNA working party and other reports consistently show chromogenic media to perform well although some require a longer incubation period than others and confirmation from this media using latex agglutination cannot be relied upon[34,39,40].

Specimen processing

Direct culture

Inoculate each agar plate with swab or other sample (Q 5 – Inoculation of culture media for bacteriology).

Enrichment culture

Remove the cap aseptically from the container and place the swab(s) or other specimen in the broth, break off (or cut) the swab-stick(s) and replace the cap.

Culture media, conditions and organisms

Clinical details/ conditions	Specimen	Standard media	Incubation			Cultures read	Target organism(s)
			Temp °C	Atmos	Time		
Direct culture	MRSA screening specimens	Chromogenic selective MRSA medium	35-37	Aerobic	18-48hr**	daily	MRSA
OR							
Enrichment culture		Nutrient broth containing 2.5% NaCl *** then subculture to (*see below*)	30	Aerobic	18-24hr	N/A	
		Chromogenic selective MRSA medium	35-37	Aerobic	18-48hr**	daily	MRSA

* Molecular methods may be considered if a rapid result is required.

**For chromogenic media refer to manufacturer's instructions for recommended incubation times.

***The bottle should contain a volume of broth sufficient to cover the swabs. The NaCl concentration should be reduced if locally prevalent strains are known to be inhibited by 2.5% NaCl.

Identification

Minimum level of identification in the laboratory

S. aureus species level, cefoxitin resistant.

Organisms may be further identified if this is clinically or epidemiologically indicated.

Molecular methods

Molecular methods for detection of MRSA require target specific detection of *Staphylococcus aureus* (via the *nuc*, gyrB, or the *Staphylococcus* protein A gene) together with identification of meticillin resistance (via SCC*mec*-orfX, fem A, or *mec*A). Different commercial kits use different combinations of these targets. However, the emergence of novel *mec* variants (eg *mec*C) means that targets for detection of meticillin resistance need continuous re-evaluation[34,41]. Assessment of available methods indicated good performance and results in 2-3hr even using in house methods[42]. Variations in the conserved regions of the SCCmec elements need to be monitored as some commercial kits fail to detect MRSA when there are nucleotide polymorphisms in this area.

Other methods used in MRSA screening

Other methods giving more rapid results may be considered, such as the latex agglutination-based method that detects the PBP2a protein which is commercially available[43]. Although consideration to local prevalence rates of MRSA needs to be considered when using them[44].

6.1.4 Post-laboratory processes (reporting procedures)

Culture

Interpreting and reporting results

Negatives

"MRSA not isolated"

Positives

"MRSA isolated"

Reporting time

Clinically urgent culture results to be telephoned or sent electronically when available.

Presumptive positive result should be reported (subject to local policy)

7 Antimicrobial susceptibility testing

Refer to EUCAST guidelines. Prudent use of antimicrobials according to local and national protocols is recommended.

This UK SMI recommends selective and restrictive reporting of susceptibilities to antimicrobials. Any deviation must be subject to consultation that should include local antimicrobial stewardship groups.

It is recommended that the antimicrobials in bold in the table below are reported. Those antimicrobials not in bold may be reported based on local decisions.

Bacteria	Examples of agents to be included within primary test panel (recommended agents to be reported are in bold depending on clinical presentation)	Examples of agents to be considered for supplementary testing (recommended agents to be reported are in bold depending on clinical presentation)	Notes
MRSA	**Oxacillin** **Flucloxacillin** Clarithromycin Clindamycin **Vancomycin** **Mupirocin***	Daptomycin Linezolid Trimethoprim Rifampicin Tigecycline Ceftaroline Teicoplanin Fucidic acid	* No breakpoint data provided by EUCAST

7.1 Reporting of antimicrobial susceptibility testing

Report susceptibilities as clinically indicated.

MRSA should not be reported as susceptible to any currently available β-lactams although there are new β-lactam agents that are being introduced that have some activity against MRSA[45].

8 Referral to reference laboratories

For information on the tests offered, turn around times, transport procedure and the other requirements of the reference laboratory see GOV.UK for user manuals and request forms.

The national Staphylococcus Reference Service in Public Health England (PHE) invites the referral of *S. aureus* strains showing unusual resistance (specifically to vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline, ceftaroline or ceftibiprole) for analysis and surveillance purposes.

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

England and Wales

https://www.gov.uk/specialist-and-reference-microbiology-laboratory-tests-and-services

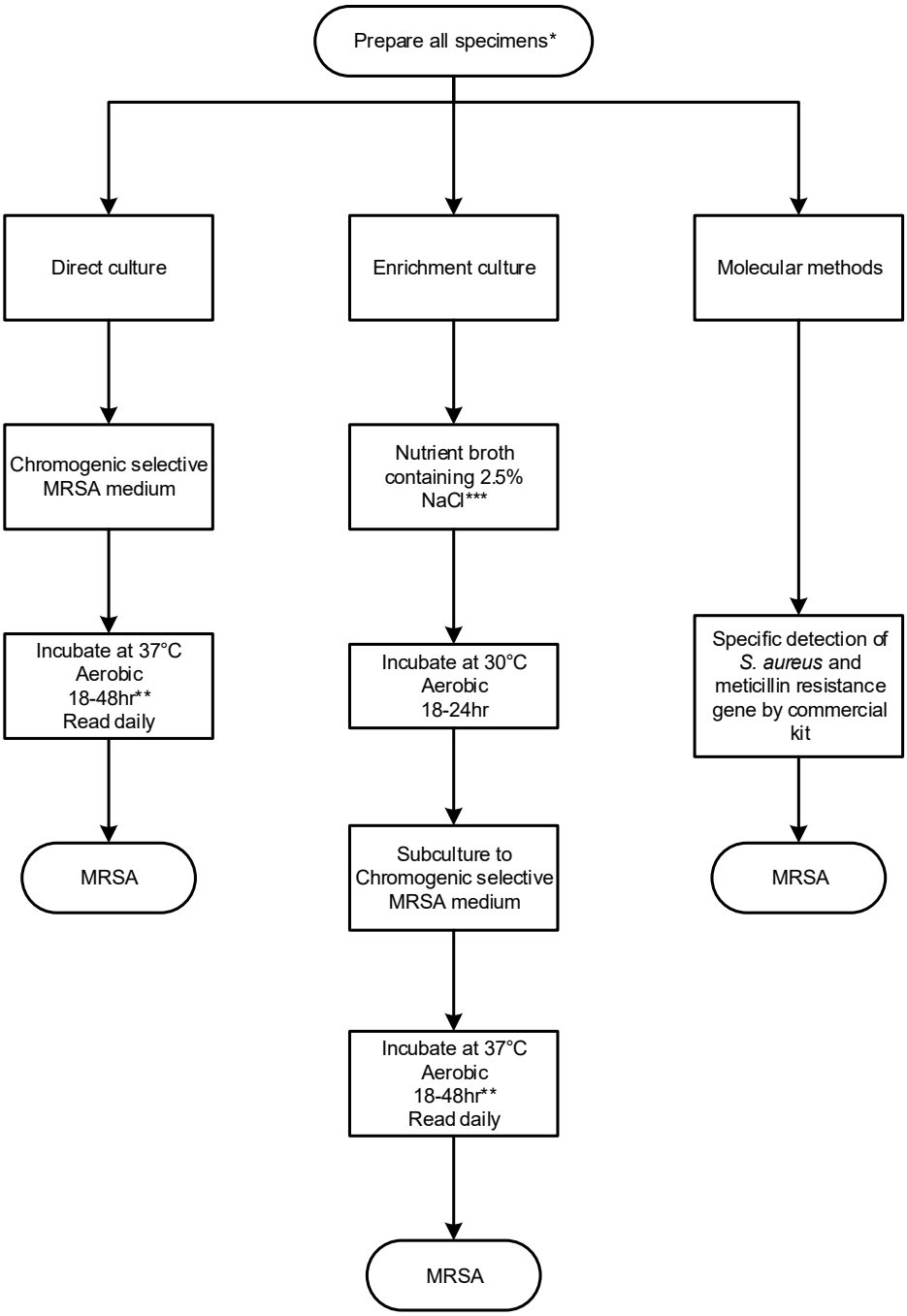
Scotland

http://www.hps.scot.nhs.uk/reflab/index.aspx

Northern Ireland

http://www.publichealth.hscni.net/directorate-public-health/health-protection

Appendix: Investigation of specimens for screening for MRSA



* Consider a molecular method if rapid results are required
** For chromogenic media refer to manufacturer s instructions for recommended incubation times
*** The bottle should contain a volume of broth sufficient to cover the swabs.

References

For the information for the evidence grade ratings given, refer to the scientific information link above in section 2.

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