

How to conduct surveillance and investigations of human infection with Middle East respiratory syndrome coronavirus using WHO's Investigations and Studies (Unity Studies 2.0) protocols

Protocol, tools and implementation guidance



Unity Studies



World Health
Organization

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Background

Middle East respiratory syndrome coronavirus (MERS-CoV), which was first identified in 2012, is considered an emerging virus. The emergence of a new virus means that understanding transmission patterns, severity, clinical features and risk factors for infection are limited. To address these unknowns, WHO has provided a number of protocols for MERS-CoV investigations. Data collected using these investigation protocols will be critical to refine recommendations for case definitions and surveillance, characterize key epidemiological features of MERS-CoV, help understand the geographical extent of MERS-CoV, its severity, the spectrum of the disease and its impact on the community; and to inform guidance for application of countermeasures such as case isolation and contact tracing. These protocols are designed to rapidly and systematically collect and share data in a format that facilitates comparison across different settings globally.

They are available on the WHO website here: <https://www.who.int/initiatives/mers-cov-investigations-and-studies>

MERS-CoV investigation and study protocols, tools and implementation guidance currently available include:

[How to conduct surveillance and investigations of human infection with Middle East respiratory syndrome coronavirus using WHO's Investigations and Studies \(Unity Studies 2.0\) protocols;](#)

[How to investigate the first few X cases and contacts of human infection with Middle East respiratory syndrome coronavirus;](#)

[How to conduct a case-control study to assess the potential risk factors related to human illness caused by Middle East respiratory syndrome coronavirus;](#)

[How to conduct a cohort study to assess the potential risk factors of Middle East respiratory syndrome coronavirus infection among health and care workers in a health-care setting;](#)

[How to sample surfaces in health-care settings for Middle East respiratory syndrome coronavirus; and](#)

[How to conduct a cross-sectional study of Middle East respiratory syndrome coronavirus infection in populations occupationally exposed to dromedary camels.](#)

Please contact MERSHQ@who.int for further information.

All of the WHO protocols for MERS-CoV are available on the [WHO website](#) together with technical guidance documents.

This document incorporates elements of previously published interim guidance entitled, [Surveillance for human infection with Middle East respiratory syndrome coronavirus \(MERS - CoV\) – Revision 1, June 2018](#), providing additional guidance to using the other five MERS-CoV Unity Study protocols. It reflects updated scientific knowledge about MERS-CoV, the results and experiences of similar studies conducted in several countries as well as experiences and lessons learned during the COVID-19 pandemic.

1. Context





This document summarizes WHO recommendations for surveillance and investigations for Middle East respiratory syndrome coronavirus (MERS-CoV) infection, in the context of how to use WHO's Pandemic Investigations and Studies (Unity Studies 2.0) templates for MERS-CoV. WHO will continue to update these recommendations as new information becomes available.

It is important to note that this guidance may be implemented in different countries with varying resources and epidemiological patterns and should be adapted accordingly.

As part of study implementation, it is important to allocate time and study funds for translation and field-testing of the questionnaires and other data collection tools. Investigators are encouraged to adapt the questionnaires to local contexts to maximize the relevance of the study's results.

2. Scientific background and rationale





Since 2012 and as of April 2024, more than 2600 cases of laboratory confirmed Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO. The virus is circulating widely in dromedary camel populations throughout the Middle East and Africa. To date, the majority of human cases have been reported in Saudi Arabia (1).

MERS-CoV appears to be inefficient at transmitting between humans in the general population, however, human-to-human transmission has occurred and been documented in several clusters in health-care facilities as well as (less frequently) among family members in households and in one dormitory setting (2-4). Large nosocomial outbreaks have occurred in Saudi Arabia and the Republic of Korea (5-8). Historically, the majority of all reported human MERS-CoV infections have occurred through human-to-human transmission in health-care settings, and as of November 2022, 17% of human MERS cases were in health and care workers (1). However, in recent years most cases reported have been sporadic or primary (with a reported link to camel exposure or their products).

MERS-CoV surveillance initially focused on patients with severe disease, and, as such, the full spectrum of the disease, including the extent of mild or asymptomatic forms of infection is not clear. The known clinical spectrum of MERS-CoV infection ranges from asymptomatic and mild (20% of reported cases) (1), to severe pneumonia presenting acute respiratory distress syndrome (ARDS) and other life-threatening complications such as septic shock and multi-organ failure. Approximately 36% of laboratory confirmed cases have had a fatal outcome (1). Co-infections with bacteria and with other respiratory viruses including parainfluenza, rhinovirus, influenza A & B, pneumococcus and ventilator-associated pneumonia have been reported.

The average incubation period (time from infection to onset of symptoms) for MERS-CoV is between 5.5 to 6.5 days, with an upper range of less than 14 days (9, 10).

The World Health Organization (WHO) provides enhanced surveillance investigation protocols and templates for sero-epidemiological studies targeting priority zoonotic diseases, including MERS-CoV. These so-called Unity Studies promote standardized epidemiological, molecular and serological methods to facilitate international comparisons so that both countries and the global community can collectively address knowledge gaps and inform an evidence-based response. Unity Studies enable countries, regardless of their resource setting, to conduct local investigations and are thus an invaluable tool for research equity. The MERS-CoV Unity Study protocols are investigation templates for countries which aim to support national public health and social measures, promote the international comparability of research and address gaps in current knowledge, given that our understanding of the transmission patterns, immunity, severity and risk factors for MERS-CoV infection is still limited.

3. Methodological considerations





3.1 Objectives of surveillance

The primary objectives of surveillance are to:

1. Detect and identify early cases of MERS-CoV infection, clusters and any evidence of sustained human-to-human transmission
2. Determine risk factors and the geographic risk area for infection with the virus

Additional clinical and epidemiological investigations (see Table 1, Figure 1) are needed to:

1. Determine key clinical characteristics of the illness, such as incubation period, spectrum of disease and the clinical course of the illness
2. Determine key epidemiological characteristics of MERS-CoV infection, such as exposures that result in infection, risk factors, secondary attack rates and investigate modes of transmission

3.2 Persons to be investigated and tested for MERS-CoV

Case definitions for MERS-CoV

Case definitions for reporting are provided by WHO and are subject to change as more information becomes available: www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/mers-outbreak-toolbox

Case definition for suspected MERS-CoV

Definition 1: a person with an acute respiratory infection, with history of fever and/or cough and indications of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory disease syndrome (ARDS)), based on clinical or radiological evidence, who requires admission to hospital, with no other etiology that fully explains the clinical presentation¹ (clinicians should also be alert to the possibility of atypical presentations in patients who are immunocompromised); **and** any of the following:

- the person resides in the Middle East in particular where human infections have been reported, and in countries where MERS-coronavirus (CoV) is known to be circulating in dromedary camels;

¹ Testing should be according to local guidance for management of community-acquired pneumonia. Examples of other etiologies include *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Legionella pneumophila*, other recognized primary bacterial pneumonias, influenza and respiratory syncytial virus.

- the person had contact with dromedary camels in the last 14 days or handled and/or consumed untreated camel products or excretions (e.g. milk, urine);
- the patient is part of a cluster of acute respiratory illness that occurs within a 14-day period, without regard to place of residence or history of travel;
- the disease occurs in a health and care worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, without regard to place of residence or history of travel;
- the person develops an unusual or unexpected clinical course, especially sudden deterioration despite appropriate treatment, without regard to place of residence or history of travel, even if another etiology has been identified that fully explains the clinical presentation.

Definition 2: a person with an acute respiratory infection, with history of fever and cough and indications of pulmonary parenchymal disease (e.g. pneumonia or ARDS), based on clinical or radiological evidence, and who has travelled within 14 days before onset of illness to the Middle East or countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred.

Definition 3: individuals with acute respiratory illness of any degree of severity who, within 14 days before onset of illness, had any of the following exposures:

- close physical contact with a confirmed or probable case of MERS-CoV infection, while that patient was ill;
- a health-care facility in a country where hospital-associated MERS-CoV infections have been reported;
- direct contact with dromedary camels or consumption or exposure to dromedary camel products (raw meat, unpasteurized milk, urine) in countries where MERS-CoV is known to be circulating in dromedary camel populations or where human infections occurred as a result of presumed zoonotic transmission.

Case definition for probable² MERS-CoV

Definition 1:

- a febrile acute respiratory illness with clinical, radiological or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or ARDS); **and**
- direct epidemiologic link (within a 14-day period before or after the onset of illness in the case under consideration) with a laboratory-confirmed MERS-CoV case; **and**

² See: Revised interim case definition for reporting to WHO – Middle East respiratory syndrome coronavirus (MERS-CoV) (Geneva: World Health Organization; 2013).



- testing for MERS-CoV is unavailable, negative on an inadequate specimen or inconclusive³.

Definition 2:

- a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or ARDS) that cannot be explained fully by any other etiology; **and**
- the person resides or travelled in the Middle East, or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred; **and**
- testing for MERS-CoV is unavailable, negative on an inadequate specimen or inconclusive.

Definition 3:

- An acute febrile respiratory illness of any severity; **and**
- Direct epidemiologic link (within a 14-day period before or after the onset of illness in the case under consideration) with a confirmed MERS-CoV case; **and**
- Testing for MERS-CoV is unavailable, negative on an inadequate specimen or inconclusive.

Case definition for confirmed MERS-CoV

A person with laboratory confirmation of MERS-CoV infection, irrespective of clinical signs and symptoms. Discarded case: Negative laboratory results.

- Laboratory confirmed cases may be further classified as:
 - o *Primary (index) MERS case:* A confirmed MERS case that does not have a history of recent exposure to a confirmed or probable MERS-CoV infected case in the 14 days before onset of their illness, to exclude cases for whom the transmission likely occurred through human-to-human transmission. May indicate zoonotic transmission (i.e. directly from dromedary camels or their products or excretions). Cases with onset dates less than 24 hours from the onset date of the primary case are considered to be “co-primary” cases.
 - o *Secondary case:* a contact who became a laboratory-confirmed case with positive test result 24 hours or more after the latest positive test date of the primary and/or

³ Inconclusive tests may include: A positive test by nucleic acid amplification assay for a single target without further testing; Evidence of sero-reactivity by a single convalescent serum sample ideally taken at least 14 days after exposure by a screening assay (ELISA or IFA) and a neutralization assay, in the absence of molecular confirmation from respiratory specimens.



co-primary case; or with onset of symptoms 24 hours or more after the latest onset date of the primary and/or co-primary case.

- o *Imported case*: a laboratory-confirmed case with a history of travel from an affected area in the 14 days before disease onset.

Notes on case definitions: Countries in the Middle East are also strongly encouraged to consider adding testing for MERS-CoV to current testing algorithms as part of routine sentinel respiratory disease surveillance and diagnostic panels for pneumonia. WHO does not advise special screening at points of entry.

Implementation tip – further explanation of some case definition terms and details

Other etiology: testing should be according to local guidance for management of community-acquired pneumonia. Examples of other etiologies include *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Legionella pneumophila*, other recognized primary bacterial pneumonias, influenza and respiratory syncytial virus

A map of the Middle East can be found here: www.un.org/geospatial/content/middle-east

A map of MERS-CoV circulation in dromedary camels as evidenced by published studies can be found in the monthly MERS-CoV situation update issued by the Food and Agriculture Organization of the United Nations (FAO) here: <https://www.fao.org/animal-health/situation-updates/mers-coronavirus>

A ‘cluster’ in this investigation protocol is defined as two or more persons with onset of symptoms within the same 14-day period and who are associated with a specific setting such as a classroom, workplace, household, extended family, hospital, other residential institution, military barracks or recreational camp.

‘Close contact’ is defined as:

- o health-care-associated exposure, including providing direct care for MERS-CoV patients, working with health and care workers infected with MERS-CoV, visiting patients or staying in the same close environment of a MERS-CoV patient;
- o working together in close proximity or sharing the same classroom environment with a MERS-CoV patient;
- o travelling together with MERS-CoV patient in any kind of conveyance;
- o living in the same household as a MERS-CoV patient.



3.3 Recommendations for specimen collection

Collection of lower respiratory specimens is highly recommended where possible. However, upper respiratory tract specimens such as a nasopharyngeal aspirate or combined nasopharyngeal and oropharyngeal swabs are a valid alternative sample type, particularly in early stages of infection and when patients do not have signs or symptoms of lower respiratory tract disease. Nevertheless, lower respiratory specimens, such as sputum, endotracheal aspirate, or bronchoalveolar lavage, have a higher diagnostic value than upper respiratory tract specimens for detecting MERS-CoV infection as evidence of shedding can be seen over a longer time period in this sample type. Upper respiratory tract samples have yielded negative results in some symptomatic close contacts of confirmed cases, who later developed pneumonia and tested positive on lower respiratory specimens.

If initial testing is negative in a patient who is strongly suspected to have MERS-CoV infection, the patient should be resampled and specimens collected from multiple respiratory tract sites. Paired acute and convalescent (14 to 21 days after onset of acute infection) sera for antibody detection should also be collected. Virus ribonucleic acid (RNA) has also been demonstrated in body fluids such as blood, urine and stool, but usually at lower titres than in respiratory tract specimens. Such specimens may be collected when good quality respiratory tract specimens are unavailable, or to monitor the presence of virus in different body compartments.

Full details for laboratory testing, specimen collection, biosafety, sample shipment and reporting of test results for MERS-CoV can be found here: <https://www.who.int/publications/i/item/10665-259952>

3.4 Recommendations for testing in clusters associated with health-care settings

Human to human transmission of MERS-CoV can become amplified in health-care settings, as has been seen in the large health-care associated outbreaks in Jeddah and Riyadh in 2014 and in the Republic of Korea in 2015. During such outbreaks WHO recommends that, if feasible, all close contacts⁴ of laboratory confirmed cases, especially health and care worker contacts and inpatients sharing rooms and/or wards with confirmed cases, regardless of the development of symptoms, be tested for MERS-CoV using reverse transcription polymerase chain reaction (RT-PCR) methods. Serologic assays are also available and should be considered as part of the evaluation to understand extent of infection in health-care settings.

⁴ Close contact' is defined as: healthcare-associated exposure, including providing direct care for MERS-CoV patients, working with health and care workers infected with MERS-CoV, visiting patients or staying in the same close environment, working together in close proximity or sharing the same classroom environment with a MERS-CoV patient; travelling together with MERS-CoV patient in any kind of conveyance; living in the same household as a MERS-CoV patient.

4. Public Health Actions





4.1 Reporting

WHO requests that probable and confirmed cases (see ‘case definitions for surveillance’, above) be reported within 24 hours of classification, through the regional contact point for International Health Regulations at the appropriate WHO regional office.

4.2 Investigations around cases of MERS-CoV infection

Many of the critical questions regarding the clinical manifestation and epidemiological characteristics of MERS- CoV infection will be answered only by careful, detailed investigations around cases.

WHO has developed guidance on the types of studies that should be considered after MERS cases are reported, or for seroepidemiological and virological inferences in regions with high dromedary camel density. In addition, WHO has updated the Initial interview form for MERS patients. The form is available at <https://www.who.int/docs/default-source/outbreak-toolkit/home-emergencies-outbreakinvestigationtoolkit-datacollectiontoolboxes-merscov-cif-en.pdf> and is designed to gather initial information.

Table 1. Investigations of and around confirmed cases of MERS-CoV infection

Purpose	Investigation (protocols available at https://www.who.int/initiatives/mers-cov-investigations-and-studies)
<p>Describe the clinical presentation and natural history of infection.</p>	<p>Complete data collection on clinical history, presentation, occurrence of complications, important laboratory and X-ray findings and course of illness.</p> <p>Sequential sampling of laboratory confirmed cases (where resources permit): ideally, sampling upper and lower respiratory tract, blood, urine and stool every 1 to 3 days until the patient is PCR negative.</p> <p>Investigation protocols:</p> <ol style="list-style-type: none"> 1. How to investigate the first few X cases and contacts of human infection with Middle East respiratory syndrome coronavirus 3. How to conduct a cohort study to assess the potential risk factors of Middle East respiratory syndrome coronavirus infection among health and care workers in a health-care setting

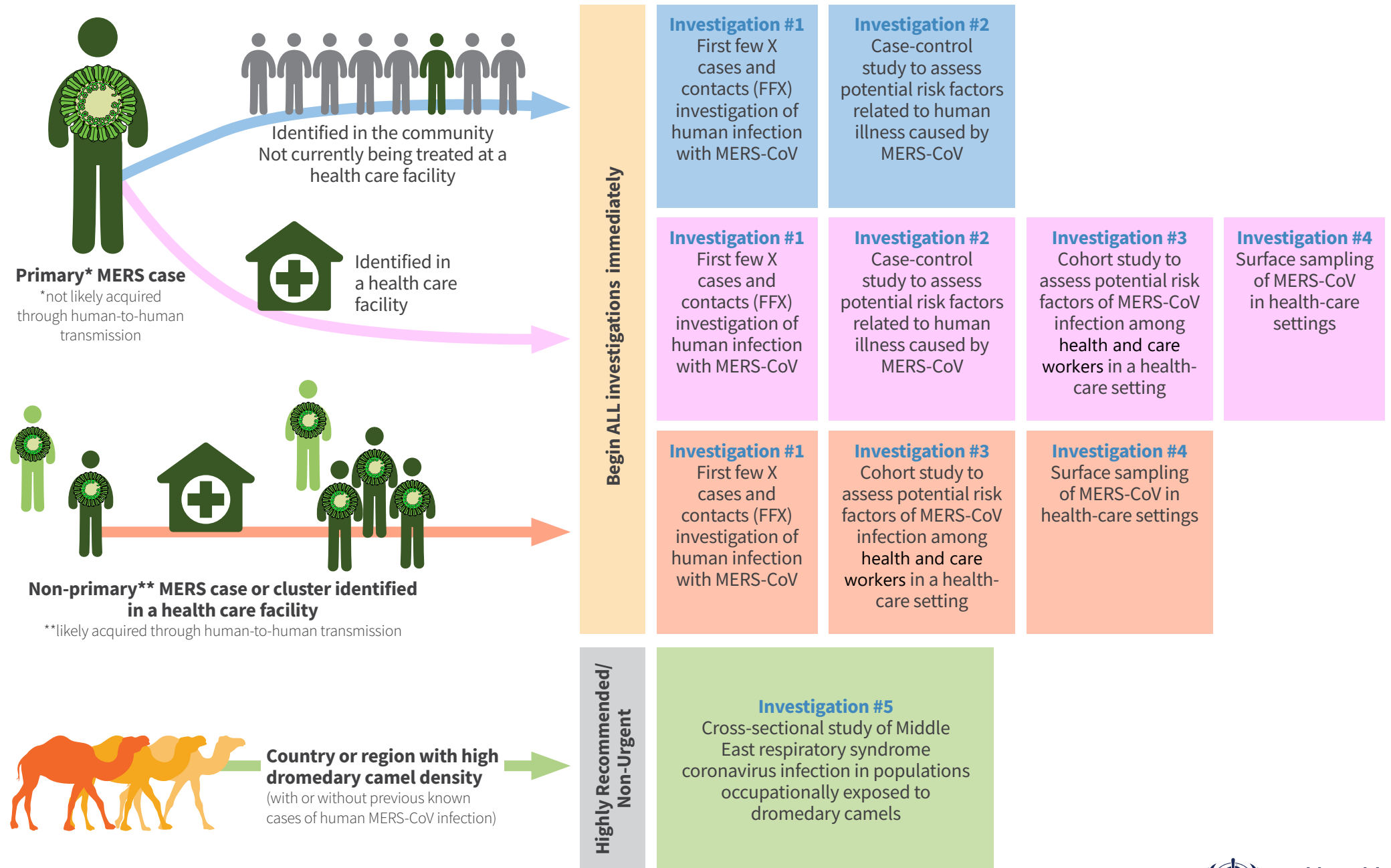
Purpose	Investigation (protocols available at https://www.who.int/initiatives/mers-cov-investigations-and-studies)
<p>Determine the source of infection and type of exposure.</p>	<p>Investigation of potential exposures in the last 14 days before onset of illness, including travel history, exposures to animals (type of animals, especially dromedary camels, and type of contact), exposures to other patients with acute respiratory infections, exposures in health-care settings and consumption of raw camel meat and camel products. Collect detailed information on time, duration and intensity of exposure and type of contact.</p> <p>Investigation protocols:</p> <ol style="list-style-type: none"> 2. How to conduct a case-control study to assess the potential risk factors related to human illness caused by Middle East respiratory syndrome coronavirus 3. How to conduct a cohort study to assess the potential risk factors of Middle East respiratory syndrome coronavirus infection among health and care workers in a health-care setting 4. How to sample surfaces in health-care settings for Middle East respiratory syndrome coronavirus
<p>Epidemiological evidence of human-to-human transmission; estimate secondary attack rates, duration of infectivity and incubation period.</p> <p>Describe spectrum of disease, especially milder cases.</p> <p>Determine the epidemiological importance of asymptomatic cases.</p>	<p>Contact tracing, including contacts in household, workplace, school and social settings. Careful history should be taken with regard to the timing of contact with sick individuals and the onset of illness. Contacts should be tested with RT-PCR and acute and convalescent serology if they become symptomatic.</p> <p>Complete investigation of asymptomatic contacts, including testing for RT-PCR and acute and convalescent serology, could be performed as a research protocol.</p> <p>Investigation protocols:</p> <ol style="list-style-type: none"> 1. How to investigate the first few X cases and contacts of human infection with Middle East respiratory syndrome coronavirus 3. How to conduct a cohort study to assess the potential risk factors of Middle East respiratory syndrome coronavirus infection among health and care workers in a health-care setting 5. How to conduct a cross-sectional study of Middle East respiratory syndrome coronavirus infection in populations occupationally exposed to dromedary camels
<p>Epidemiological evidence of human-to-human transmission, effectiveness of personal protective equipment (PPE).</p>	<p>Survey of health and care workers working in the environment where cases are cared for. Survey should include those not directly involved in care but working in the same ward or unit as well as those who provide intermittent care, such as radiologists, respiratory and physical therapists, etc. Include information on timing, duration and intensity of contact, type of interaction, use of PPE and other potential exposures outside of health-care setting (e.g. animals in the home environment).</p> <p>Investigation protocols:</p> <ol style="list-style-type: none"> 1. How to investigate the first few X cases and contacts of human infection with Middle East respiratory syndrome coronavirus 3. How to conduct a cohort study to assess the potential risk factors of Middle East respiratory syndrome coronavirus infection among health and care workers in a health-care setting
<p>Detect signals of background transmission of MERS-CoV.</p>	<p>Investigations for recent increases in respiratory disease activity in the community. This would include review of local hospital admission records and outpatient records of selected general practitioners in the community where infection is thought to have been acquired.</p>
<p>Detect the pre-existence of virus in the community.</p>	<p>Retrospective testing of stored specimens from patients with respiratory disease. Seroepidemiological surveys among occupationally exposed populations.</p> <p>Investigation protocols:</p> <ol style="list-style-type: none"> 5. How to conduct a cross-sectional study of Middle East respiratory syndrome coronavirus infection in populations occupationally exposed to dromedary camels



Purpose	Investigation (protocols available at https://www.who.int/initiatives/mers-cov-investigations-and-studies)
Determine the animal reservoir and origin of the virus.	Retrospective testing of stored animal specimens for presence of MERS-CoV or antibodies. Risk factors for infection analysis with primary MERS cases. Investigation protocols: 2. How to conduct a case-control study to assess the potential risk factors related to human illness caused by Middle East respiratory syndrome coronavirus
Identify types of exposure that result in infection.	Serological surveys of potentially exposed groups of individuals such as animal workers, market workers, health and care workers and office workers (as a comparison group). Detailed information should be collected from each participant on the type and degree of exposure. Investigation protocols: 5. How to conduct a cross-sectional study of Middle East respiratory syndrome coronavirus infection in populations occupationally exposed to dromedary camels



Figure 1. MERS Case Investigation and Surveillance Protocols



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Emerging Diseases and Zoonoses Unit
Epidemic and Pandemic Preparedness and Prevention Department
20, Avenue Appia
1211 Geneva 27
Switzerland
Email: MERSHQ@who.int
Website: <https://www.who.int/initiatives/mers-cov-investigations-and-studies>

