Laboratory Testing for Middle East Respiratory Syndrome Coronavirus

Interim guidance (revised)

January 2018

WHO/MERS/LAB/15.1/Rev1/2018

World Health Organization

1. Introduction

The purpose of this document is to provide interim guidance to laboratories and stakeholders involved in laboratory testing for Middle East respiratory syndrome coronavirus (MERS-CoV). WHO publishes regular updates on the current status of the MERS-CoV event at: http://www.who.int/csr/disease/coronavirus_infections/en/.

The first edition of this guidance was published in December 2012 and since then our understanding of the virus and the disease it causes in humans and animals has increased significantly. The recommendations were updated in September 2013 to incorporate new information on diagnostic assays.

The September 2014 edition of the guidance was prepared following an international meeting of laboratory experts in Lyon, France with an updated version published in June 2015. The current guidance incorporates the latest information on human viral infection and the immune response it elicits.

WHO continues to monitor developments related to this virus and will revise these recommendations when necessary. Unless revisions are made earlier, this document will expire on December 2019.

These recommendations cover laboratory testing for MERS-CoV in humans. The World Organisation for Animal Health (OIE) has published a case definition for MERS-CoV infection in camels available at http://www.oie.int/scientific-expertise/specific-information-and-recommendations/mers-cov/.

2. Indications for testing

WHO recommends that clinicians, epidemiologists and laboratory scientists consult http://www.who.int/csr/disease/coronavirus_infections/surveillance-human-infection-mers/en/, for advice on which patients should be tested ,and http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/index.html for case definitions. The case definitions are being regularly reviewed and updated as new information becomes available. The decision to test should be based on clinical and epidemiological factors and linked to an assessment of the likelihood of infection. Testing for other respiratory pathogens using routinely available laboratory procedures, as recommended in local management guidelines for community-acquired pneumonia, should also be performed but should not delay testing for MERS-CoV. Examples of other aetiologies in patients with pneumonia or severe lower respiratory tract infection include *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Legionella pneumophila*, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, respiratory syncytial virus, human metapneumovirus and human parainfluenza viruses.

3. Specimen collection and shipment

Whenever specimens are collected from cases under investigation, appropriate infection control guidelines must be followed. Guidance documents on infection control are available at http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/.

Key points to remember are;

- all health-care workers who collect specimens from patients suspected or confirmed to be infected with MERS-CoV must wear appropriate personal protective equipment (PPE); and
- all those involved in collection and transporting specimens should be trained in safe handling practices and spill decontamination procedures.

The Dipeptidyl peptidase 4 (DPP4) has been identified as the cellular receptor for MERS-CoV (1). The receptor is expressed on non-ciliated bronchial epithelial cells (1) and alveolar epithelial cells and macrophages but not in upper respiratory tract epithelium (2). In addition, it has been suggested that pre-existing pulmonary disease could increase MERS-CoV receptor abundance and predispose individuals to MERS morbidity and mortality (3).**This would explain the observation that lower respiratory tract specimens such as bronchoalveolar lavage, sputum and tracheal aspirates contain the highest viral loads (4, 5, 6, 7) and lower respiratory tract specimens should be collected whenever possible.** A report of a case series of MERS-CoV infections detected in Saudi Arabia (8) also demonstrated the value of upper respiratory tract specimens such as nasopharyngeal / oropharyngeal swabs for detecting the virus however care should be taken to ensure that nasopharyngeal swabs are taken from the nasopharynx and not just from the nostril. Details on how to collect nasopharyngeal swabs can be found at http://www.who.int/csr/resources/publications/surveillance/CDS_EPR_ARO_2006_1.pdf

When collecting nasopharyngeal and oropharyngeal specimens, swabs specifically designed for collecting specimens for virology must be used. These swab kits should contain virus transport medium. The nasopharyngeal and oropharyngeal swabs should be placed in the same tube to increase the viral load. To emphasize; **whenever possible, it is recommended that both upper and lower respiratory tract specimens be collected**.

While MERS-CoV has been detected in other body sites it is usually at lower concentrations than in the respiratory tract. Hence collection of specimens from sites outside the respiratory tract is not recommended for routine diagnostic testing.

In patients in whom MERS is suspected, a single negative test result, particularly if this is from an upper respiratory tract specimen does not exclude the diagnosis. Repeat sampling and testing, especially with lower respiratory specimens, is strongly recommended.

In confirmed hospitalised cases, repeat sequential sampling and testing is strongly encouraged. To confirm clearance of the virus, respiratory samples should continue to be collected until there are two consecutive negative results in clinically recovered persons. The frequency of specimen collection will depend on local circumstances but should be at least every 2-4 days. If the release of a patient from an isolation ward requires consecutive negative RT-PCR results, specimens can be collected daily.

For antibody detection, paired serum samples are required for confirmation of infection but single samples may also be of value for identifying probable cases or prior infections, providing the interval between illness onset and sample taking is at least 21 days. Paired serum samples should ideally be collected 3-4 weeks apart, with the first being taken during the first week of illness. If only a single sample can be collected, this should be done at least 14 days after the onset of symptoms. Table 1 lists the specimens that can be collected from symptomatic patients or contacts along with the appropriate storage and transportation requirements. Routine sampling of exposed asymptomatic contacts of cases, especially health care workers, should be considered in settings with high exposure risks, such as the use of nebulizers or other aerosolizing procedures.

Table 1. Specimens to be collected from symptomatic patients and asymptomatic contacts

Patient	Test	Type of sample	Timing	Storage and transportation	Remarks
Symptomatic	NAAT	**Lower respiratory tract** - sputum - aspirate - lavage **Upper respiratory tract** - naso pharyngeal and - oro pharyngeal swabs - naso pharyngeal wash/naso pharyngeal aspirate	Collect on presentation. To confirm clearance of the virus, sample collection to be repeated until the results are negative on 2 sequential samples.	If the specimen will reach the laboratory in less than 72 hours, store and ship at 4°C. If the specimen will reach the laboratory in more than 72 hours, store at -20°C or ideally-80°C and ship on dry ice or liquid nitrogen.	Follow national regulations for in-country shipping and WHO guidance for international movement of specimens including the use of triple package systems.
Symptomatic	Serology	Serum for serological testing. Only if NAAT is not available	Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 3-4 weeks later. If only a single serum sample can be collected, this should occur at least 3-4 weeks after onset of symptoms for determination of a probable case.	As above, with storage and shipping at -20°C being sufficient.	As above.
Asymptomatic Contact (particularly in health-care centre associated outbreaks or other outbreak settings involving high-intensity contact. Testing asymptomatic individuals not associated with outbreaks is not recommended)	NAAT	Nasopharyngeal and oropharyngeal swabs; lower respiratory tract specimens if possible.	Within 14 days of last documented contact.	As above for NAAT.	As above.
	Serology	Serum	Baseline serum taken as early as possible within 14 days of contact and convalescent serum taken 3-4 weeks after last contact. If only a single sample is possible, collect at least 3-4 weeks after last documented contact	As above for serology.	As above.

Specimens for virus detection should reach the laboratory as soon as possible after collection. Correct handling of specimens during transportation is essential. Specimens which can be delivered promptly to the laboratory can be stored and shipped at 4°C. When there is likely to be a delay of more than 72 hours in specimens reaching the laboratory, it is strongly recommended that the specimens be frozen to -20°C or ideally -80°C and shipped on dry ice. It is important to avoid repeated freezing and thawing of specimens. Specimens for serological testing may be stored at -40°C if lower temperature storage (-80°C freezer, liquid nitrogen or dry ice) is not available. The storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations.

Transport of specimens within national borders should comply with applicable national regulations. International transport of MERS-CoV specimens should follow applicable international regulations, as described in WHO's *Guidance on regulations for the transport of infectious substances 2017–2018* available at http://www.who.int/ihr/publications/WHO-WHE-CPI-2017.8/en/

4. Laboratory biosafety

Any testing for the presence of MERS-CoV should be performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures. National guidelines on the laboratory biosafety should be followed in all circumstances.

Key points:

- Each laboratory should conduct a risk assessment to ensure it is competent to safely perform this testing.
- When handling and processing specimens, including blood for serological testing, laboratory practices and procedures that are basic to good microbiological techniques (GMT) should be followed.
- The handling and processing of specimens from cases with suspected or confirmed MERS-CoV infection intended for additional laboratory tests such as haematology or blood gas analysis should follow local guidelines for processing potentially infectious material.
- Non-culture diagnostic laboratory work including NAAT on clinical specimens from patients who are suspected or confirmed to be infected with MERS-CoV should be conducted adopting practices and procedures described for basic laboratory – Biosafety Level 2 (BSL-2) in the WHO Laboratory Biosafety Manual, 3rd edition. http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/
- Initial processing of all specimens including those for NAAT should take place in a class 2 or class 3 biosafety cabinet with current certification.
- All technical procedures should be performed in a way that minimizes the generation of aerosols and droplets.
- Appropriate personal protective equipment (PPE) should be worn by all laboratory staff handling these specimens
- Handling of material with high concentrations of live virus (such as when performing virus isolation or neutralization assays) should be performed only in laboratories capable of meeting additional essential containment requirement including practices recommended for biosafety level 3 (BSL-3) laboratories in the WHO Laboratory Biosafety Manual.

5. Algorithm for detecting MERS-CoV by PCR and sequencing

Routine confirmation of cases of MERS-CoV infection is based on detection of unique sequences of virus RNA by NAAT such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when necessary. See Section 6 below for information on serological testing for MERS-CoV.

Virus culture is not recommended as a routine diagnostic procedure.

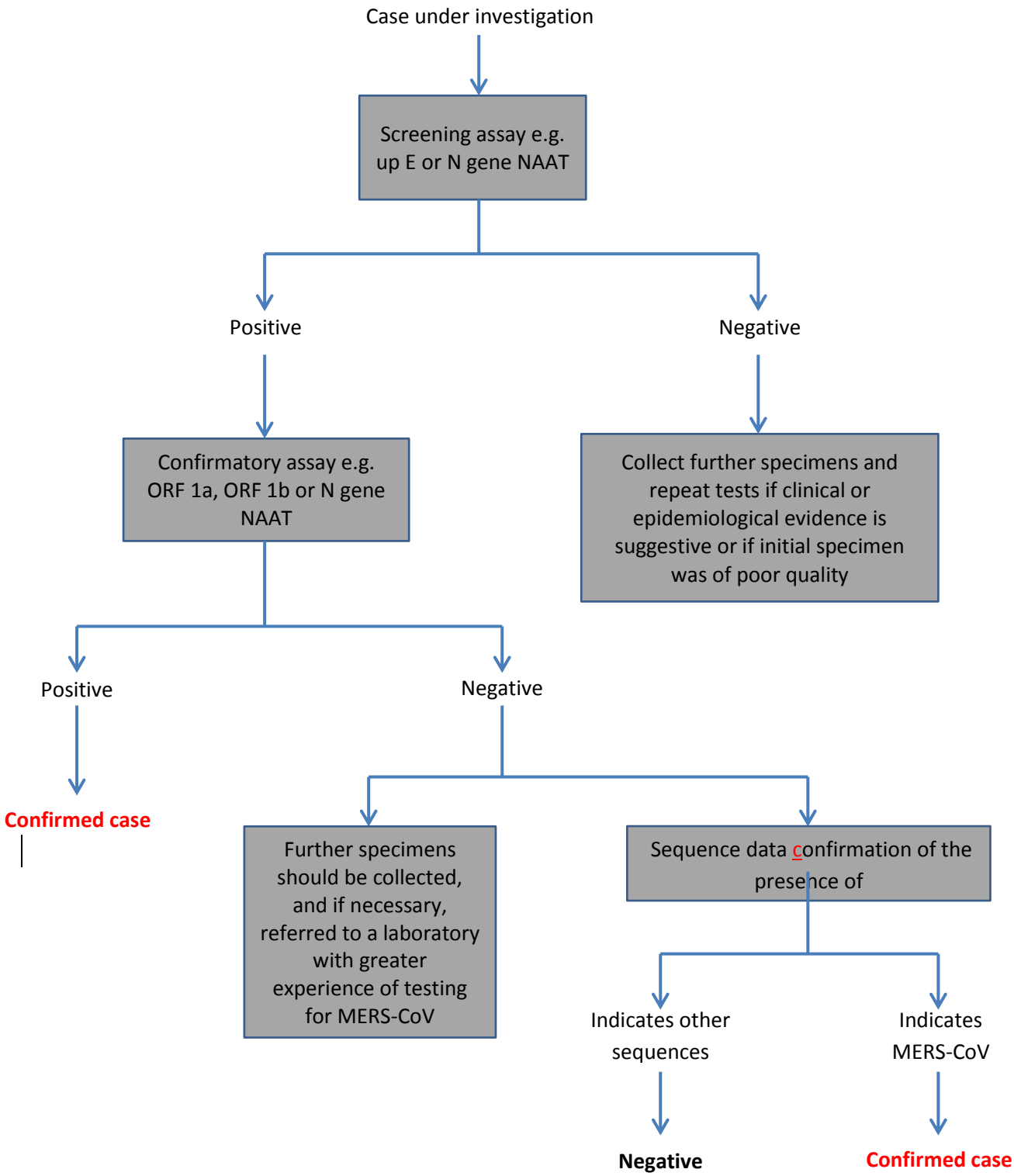
Individual WHO Member States will decide which, if any, of their laboratories should perform MERS-CoV diagnostic tests. Each NAAT run should include both external and internal controls, and laboratories should participate in external quality assessment schemes whenever possible.

Three rRT-PCR assays for routine detection of MERS-CoV have been developed and their details published. Currently described tests are an assay targeting upstream of the E protein gene (upE) (9) and assays targeting the open reading frame 1b (ORF 1b) (9) and the open reading frame 1a (ORF 1a) (10). The assay for the upE target is considered highly sensitive and is recommended for screening, with the ORF 1a assay considered of equal sensitivity. The ORF 1b assay is considered less sensitive than the ORF 1a assay. An alternative approach involving two rRT-PCR assays targeting the MERS-CoV nucleocapsid (N) protein gene, which can complement upE and ORF 1a assays for screening and confirmation has also been published (11). To date, these rRT-PCR assays have shown no cross-reactivity with other respiratory viruses including human coronaviruses and were suitable to detect all known MERS-CoV strains in humans and dromedary camels.

Methods for sequence confirmation have been published (10).

Figure 1 shows a testing algorithm for investigation of suspected cases of MERS-CoV by NAAT.

Figure 1 Algorithm for testing cases under investigation for MERS-CoV by NAAT



Laboratories with limited experience in testing for MERS-CoV are encouraged to work with laboratories with more experience with this pathogen to have their initial test results confirmed and to improve their own performance. WHO can assist Member States to identify laboratories able to provide this support. Additionally, laboratories may wish to check their own positive results by repeating the nucleic acid extraction and retesting the sample.

When there are discordant results with two NAAT assays targeting unique sites on the MERS-CoV genome, the patient should be resampled. In addition, sequencing of material from the original specimen or of an amplicon generated from an appropriate NAAT assay such as for RdRp or N genes (10) should be attempted to confirm the test result.

In addition to providing confirmation of the presence of the virus, sequence data, when analysed in real time, can also provide valuable information for understanding the origins of the virus and how it is spreading, hence, it is recommended to sequence MERS-CoV nucleic acid from as many positive specimens as possible. Full genome sequencing and sequencing of the gene encoding the spike (S) protein directly from clinical samples is particularly desirable, but should be carried out by facilities with experience in this area.

Four endemic human coronaviruses (HCoVs) are known causes of respiratory tract infections of mild to moderate severity. These are the betacoronaviruses HCoV-OC43 and HCoV-HKU1 and the alphacoronaviruses HCoV-229E and HCoV-NL63. Commercial multiplex PCR assays for respiratory pathogens may detect these viruses. It is important that positive results for these viruses should not be confused with MERS-CoV.

A series of negative results should not absolutely rule out the possibility of MERS-CoV infection. A number of factors could lead to false-negative results, including:

- poor quality of the specimen, containing little actual material or material mostly from the upper respiratory tract
- the specimen was collected late or very early in the illness
- the specimen was not handled and shipped appropriately
- technical reasons inherent in the test, e.g. virus mutation or PCR inhibition.

If a negative result is obtained from patients with a high index of suspicion for MERS-CoV infection, particularly when only upper respiratory tract specimens were collected, additional specimens, including from the lower respiratory tract if possible, should be collected and tested. Laboratories may also consider sending one or more negative specimens to outside laboratories for confirmation.

To consider a case as laboratory-confirmed by NAAT, one of the following conditions must be met:

- A positive NAAT result for at least two different specific targets on the MERS-CoV genome using a validated assay; OR
- One positive NAAT result for a specific target on the MERS-CoV genome and MERS-CoV sequence confirmation from a separate viral genomic target.

A patient with a positive NAAT result for a single specific target without further testing but with a history of potential exposure and consistent clinical signs is considered a **probable** case.

6. Serological testing for MERS-CoV

There are three situations where laboratories may wish to conduct serological testing for MERS-CoV, namely:

1) serology in relation to defining a sporadic MERS-CoV case for reporting under the International Health Regulations (IHR). This is likely to occur only in those rare situations where NAAT is not possible;
2) The use of serology as part of an investigation of an ongoing outbreak.
3) Serological surveys, including to retrospectively assess the extent of an outbreak.

1) Use of serology in relation to defining a MERS-CoV case for reporting under the International Health Regulations

A number of different technical approaches to confirming MERS-CoV infection using serology have been developed. Details of two immunofluorescence assays to detect antibodies to MERS-CoV have been published (10), and these assays, along with a serum neutralization test, were used in a 2 to 3 stage procedure to screen contacts of a case in Germany and determine population seroprevalences in KSA (9, 12, 13, 14,). An assay for detection of MERS-CoV antibodies using protein microarray technology has also been developed and the details published (15, 16) suggesting it is highly specific. Another two-stage approach with a screening test using a recombinant nucleocapsid (N) and spike (S) protein-based indirect enzyme-linked immunosorbent (ELISA), followed by a confirmatory microneutralization has also recently been described (17). Details of a neutralisation test based on retroviral pseudoparticles which also demonstrates high levels of specificity to MERS-CoV have also been published (18).

Where a patient has evidence of **seroconversion** in at least one screening assay (e.g. ELISA, IFA) and confirmation by a neutralization assay in samples ideally taken at least 14 days apart, this patient can be considered a **confirmed case**, regardless of the results of NAAT assays. A four-fold increase in MERS-CoV antibody titre by neutralization tests in acute and convalescent serum samples performed in parallel (i.e. on the same day) is needed for confirmation. Our understanding of the antibody response to MERS-CoV is still evolving, however based on data available so far,

while a proportion of patients with MERS-CoV infection demonstrate a four-fold or greater increase in antibody titre by day 21 of illness, a number of patients with rRT-PCR confirmed infection fail to sero-convert (19).

When a symptomatic patient, with a history of contact with a confirmed case but without a positive NAAT has a positive result for at least one screening assay (e.g. ELISA or IFA) plus a positive result for a neutralization assay in a single specimen this would indicate a **probable** case.

When a case is confirmed by NAAT, the taking of sequential serological samples, where possible, is encouraged in order to add to knowledge on the kinetics of the antibody response. Routine testing of asymptomatic contacts of confirmed cases may be justified in circumstances such as the investigation of nosocomial outbreaks**.**

An asymptomatic contact with positive serological test results on a single specimen does not meet the current WHO surveillance case definition for a confirmed or probable acute case.

2) The use of serology as part of an outbreak investigation.

When investigations of outbreaks or contacts of confirmed MERS patients are being undertaken, serology can provide additional useful information. It is advised that serum samples are collected from contacts as early as possible after date of contact and a second serum sample is collected 3-4 weeks after the last contact. Sera may be tested by a screening serological test (ELISA or IFA) and positive screening results need confirmation with neutralization tests. In the event of symptoms, appropriate respiratory specimens should also be collected for NAAT testing.

At present, it is not clear if asymptomatic contacts with evidence of seroconversion to MERS-CoV are able to infect others.

3) Use of serology in relation to population-based serosurveys and investigations of past exposures

Usually only a single specimen is available from each person in the survey. The same criteria for interpretation would apply as for asymptomatic contacts of cases mentioned above, i.e. a positive result for at least one screening assay (e.g. ELISA or IFA) plus a positive result for a neutralization assay would indicate a **past infection** (16)**.** With a single specimen it is not possible to determine the time of infection.

7. Reagents

As the primer and probe sequences for the rRT- PCR assays for MERS-CoV have been published, laboratories can order these from their usual suppliers. Positive control material for the upE and ORF 1a specific rRT-PCR assays can be ordered from the European Virus Archive portal: https://www.european-virus-archive.com/search/node/MERS-CoV.

Member States requiring support for obtaining control material for NAAT assays should approach their WHO Country or Regional Office for assistance.

At least 20 different commercial kits are available for detection of MERS-CoV infection. Not all of which are licensed in all countries. Information on commercial kits is readily available online. **WHO does not endorse any particular product** and laboratories are encouraged to make their own enquiries to determine which kit, if any, is appropriate to their particular circumstances and has obtained necessary regulatory approval.

Laboratories planning to perform serological testing for MERS-CoV are encouraged to work with an international laboratory experienced in the performance of serological assays for this virus. WHO will support member states to identify laboratories who can provide serologic testing, if requested.

8. Global Laboratory Networking

Timely and accurate laboratory testing of specimens from cases under investigation is an essential part of the management of this emerging infection. All countries should have access to reliable testing, either nationally or internationally, in laboratories willing to perform primary detection or confirmatory testing. WHO can assist Member States to access testing internationally should the need arise. Member States may wish to sign material transfer agreements (MTAs), covering such topics as ownership of clinical material and intellectual property rights, with international laboratories before shipping specimens.

9. Reporting of cases and test results

Laboratories should follow national reporting requirements, but in general, in countries with no confirmed cases or only sporadic cases of MERS-CoV infection relevant public health authorities should be notified as soon as the laboratory receives a specimen, even before any testing is performed. All test results, whether positive or negative, should likewise be immediately reported to national authorities. If the infection becomes widespread, laboratories should notify public health authorities immediately of each new confirmed case or positive screening test if there will be a delay in confirmatory testing. Laboratories should also periodically report the number of negative test results to public health.

As part of reporting under the International Health Regulations (2005), Member States are requested to notify WHO immediately of all confirmed cases and of positive screening results if there will be delay in confirmatory testing or if specimens are being sent internationally for confirmation. Details of the particular assays performed should be included with the notifications.

10. Acknowledgements

The following people contributed to the current revision of this guidance:

Christian Drosten, Charite Universitatsmedizen, Germany; Lia Haynes, US CDC, US; Ali Mohammed Kheyami, Ministry of Health, Kingdom of Saudi Arabia; Marion Koopmans, Erasmus Medical Centre, Netherlands; Marcel Muller, Charite Universitatsmedizen, Germany; Christopher Oxenford, WHO Health Emergencies Programme, France; Malik Peiris, University of Hong Kong, Hong Kong China; Natalie Thornburg, US CDC, US; Maria Van Kerkhove, WHO Health Emergencies Programme, Switzerland; Maria Zambon, Public Health England, UK.

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Suggested citation. Laboratory Testing for Middle East Respiratory Syndrome Coronavirus, Interim Guidance. Geneva, Switzerland: World Health Organization; 2018 (WHO/MERS/LAB/15.1/Rev1/2018). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.