How to conduct a case-control study to assess the potential risk factors related to human illness caused by Middle East respiratory syndrome coronavirus

Protocol, tools and implementation guidance

Unity Studies

World Health Organization

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Contents

List of tables

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An initial version of this protocol was developed by the Consortium for the Standardization for Influenza Seroepidemiology (CONSISE), a global partnership aiming to develop influenza investigation protocols and standardize seroepidemiology to inform public health policy for pandemic, zoonotic and seasonal influenza.

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 WHO protocols for MERS-CoV are available on the WHO website together with technical guidance documents.

This protocol incorporates elements of previously published interim guidance entitled, Case-control study to assess potential risk factors related to human illness caused by Middle East respiratory syndrome coronavirus (MERS-CoV) – Version 6, 15 July 2014, providing additional aspects of investigation implementation and detailed questionnaires. It reflects updated scientific knowledge about MERS-CoV and the results and experiences of similar studies conducted in several countries. The protocol was also adapted from and supplemented by protocols developed and used during the COVID-19 pandemic through WHO's Investigations and Studies (Unity Studies): a standardized preparedness framework for an effective and proportionate response, as well as experiences and lessons learned during the COVID-19 pandemic.

Protocol summary

Case-control study to assess potential risk factors related to Middle East respiratory syndrome coronavirus (MERS-CoV) infection in humans	
Study population	Infected persons without known contact to another human MERS case (primary or sporadic MERS-CoV cases, index cases of clusters) and matched uninfected controls (neighbourhood and hospital) * Note: this is in attempt to work with cases resulting from zoonotic transmission and/or spillover
Potential output and analysis	Determine risk factors for MERS-CoV infection, which may be: • modifiable (e.g. behaviors, practices) • other characteristics (e.g. pre-existing medical conditions) Secondary outputs may include: describing the range of clinical presentation of MERS-CoV among cases, determine the serological response to MERS-CoV among cases
Study design	Case-control study
Study duration	In order to recruit a sufficient number of cases (sporadic individual MERS cases, or index cases of sporadic transmission clusters) to do risk factor analysis, this study is likely to be conducted in a rolling fashion, with a predetermined time period (e.g. 1 year) decided upon by investigators, in which all reported MERS cases in the region are approached for recruitment. *Per case* (+ 4 controls) the study would take a *minimum* of approximately 1 month, including identification, recruitment, baseline sampling and questionnaires for both cases and controls, and retrieval of a second (paired) serum sample from cases after 21 to 28 days.
Information and specimens to be obtained from participants	**Data:** Baseline questionnaire with demographic, clinical, epidemiological and behavioral exposure information (cases and controls), as well as one follow-up questionnaire (at 28 days) on symptoms (cases) **Specimens:** • A baseline serum sample (cases and controls) • A second, i.e. paired, serum sample (cases)

Implementation tips are provided in boxes throughout the document.
This is a *protocol template* – the user should read through the template and guidance and then modify (and make choices about) the methods according to the local context in which this study will be carried out. If being adapted for use as the investigation protocol, the user should remove any non-relevant sections and modify the language appropriately (e.g. Change the phrase "Investigators should create a detailed map(s) of the facility; within this map(s) and its legend(s), the following details should be included:…" to "We have created a detailed map of facility X, where the MERS-CoV positive patient was identified on [date], this map includes the following details:…"). Background information referenced in this document should be checked for updates by investigators at the time of protocol implementation.

1. Scientific background and rationale

As of April 2024, over 2600 laboratory-confirmed cases of human infection with Middle East Respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO *(1).* The virus appears to be circulating widely in dromedary camel populations throughout the Middle East and Africa, and has also been detected in a few countries in South and Central Asia *(2).* The majority of human cases have been reported from Saudi Arabia *(1).*

MERS-CoV is a zoonotic virus and dromedary camels are the single known maintenance host and primary reservoir *(2–7),* but the route of transmission to humans is unknown *(7).* MERS-CoV nucleic acid has been identified in dromedary camels in Burkina Faso, Egypt, Ethiopia, Islamic Republic of Iran, Jordan, Kenya, Saudi Arabia, Nigeria, Oman, Pakistan, Qatar, Senegal, Tunisia and the United Arab Emirates. Additionally, sera from dromedary camels (Bangladesh, Israel, Morocco and Uganda), Bactrian camels (Mongolia, United Arab Emirates), hybrid camels (United Arab Emirates), llama and alpaca (both Israel) have been found to have antibodies to MERS-CoV *(2).* Investigations in other livestock (e.g. cattle, sheep) and wild animals (e.g. birds) have not shown any evidence of MERS-CoV *(8, 9).*

Human-to-human transmission has occurred and been documented in several clusters in health care facilities in Jordan, Saudi Arabia, the Republic of Korea and the United Arab Emirates *(10).* Additionally, one instance of nosocomial transmission was documented in France in 2013 *(11).* Since 2020, instances of nosocomial transmission have only been documented in Saudi Arabia *(1).* Person-to-person transmission has also been identified through investigations of clusters of cases in households and other settings *(1, 12–21).* However, the initial routes of transmission of MERS-CoV from animal sources (i.e. dromedary camels and possibly other camelids) to humans are not well understood. Currently, direct exposure to dromedary camels and drinking their unpasteurized milk, are known to be risk factors for primary infection *(3, 22).* Spatial associations of human primary MERS-CoV infections with season, dromedary camel density, and dromedary camel age and sex have also been found and need further investigation *(23).* MERS-CoV ribonucleic acid (RNA) has frequently been detected in dromedary camel respiratory tract specimens, rectal specimens and milk *(2),* but has also been detected in dromedary camel seminal fluid, conjunctival samples, saliva and breath *(24–26).* There is a need to further investigate the routes and mode of transmission to humans from dromedary camels, the types of exposures that result in infection and to understand how this may vary in different regions. Additional risk factors for zoonotic MERS-CoV infection may include direct contact with other dromedary camel products or excretions (e.g. meat, excrement, urine), or contact with the environment where an infected dromedary camel has recently been. Finally, risks associated with direct and indirect contact with other MERS-CoV infected animals (if any) and their products and excretions need to continue to be monitored and confirmed.

Understanding the specific exposures that result in transmission of MERS-CoV to humans will allow measures to be taken to interrupt transmission. This case-control investigation will provide data to evaluate risk factors for infection by reviewing exposures of known cases and comparing them to rates of exposure in similar uninfected individuals in the general population; few studies of this design have yet been undertaken for MERS-CoV *(3).* For the purpose of this investigation, the cases under consideration will be those that are presumed not to have acquired their infection from another infected human (i.e. primary MERS-CoV infections).

1.1 Study objectives

1.1.1 Primary objectives

The primary objective of this study is to:

1. Identify risk factors (both modifiable and non-modifiable) associated with MERS-CoV infection in persons without known contact with another human MERS case

1.1.2 Secondary objectives

This investigation can provide rich data to assess optional secondary objectives, including, but not limited to:

2. Describe the range of clinical presentation of human MERS-CoV infection, including disease duration and outcome.; and
3. Determine serological responses to MERS-CoV in persons with confirmed infection

2. Methods

2.1 Study design and duration

This study uses a case-control design to examine the differences in types of exposures between index and/or sporadic cases with laboratory confirmed MERS-CoV infection (also called primary cases or primary infections) and MERS-CoV negative controls in order to determine the risks associated with different exposures. Data collection is meant to start as soon as a confirmed primary MERS case has been identified. The final data collection will be complete approximately 28 days after the start of the investigation for each reported or identified MERS primary case. The total duration of the study is therefore partially to be determined by the investigators:

- *Minimum duration of approximately 1 month* – this would be the case if the study starts after one MERS primary case is reported, and ends after a case-control investigation is conducted for only that case. In this instance, you would not be able to perform statistical analysis of risk factors using your data alone; data sharing with WHO and/or other regions or health authorities who are performing this investigation is highly encouraged so that your valuable data can be merged with regional or global data sets for statistical analysis.

- *Maximum duration of multiple years* – this would be the case if your region or health authority has opted to do rolling inclusion of cases, to capture all MERS sporadic cases and index cases of clusters over a set period of time (determined by investigators).

For the full length of time it will take to conduct this study, the mentioned duration would then be added to the time it takes to set-up the study (approvals, training), process specimens, perform data analysis and generate reports.

2.2 Study population and recruitment

2.2.1 Case definitions

Case definitions for reporting MERS-CoV are provided by WHO and are subject to change as more information becomes available. They can be found at the MERS Outbreak Toolbox.

Below, those MERS case definitions which would be applicable to defining a case for this case-control study, have been copied. Notably, this includes all those MERS case definitions in which there is no suspected epidemiological link to another case, and where primary (zoonotic) infection may be reasonably suspected.

Case definition for confirmed MERS-CoV: A person with laboratory confirmation of MERS-CoV infection, irrespective of clinical signs and symptoms.

- Primary (index) MERS case: A confirmed MERS case that does not have a history of recent exposure to a confirmed or probable MERS 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. Identification of these cases 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 (further details of how these cases should be considered for inclusion and analysis is mentioned later in the document).
  - It is recommended to use confirmed primary MERS cases for this study.

Case definition for probable MERS-CoV:
There are currently 3 definitions for probable MERS cases (all can be seen using the link at the top of this section), for the purpose of this study, only the following probable case definition should be considered, along with the condition that the person does not have a history of recent exposure to a confirmed or probable MERS infected case in the 14 days before onset of their illness (primary cases):

- 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 (*see next tip box*), or in countries where MERS-CoV is known to be circulating in dromedary camels; and
- testing for MERS-CoV is unavailable, negative on an inadequate specimen or inconclusive (see section 2.3 laboratory testing)

It is not recommended to use probable primary MERS cases for this study as it may dilute associations found in the study. If including probable MERS cases, investigators should make sure that they are clearly identified to allow for sensitivity analyses that do not include them.

Case definition for suspected MERS-CoV:
It is not recommended to include persons with suspected MERS as cases in this study, however, the definitions below, which do not include any known or suspected link to another human MERS case, could be considered as suspected primary cases, and would be technically eligible. For the purposes of this study, it would be recommended to enroll highly suspected cases while waiting for confirmation (ceasing investigation if they do not eventually have laboratory evidence of MERS-CoV).

- *Definition 1:* a person with an acute respiratory infection, with history of fever 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 (*see next tip box*) that fully explains the clinical presentation (clinicians should also be alert to the possibility of

atypical presentations in patients who are immunocompromised); and any of the following:
  - o the person resides in the Middle East in particular where human infections have been reported, and in countries where MERS-CoV is known to be circulating in dromedary camels
  - o 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);
  - o 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 (*see next tip box*) 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 (*see next tip box*) 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 the following exposure:
  - o 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.

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' 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.

2.2.2 Recruitment of cases

While there are many questions about the mode of MERS-CoV transmission and risk factors for human-to-human transmission, the primary purpose of this study is to determine the non-human source of infection, such as exposures to dromedary camels (or other animals) and their products or excretions. Therefore, study participants will include only primary MERS cases, meaning either sporadic MERS cases with presumed non-human exposures that resulted in infection or index cases from human-to-human transmission clusters where a prior MERS-CoV epidemiological link for the index case is not known or suspected (*see next tip box* for expanded definitions).

Therefore, there are two scenarios for recruitment into this study after reporting of a confirmed primary MERS case to a local authority – primary cases may either appear as an isolated sporadic case, or they may be the index cases in a sporadic cluster of MERS cases:

A. After a sporadic MERS case (i.e. isolated geographically and temporally – not obviously part of any cluster) is reported to the regional or national health authority, an investigative team should be sent to the location to confirm eligibility criteria (see section 2.2.3, to determine if they are a primary case) for the case, ask for informed consent to participate in the study (see section 2.5.1) and interview them. If the case is deceased or too sick to be interviewed (e.g. is on mechanical ventilation), a proxy can be interviewed instead. The proxy should be a family member or close friend who knows about the activities of the case in the time before their illness and their usual habits. It may be that more than one proxy will be used for each case, though conflicting information will have to be resolved by further discussion with the proxies.

B. After a sporadic cluster of MERS cases is reported to the regional or national health authority, an investigative team should be sent to the location to investigate the cluster and determine the identity of the index case – if the index case is not known to have had contact with another MERS case they may be assumed to be a primary case and eligible for this investigation. Only the index case – that is the case with the earliest date of onset of illness and believed to have acquired infection from a non-human source – should be recruited into the study. The investigators should confirm eligibility criteria (see section 2.2.3) for the index case, ask for informed consent to participate in the study (see section 2.5.1) and interview them or their proxy.

In some clusters, more than one index case may appear simultaneously (co-index cases) and it may be possible to tease out the transmission dynamics and identify a single index case. If not possible to pinpoint a single index case, one option for analysis would be to exclude all co-index cases from this case-control study; however, due to the fact that the number of cases eligible for this study is likely to be very limited, it is recommended to retain both (or all) co-index cases in primary analysis and do a sensitivity analysis excluding them.

2.2.3 Eligibility criteria – cases

All eligible individuals, regardless of whether or not they are well or unwell should be considered for participation in the investigation, and their health status recorded. The participation in another study should also not preclude inclusion in this investigation.

Inclusion criteria:

- Laboratory confirmation according to current WHO guidelines (see section 2.3)

Exclusion criteria:

- Has an epidemiological link* (i.e. possible exposure) in the 14 days prior to onset of their MERS illness with either another documented case of MERS infection or someone admitted to hospital with a respiratory illness of unknown cause.

- Refusal to give informed consent either personally, or a proxy refuses to give informed consent (if deceased or too ill to give consent personally).

* An epidemiological link includes: Close physical contact, health care associated exposure, including providing direct care or working or staying in the same close environment, working together in close proximity or sharing the same classroom environment, traveling together in any kind of conveyance, living in the same household.

Notes:

- Care must be taken in the inclusion of cases not to bias the selection in favor of having had animal contact. That is, cases should be excluded only on the basis of whether or not they have had contact with another human case before their illness, and not whether they have had contact with animals.

- Working in a health care facility is not on its own an exclusion criterion for cases in this study. If there has been no suspected (or probable or confirmed) case of MERS in the health care facility in the recent time period (e.g. ~ 30 days) and if the person working at the health care facility has no other known epidemiological link to a MERS case (of any level).

2.2.4 Recruitment of controls

To understand how rates of exposures to potential sources of infection differ between primary MERS cases and uninfected individuals, it is necessary to recruit age- and sex-matched control participants into the study. To maximize the power to show differences in exposures, up to four controls should be recruited for each MERS case that has been included.

Age matching for adult MERS cases should be conducted within ± 5 years of age of the case for which the control is being selected. For children the age range could be reduced, e.g. ± 1 year, at the discretion of the investigator.

Random selection of controls

Two types of randomly selected controls could be included in this study 1) randomly selected neighborhood controls matched on age and sex and 2) randomly selected hospital controls matched on date of admission, age and sex. Each will yield a different perspective on the factors that influence risk of primary MERS-CoV infection. If resources are limited, recruitment of four neighborhood controls should be prioritized for this study. If resources allow and if the MERS case has been admitted to hospital during their course of their illness, recruitment of an additional 2 to 4 hospital controls is optional but recommended to yield other information on risk factors for illness.

Neighborhood Controls: Investigators should identify the home address and, through this, the neighborhood (physical community) of the MERS case that was enrolled into the study. Then, investigators will go to the neighborhood and directly select, and attempt recruitment of, controls through a random selection process on site. Upon arriving in the neighborhood, the investigators will:

1) First, go to the enrolled case's residence.

2) Then, choose a direction to go from the case's residence. There are two possibilities for choosing the direction, a) by a coin toss if there are only two directions possible (e.g. in the middle of a lone street), or, b) by spinning a pencil on a sheet of paper if there are many possible directions (e.g. at an intersection, or in a community with clusters of houses without clearly designated roads). "Possible directions" in this context refers to areas or streets with residence where controls may be recruited.

3) Proceed in the chosen direction for the number of residences equal to a random number between 1 and 10. This random number would ideally be chosen in advance but can also be conducted on-site. There are two methods with which this random number may be chosen: a) a random number generator, which can be found online, or using statistical software, or, b) write the numbers 1 to 10 separately on pieces of paper, shuffle the pieces of paper and stack them into a pile, draw one piece of paper from the pile.

4) Upon arriving at the residence signified by the chosen random number (e.g. #5 = the fifth household), inquire as to whether or not there is a household member there who fits the eligibility criteria (see section 2.2.5) AND who can be matched in age range and sex to the case. If yes, request informed consent (see section 2.5.1) for the eligible control participant to participate in the study. If no eligible control was found at the household still proceed to step 5).

5) To choose subsequent controls, continue in the same direction selecting residences at the same random number interval as the initial one was selected (e.g. #5 = five further households away from the one where you just attempted recruitment).

When faced with further, or other, choices of directions, use a random selection method such as a coin toss, or further random number selection, to decide which direction to go. For example, if the residence is an apartment building or other multifamily type dwelling, use similar random selection methods to choose the floor to start with, the direction to go from the elevator and the first apartment to interview.

If multiple household members at a selected home fulfil all eligibility and matching criteria, choose randomly which one will participate using the same random number selection method (see step 3) above).

Hospital Controls: Patients who were admitted to the same health care facility on the same date as the index MERS patient will be identified from the health care facility records. Four controls will be chosen at random from the health care facility records; this random selection can be conducted using a random number generator (online or via statistical software) that only considers the records matched on admission date, age and sex. Initial contact with the four identified controls will be made by telephone and/or in person interview(s) and they will be asked to participate in the study. If any of the identified controls refuses to participate, the investigation team will identify another (or other) randomly selected control(s) matched on date of admission, age and sex, following the same procedure as above, until four controls per case are enrolled in the study.

2.2.5 Eligibility criteria – controls

The following inclusion and exclusion criteria should be applied for controls.

Inclusion criteria:

A person randomly selected through the recruitment procedures mentioned and matching on the following factors to a MERS primary case:

- Age range
- Sex
- Date of admission (hospital controls only)

Exclusion criteria:

- Being classified as any of a suspected, probable, or confirmed MERS case (see case definitions in section 2.2.1)
- Has an epidemiological link* with either a documented case of MERS-CoV infection or someone admitted to hospital with a respiratory illness of unknown cause in the 14 days prior to onset of their MERS illness
- Has been admitted to hospital within 14 days prior to the onset of the MERS illness in the case they are being matched with (for neighborhood controls), or was also admitted to hospital in the 14 days prior to date of their current admission (for hospital controls)
- Refusal to give informed consent

* An epidemiological link includes: Close physical contact, health care-associated exposure, including providing direct care or working or staying in the same close environment, working together in close proximity or sharing the same classroom environment, traveling together in any kind of conveyance, living in the same household.

2.2.6 Data collection

Each participant (cases and controls) will have a blood sample (serum) taken (see section 2.3), although this is optional for cases, and will be asked to complete a questionnaire (Annex 2) which covers identifying information, demographic information, date of onset and a series of detailed questions about behaviors, practices, exposures and underlying medical conditions. The questionnaire on Day 1 of the study is the same for both cases and controls. Optionally (depending on the specific objectives of the study), further data can be collected from MERS cases 21 to 28 days after the start of the study – this would include a paired serum sample (optional and only if a serum sample was taken from cases at day 1, see section 2.3) and a second questionnaire that captures the full range of symptoms experienced.

Note: Although these serum samples are optional for cases, determination of the MERS-CoV serological response among persons with primary MERS-CoV infection will only be possible if they have been collected.

It is highly recommended that control participants be asked to contact the study team if they develop respiratory symptoms in the 21-day time period after their enrolment, at which time the study team should arrange for the participant to be visited by a study team member and a nasopharyngeal or oropharyngeal swab taken so that current MERS-CoV infection in the control participant can be excluded.

2.3 Specimen collection and laboratory evaluations

All those involved in collection and transporting specimens should be trained in safe handling practices and spill decontamination procedures. Appropriate PPE must be worn by study personnel during the collection of any specimen (see Section 2.5.5 for more details). 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

If any participants return a positive polymerase chain reaction (PCR) test for MERS-CoV, they should be reported to the national health authorities under the requirements of the International Health Regulations. Authorities will also conduct the identification and follow-up investigation of all contacts for 14 days (regardless of whether or not they are participants in this study). Each newly confirmed case of MERS-CoV infection will initiate a new contact investigation as outlined above. See: https://www.who.int/publications/i/item/10665-178252

2.3.1 Specimen collection

At the time of recruitment (Day 1), from both cases (optional) and controls, 5 to 10 mL of blood will be collected in a serum tube according to standard procedures and labeled with a coded identification number that will also be recorded on the interview questionnaire (Annex 2).

***(Optional but highly recommended)* at the time of recruitment (Day 1), from controls who've experienced respiratory symptoms in the 14 days prior to enrolment,** upper respiratory tract specimens (nasopharyngeal and oropharyngeal swabs)

***(Optional but highly recommended)* Day 1 to 21, from controls who've experienced respiratory symptoms in the 21 days following enrolment,** upper respiratory tract specimens (nasopharyngeal and oropharyngeal swabs)

***(Optional and only if a serum sample was taken from cases at day 1)* Day 21 to 28, from cases,** 5 to 10 mL of blood will be collected in a serum tube according to standard procedures and labeled with a coded identification number that will also be recorded on the interview questionnaire (Annex 2).

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.

All specimens will be collected according to standard procedures and labeled with a coded identification number that will also be recorded on the interview questionnaire (Annex 2). Date and time of collection, location and name of person collecting the specimen will also be recorded. Specimen tubes will be stored temporarily on cool packs carried by the study teams until they can be transported to the laboratory. All those involved in the collection and transportation of specimens should be trained in appropriate personal protection, safe handling practices and spill decontamination procedures.

Implementation tip For serum samples, the specific volume of blood is to be determined by study personnel, bearing in mind that the minimum required volume is 5 mL.

Some serologic assays or full genome sequencing may not be possible to perform in country, therefore specimens should be aliquotted so that specimens remain in country and only aliquots are sent to a reference laboratory.

2.3.2 Specimen transportation

For each biological sample collected, the date and time of collection, the conditions for transportation and the date and time of arrival at the study laboratory will be recorded. Samples should be collected and immediately stored on cool packs until they can be transferred to the participating laboratory for serologic testing. Specimens should reach the laboratory as soon as possible after collection. Serum should be separated from whole blood and can be shipped at 4 °C or frozen to -20 °C or lower (at -80 °C) and shipped on dry ice. If the specimen is not likely to reach the laboratory within 72 hours, specimens should be frozen, preferably at -80 °C, and shipped on dry ice. It is, however, important to avoid repeated freezing and thawing of specimens. It is recommended to aliquot samples prior to freezing, to minimize freeze thaw cycles.

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 the WHO Guidance on Regulations for the Transport of Infectious Substances 2021–2022. Appropriate Material Transfer Agreements will need to be signed if samples are to be transported between laboratories within or outside the country.

Implementation tip For labeling and shipping of specimens – it is key to use a basic triple packaging system, correct marking and labeling of specimens and use of appropriate shipping documents. The receiving laboratory should always be contacted before specimens are shipped.

2.3.3 Laboratory evaluations

A MERS case may be laboratory confirmed by detection of viral nucleic acid or by paired serology. WHO case definitions for MERS-CoV can be found t the MERS Outbreak Toolbox.

The following laboratory testing recommendations are subject to further updates as diagnostic tests and approaches become available. Please check the Middle East respiratory syndrome coronavirus (MERS-CoV) (who.int) for updates.

Serologic testing: Serological testing can be carried out in collaboration with an external laboratory partner as needed. Multiple serological assays will be needed to confirm seropositivity, and may include fluorescent antibody testing, enzyme linked immunosorbent assay (ELISA), luciferase assay, or other. In addition, all samples should be tested using a neutralization assay. These four types of assays each have advantages and disadvantages but appear to have similar utility. Until their interoperability and comparability are better understood, more than one assay should be performed for each serum sample. Testing will be conducted for antibodies against MERS-CoV specific proteins of the spike and nucleocapsid. At least two aliquots of sample will be made and one kept for future analysis. See Annex 1 for more background information about MERS-CoV serological testing methods. An algorithm has been developed to indicate which combinations of serological test results can be considered "positive" for the purpose of comparative analysis, see MERS Outbreak Toolbox.

Implementation tip Only a limited number of laboratories have the facilities for MERS-CoV serologic testing and therefore collaboration between countries without current capacity and designated reference laboratories is possible. Collaboration is at the discretion of Member States carrying out the investigation, but WHO strongly supports such collaboration and would willingly facilitate collaboration and possible shipment elsewhere for testing. For serologic testing, if capacity for performing ELISA and/or neutralization does not exist in country, WHO is able to facilitate coordination and collaboration with an external laboratory. Please contact MERSHQ@who.int.

Molecular testing (optional, from controls reporting symptoms in the 14 days prior to, or 21 days following, enrolment): Three real-time reverse transcription (rRT)-PCR assays for routine detection of MERS-CoV have been developed and their details published; assays targeting upstream of the E protein gene (upE) and assays targeting the open reading frame 1a (ORF 1a) are considered equally sensitive and are recommended for screening. To date, these rRT-PCR assays have shown no cross-reactivity with other respiratory viruses including human coronaviruses and are all suitable to detect all known MERS-CoV strains in humans and dromedary camels. See Annex 1 for more background information about MERS-CoV molecular testing methods, other assays and complimentary confirmation methods.

Implementation tip – genome sequencing

Where possible, MERS-CoV full genome sequencing from PCR-positive biological samples may provide further details on the genetic relationship of the viruses detected with other viral isolates. A RT-PCR assay for MERS-CoV targeting a 615 bp spike fragment may already provide a phylogenetic clustering of MERS-CoV variants comparable to that of full-length genomes, but this may often be insufficient for detailed molecular epidemiological investigations. Full genomes obtained by Next Generation Sequencing (NGS) using sets of specific primers to amplify the full genome for instance delivers a more detailed picture of genetic differences between viruses. Virus grown in culture may be used as an alternative source of the viral RNA.

Acquired sequence information should be shared and reported via publicly available databases; doing so will contribute valuable information to the global effort to understand MERS-CoV epidemiology and perform risk assessment.

Material and more detailed methods for MERS-CoV sequencing are described in the following bibliography of further reading:

Corman VM, Muller MA, Costabel U, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Euro Surveill 2012;17(49):20334.
Cotten M, Watson SJ, Kellam P, et al. Transmission and evolution of the Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive genomic study. Lancet 2013;382:1993–2002.
Cotten M, Watson SJ, Zumla AI, et al. Spread, circulation, and evolution of the Middle East respiratory syndrome coronavirus. mBio 2014;5.
Smits SL, Raj VS, Pas SD, et al. Reliable typing of MERS-CoV variants with a small genome fragment. J Clin Virol 2015;64:83-7.

2.3.4 Sample storage

In the case that serum samples cannot be processed immediately they can be stored for up to 5 days at 2 to 8 °C after which they should be stored at -80 °C (see section on specimen collection and transport above for more details). If -80 °C storage is not available the samples can be stored at -20 °C. It is recommended to aliquot samples prior to freezing, to minimize freeze thaw cycles. The storage of serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations.

2.4 Data management

Demographic, clinical and behavioral data should be stored in a secure, password-protected database in the country where it is collected. Patient identity will be protected and only aggregate summary data released publicly. Original data collection forms will be kept in locked storage.

2.5 Ethical considerations

Ethical requirements will vary by country. In all cases, national and local regulations need to be followed. Investigators should confirm the requirements before implementation which may cover national ethics review only, or national and institutional review.

Implementation tip Ethical approval may be obtained from relevant ethical or institutional review boards in advance using a generic protocol such as this one before an outbreak occurs. If an outbreak occurs, the study design, questionnaires, sampling and consent forms can be modified rapidly to reflect the current outbreak situation. This will likely have to be resubmitted for ethical approval, but if the generic protocol has already been approved, the process is possible that second review may be more rapid, minimizing delays to the start of investigations.

WHO guidelines on ethical issues in public health surveillance can be found here: https://www.who.int/publications/i/item/9789241512657

2.5.1 Informed consent

The purpose of the investigation needs to be explained to all individuals identified for recruitment into the investigation. Informed consent will be obtained from all individuals willing to participate in the investigation before any procedure is performed as part of the investigation, by a trained member of the investigation team.

Consent, or assent for children under the legal age of consent, will be obtained according to the country's national ethical requirements and thus need to comply with local regulations:

- **Consent** for:
  - adults; and
  - children under the legal age of consent (usually this is 18 years but it will vary from country to country) from a parent or legal guardian.

Implementation tip The age of consent may vary by country. Check the requirements of local, regional or national authorities.

- **Assent** from:
  - children and adolescents under the legal age of consent, but who can understand the implications of informed consent and go through the necessary procedures. This is usually children over the age of 12 to 13 years, but this will vary from country to country. A consent form from a parent or legal guardian will also be collected.

All eligible individuals, regardless of whether or not they are well or unwell, or receiving medical care for confirmed or suspected MERS-CoV, should be considered for participation in the investigation. For individuals who lack the decisional capacity to consent at the time of the investigation, consent or assent by proxy (guardian or spouse or family member) may be considered so as to not unduly exclude individuals from participating in the investigation. However, some sites may decide to exclude those cases with severe disease who are unable to complete the questionnaire (Annex 2) ***if*** it is not possible to find a proxy. In either case, the exclusion criteria need to be clearly stated in the adapted protocol, and in the reporting of the results.

An appropriately trained member of the investigation team will need to explain to each participant that participation in the investigation is voluntary and that s/he is free to withdraw, without justification, from the investigation at any time without consequences and without affecting professional responsibilities. A member of the investigation must also be able to answer any questions any individual willing to participate in the investigation may have related to the procedures of the investigation.

The processes related to withdrawal of a participant need to be described both in the protocol and in the information for the participant. In this description it must be made clear that a participant can withdraw from the investigation, without justification, at any time by informing one of the members of the investigation team. The contact details of one of the members of the investigation need to be provided in the information for the participant. If any participant decides to withdraw during the investigation, the samples collected and data should be discarded, except if the participant indicates that these can be kept for the purpose of conducting the investigation, or for future studies of other infectious pathogens.

Informed consent will seek approval to collect: blood, demographic and/or clinical and/or medical history data, information related to dromedary camel exposure and other epidemiological data (e.g. behaviors) intended for the purpose of this investigation. It will also seek approval that samples may be shipped outside of the country for additional testing and, in accordance with national regulations, that samples may be used for future research purposes. The investigators will need to describe in the consent or assent forms how data and specimens will be securely stored. Informed consent will also indicate that any suspected or confirmed MERS-CoV infection may be notified to the national health authorities under the requirements of the International Health Regulations.

2.5.2 Risks and benefits for participants

This investigation poses minimal risk to participants, involving the collection of a small amount of blood from both cases and controls. Benefits of the study are indirect in that data collected will help improve and guide efforts to understand risk factors for MERS-CoV infection, the serological response to MERS-CoV and the full range of illness associated with MERS-CoV.

Implementation tip If local Institutional Review Board (IRB) regulations permit, participants may be offered reimbursement for reasonable out of pocket expenses related to the investigation; however, the level of compensation should not be such that participants are unduly influenced into consenting to participate.

2.5.3 Reporting of serious adverse events, including death of a participant

Any serious adverse event, including death, of a participant during the investigation period, needs to be immediately (within 24h) reported to the Principal Investigator and the institution responsible for the investigation. The contact details for reporting serious adverse events needs to be provided to each member of the investigation team.

In accordance with national regulations, any serious adverse event, may also have to be reported to the local ethical review committee, if the adapted protocol was not deemed exempt from local ethical review committee.

2.5.4 Confidentiality

National laws and regulations for data protection requirements must be followed.

Participant confidentiality needs to be maintained throughout the investigation. All subjects who participate in the investigation should be assigned a study identification number by the investigation team for the labelling of questionnaires and specimens. The link of this identification number to individuals will be maintained by the investigation team and the Ministry of Health (or equivalent), separately from the investigation files, and will not be disclosed elsewhere.

Data and specimens will be securely stored nationally. If the data are shared by the implementing organization with WHO or any agency or institution providing support for data analysis, data shared will include only the investigation identification number and not any identifiable information. Data sharing outside the country will be managed according to national laws and regulations, as appropriate.

Article 45 of the IHR (2005) describes the "treatment of personal data". Person identifiable data collected under the IHR should be kept confidential and processed anonymously, as required by national law. However, such data may be disclosed for assessments and management of public health risks, provided the data are processed fairly and lawfully.

2.5.5 Prevention of infection

Participants. As part of the recruitment process, all eligible participants should be provided information as to how MERS-CoV spreads and what measures can be taken to avoid infection. This should include information as to where to seek medical advice related to the investigation, the symptoms associated with MERS-CoV infection and what to do if symptoms develop during the investigation.

Investigation personnel. All personnel involved in the investigation need to be trained in infection prevention and control (IPC) procedures (standard contact and droplet precautions, as determined by national or local guidelines). These procedures should include proper hand hygiene and the correct use of personal protective equipment (such as surgical or respiratory face masks, gloves, etc.), as per national or local guidelines, provided to members of the investigation team, not only to minimize their own risk of infection when in close contact with individuals with high-risk for MERS-CoV, but also to minimize the risk of spread among other participants in the investigation. Any investigation personnel who develop symptoms consistent with MERS-CoV should be immediately isolated, tested with a nasopharyngeal and oropharyngeal swab and managed as a suspect case of MERS-CoV according to the national or local guidelines.

Implementation tip Where possible, to mitigate infection risk, investigation personnel may consider administering questionnaires (Annex 2) for participants over telecommunications (e.g. phone, videoconferencing, etc.). The feasibility of this strategy would depend on logistical factors (e.g. study personnel available / investigation partners) as well as local context (likelihood that all participants have phones or computers).

For example, an initial in-person visit by a study team member may include informed consent and biological sampling, with a phone-interview for the other questionnaires later on the same day, or the following day. This will work particularly well if, in any case, the study personnel doing biological sampling is not the same as the one doing the questionnaires.

WHO technical guidance on infection prevention and control (IPC) specific to MERS-CoV can be found here: https://www.who.int/publications/i/item/10665-174652

2.5.6 Mitigation of stigmatization of participants

Stigma during MERS-CoV outbreaks involves negative social effects on a person or group due to the (real or perceived) presence of infection and/or risks of infection to others. Stigma can be particularly significant for pathogens such as MERS-CoV that are associated with large potential risks to individuals and communities and therefore significant negative social effects during outbreaks.

Individuals enrolled in MERS-CoV investigations or studies may face risks of stigma. Investigators, along with the relevant national or regional public health authorities, should therefore consider the stigma-related risks faced by individuals and weigh these against the benefits of the investigation. Enrolment of individuals in investigations and studies requires an ethical judgement that the likely public health benefits of enrolment outweigh additional risks specifically associated with the investigation, including those related to stigma. Measures to reduce stigma may include anonymity of enrolment to protect participants. However, full anonymity may not be possible due to the presence of staff involved in the investigations and public health measures (e.g., isolation). Public engagement regarding the disease and/or the investigation taking place, if carefully conducted, may also help to reduce stigma (e.g., by clarifying that infected individuals do not pose risks to others after the resolution of acute infection). For more reading on this subject, please consult the following resources:

- Collective Service (International Federation of Red Cross and Red Crescent Societies (IFRC), United Nations Children's Fund (UNICEF), World Health Organization (WHO) and Global Outbreak Alert and Response Network (GOARN) project): https://www.rcce-collective.net/

- Guidance for managing ethical issues in infectious disease outbreaks. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250580)

- WHO community engagement framework for quality, people-centred and resilient health services. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259280)

The investigators will need to provide specific information on how the risks of stigmatization will be mitigated as part of the implementation of the investigation and the communication of the findings.

3. Statistical analysis

The following section discusses sample size considerations, the epidemiological indicators that can be calculated with the data collected through this study (sometimes called 'study endpoints') and the statistical analyses that should be performed to do so.

3.1 Sample size considerations

The study-specific sample size will be determined by the number of primary or sporadic MERS cases, or human-to-human transmission clusters (each with an assumed single index case) reported to the health authority in the region of study during the time period of the study, as has been decided upon by investigators.

- ***Minimum duration*** (collecting information on, and enrolling only, one reported primary case and four matched controls) – there are no sample size considerations applicable. In this instance, you would not be able to perform statistical analysis of risk factors using your data alone, so data sharing with WHO and/or other regions or health authorities performing this investigation is highly encouraged to incorporate your valuable data into a multinational effort to understand MERS-CoV risk factors. Contact MERSHQ@who.int for details.

- ***Multi-month to multi-year study*** – this would be the case if your region or health authority has opted to do rolling inclusion of cases, to capture all MERS sporadic cases and index cases of clusters over a set period of time (determined by investigators). In this instance, which you do not technically have control over how many cases will be reported and/or included, you can make assumptions of what your sample size may be, based on reported numbers of MERS primary cases, or transmission clusters, in the same time period in previous years. See the *implementation tip* below for an example.

Sample size considerations need to take into account that this is a matched analysis. Generally, it is important to note that the smaller the sample size, the larger the observed effect will need to be for the investigators to detect it (whereas, with a larger sample size, smaller observed effects will be detectable).

Implementation tip

Although the sample size of this specific study is out of the control of the investigators, it will still be useful for study planning and for local administrative procedures to provide an estimate of the expected number of participants, and with that what types of associations (i.e. what values of odds ratios) you would have the power to detect in your study. For matched case-control studies, such as this one, the free open-source statistical environment R, using the package epiR, has a tool for doing sample size and power calculations. An online version of this tool, hosted by the University of Melbourne, can be found here: https://shiny.vet.unimelb.edu.au/epi/sample.size.mccs/

For example, investigators in country X would like to begin a MERS-CoV case-control study, including all primary MERS-CoV cases, reported to Ministry of Health X over the next 3 years. They know based on their records that 12 and 18 primary MERS-CoV cases (a mix of sporadic cases and index cases from small transmission clusters) were reported over the previous two years in country X. They assume, therefor, an average of 15 primary cases may be enrolled per year in their study (x3 years = 45 cases total, x4 controls per case = 180 controls total). Using the link from the University of Melbourne (above), the investigators input the following:

- ***Exposure amongst controls = 30%*** – this is the percentage of controls who may have the same behavior/characteristic of interest, such as dromedary camel handling, as cases. You can play around with this and make different assumptions depending on your expertise, local context and the risk factor of interest.
- ***Matched controls per case = 4***
- ***Alpha (%) = 5*** – this represents the likelihood of making a type 1 error, and a value of 5% is typically used.
- ***Power (%) = 80%*** – power is the inverse of the likelihood of making type 2 error, 80% is the lowest/most generous value typically considered acceptable.
- ***Correlation: 0.2*** – this represents how much the factors we matched on, i.e. age and sex, are also associated with MERS-CoV infection. As it is known that persons with reported primary MERS-CoV infection are often older males, we must assume some correlation. You can play around with this and make different assumptions between 0.1 and 0.6, and see how it affects your estimates.
- ***Odds ratio =*** the investigators start by inputting 1.5, and then move up in 0.5 increments (pressing 'update view' after each changed increment) until, in the right side of the screen, in 'number of cases required' they have a value of (or as close as possible to) 45.

The investigators find that, with the above values input, they have power to detect an odds ratio of 2.75 or greater (meaning the odds the risk factor in persons with MERS-CoV is 2.75 or more times greater than the odds that the risk factor is in the controls).

The online tool gives an output of an interpretative statement for this sample size calculation which could be useful for your study protocol, and for submission to local administrative review boards.

Note: if using the R package epiR for your sample size calculation, either in the R program itself or via the link above, please cite the following reference in your study protocol: Stevenson M, Nunes T, Heuer C, Marshall J, Sanchez J, Thornton R, Reiczigel J, Robison-Cox J, Sebastiani P, Solymos P, Yoshida K, Firestone S. (2015) epiR: An R package for the analysis of epidemiological data. R package version 0.9-69.

3.2 Epidemiological indicators (study outcome measures)

Note: for all analyses, you will not be able to determine risk factors for MERS-CoV infection based on age or sex as the enrolled controls have been matched on these factors.

Descriptive analysis – for small studies that include only one primary case, or a handful of cases, along with their controls, a descriptive analysis will provide some insight into the clinical spectrum and course of MERS disease in your setting, as well as demographic, behavioral and other characteristics of persons with primary MERS-CoV infection. The summarization of study results would include a written description of the time (meaning date) that case(s) were reported, place(s) and regions in which they reside with community characteristics and details (i.e. characteristics as per the questionnaire [Annex 2]) about the person(s) infected. For studies with very few participants, descriptive analysis should take utmost care to protect the identity of participants – put together, exact data such as the name of the community, with precise age and medical history, as well as occupational and/or other lifestyle details of the primary MERS case would be identifying; instead you might use only the region name, with an age range, categories of medical history, etc. In the instance of having a small study (1 or a handful of cases) you would not be able to perform statistical analysis of risk factors using your data alone, so data sharing with WHO and/or other regions or health authorities performing this investigation is highly encouraged to incorporate your valuable data into a multinational effort to understand MERS-CoV risk factors.

Statistical analysis – for larger studies that include 10+ cases (and controls), or studies with case-control data merged over multiple regions or countries Table 1 below provides an overview of the epidemiological characteristics that can be measured as part of this investigation. Not all of these will be a resulting outcome of each specific study using this protocol – this will depend on which aspects of this protocol are implemented. In the case of larger studies (in terms of sample size) including pooled analyses, investigators should consider a sensitivity analysis which excludes co-index cases (i.e. when two or more primary cases in a specific investigation who are temporally and spatially linked but where timing of symptoms does not clearly distinguish one case as being 'first').

Table 1: Epidemiological characteristics that can be calculated as part of this study

Study Objective	Epidemiological characteristics	Definition	Comments, limitations
1. Determine the risk factors for primary MERS-CoV infection	Unadjusted association of the risk factor with MERS-CoV infection **OR** adjusted odds ratios	***Unadjusted (bivariable) associations:*** an assessment of whether a risk factor is more frequent (i.e. a higher proportion) among those with MERS-CoV infection vs in those without. **Odds ratio:** odds of a risk factor and/or characteristic of interest being present in a person with MERS-CoV infection vs odds of a risk factor and/or characteristic of interest being present in a control. Regression models including other factors of interest or key baseline characteristics will give an **adjusted** (preferable) odds ratio.	The significance of bivariable (unadjusted) associations between risk factors and MERS-CoV infection can be estimated using the chi-square statistic or 2-sided Fisher's exact test. However, expression of the associations as an odds ratio with 95% confidence intervals is preferred over only reporting p-values of significance tests. Unadjusted odds ratios can be generated using univariable logistic regression. Multivariable logistic regression can be used to identify independent risk or protective factors. These models adjust for known or potential confounders (e.g. baseline characteristics like occupation); however, the use of multivariable logistic regression is limited by your sample size. Note that the use of a matched analysis does not eliminate confounding based on the matching factors which is why an adjusted analysis is key. Please see https://www.bmj.com/content/352/bmj.i969 for an interesting discussion of this.
2. Characterize the range of clinical presentations of primary MERS-CoV infection	Frequency of each symptom type, severity of illness, duration of illness	*Frequency of each symptom type* – proportion of MERS-CoV infected persons with the specific symptom over total # of primary MERS cases (or, shown separately, controls). *Severity of illness* – proportion of MERS-CoV infected persons with indicators of severe illness over total # MERS-CoV infected persons. *Duration of illness* – mean (average) or median number of days that symptoms are experienced across all cases.	For severity of illness, this may involve summarizing a variety of dichotomous (yes or no) standard severity outcomes such as hospitalized vs not hospitalized, or 'needed ventilation' vs 'did not need ventilation', or survival. Established respiratory illness scales (either already used for MERS-CoV or published for other respiratory illnesses) could also be used – e.g. mild vs moderate vs severe acute respiratory distress syndrome, and others.

Study Objective	Epidemiological characteristics	Definition	Comments, limitations
3. **Determine the MERS-CoV serological response among persons with primary MERS-CoV infection** (only possible if paired serum samples have been collected)	Serological response to MERS-CoV infection Proportion of primary MERS cases who seroconvert	*Serological response* – change in serum level (increase or decrease in titre) of specific antibodies to MERS-CoV over a period of time *Seroconversion proportion* – the number of cases with MERS-CoV antibodies (serum sample) detected at 21+ days via serum sample, over total number who were positive via molecular testing.	Serological response as defined here can only be calculated with the addition of further specimens (serial[a] serum sampling over the first 21 days, and extending past 21 days). See Annex 1 for more background information on antibody kinetics.

[a] Serial serum sampling may be used to better understand seroconversion. It is ideal to collect at least one sample within 5 to 7 days of the suspected infection (symptom onset in most cases) as well as one serum sample between days 14 and 21.

3.3 Interpretation of results

The following considerations are needed when interpreting the results of this investigation:

- The region of study globally – was the study performed in the Middle-East region, African region, or Central Asia, where different strains may be present?
- The specific region or areas in which there were communities frequently reporting cases – is there a high density of dromedary camels or other animals in that area? What are general behaviors (e.g. job types) and other lifestyle factors in this region? Did any environmental or ecological change happen recently in this region or these communities (e.g. influx or emigration of persons, landscape change due to natural resource harvesting, natural disaster)?
- The season and time that the study took place – are there known differences in the frequency of primary MERS cases being reported in the region of study by time of year? Did any large event (e.g. camel breeding season, cultural festival, etc.) take place during the time of the study which may have altered risk factors and/or changed behaviors in any way?
- The timeline of case identification and recruitment of controls – were cases and controls identified and interviewed in a timely manner (within a few days of the confirmed or probable MERS case)? If not, what are the potential limitations to recall (for exposure data, etc.)? Were cases identified at late or early stages in their illness and how might this bias estimates of clinical severity and case fatality?
- The serologic assay used – what are the specificity and sensitivity characteristics of the assay itself?

Increasing our understanding of MERS-CoV epidemiology, risk factors and severity. The findings of this investigation will increase our global understanding of origins and risk factors for MERS-CoV infection, the spectrum of MERS-CoV disease and the serological response to primary MERS-CoV infection. These findings will aid in creating local and international policies for preventing MERS-CoV transmission.

4. Dissemination of results

Recruitment method allowing, all participants should be informed of their individual results using the contact information collected as part of the investigation. The health authority in the region which the investigation is implemented, and the Ministry of Health (or equivalent) also needs to receive a report on the overall findings of the investigation. This should include reporting on the following information:

(1) The study design and specific procedures used (e.g. study duration, selection of controls, eligibility criteria, laboratory techniques, etc.);

(2) The number of primary MERS cases reported during the study time period, the number of cases and controls eventually included, the age and sex of all individuals included (cases and controls);

(3) A map or other depiction of the regions and/or communities in which primary MERS cases were reported;

(4) Descriptive summary of findings (small studies) or results of statistical analysis conducted (larger studies) for all epidemiological characteristics of interest for the specific study, as per section 3.2;

(5) Any other key findings, as per the specific study objectives chosen (e.g. spectrum of illness, serological response, etc.).

An integrated approach which engages both researchers and stakeholders should be used for conducting dissemination activities in joint efforts by the researchers involved and advisory committee members.

Dissemination activities could include:

- Submitting progress and final research reports to regional health authorities, national Ministries of Health and to WHO.
- Publishing the research findings as preprints and subsequently in peer-reviewed journals and making them available in open access format. The STROBE guidelines for cross-sectional studies should be used for reporting of this study: https://www.equator-network.org/reporting-guidelines/strobe/
- Organizing meetings, seminars and workshops involving a panel of the research team beside other research experts (from human and animal health) to discuss the research findings and how they may influence public health interventions and policies.
- Developing policy briefs for national health authorities.

Implementation tip The *timely* dissemination of the results of this study are critical in understanding transmission of the MERS-CoV virus to inform guidance for policy to direct national and international public health responses.

5. Composition of study team

This investigation calls for a multi-disciplinary research study team to undertake this study. The composition of the study team will be determined by each country. It is recommended that members from the Ministry of Health, national laboratories and other partners are included in the implementation and interpretation of this investigation. Coordination of investigations and sharing of information in real-time will be needed at both country and global levels. Epidemiologists, modelers, virologists, statisticians, clinicians and public health experts will all be necessary to include in this study that will help define key clinical, epidemiological and virological characteristics of MERS-CoV. Importantly, these specialists should all be included from an early stage to ensure that the study protocol and procedures adhere to best practices; e.g. making sure to include statisticians early on in the design of the study and not only after all data collection has been conducted as this may lead to having data which is not amenable to analysis.

Implementation tip A table such as the one below may be useful for designating roles and responsibilities and identifying study partners during the planning stage of this investigation.

Table 2. Coordination matrix of roles and responsibilities in Country X

What?	Who?
Overall coordination of the investigation	*[Cite institution/ body/person(s)]*
Identification of study population	*[Cite institution/ body/person(s)]*
Input on dromedary camel sampling strategy	*[Cite institution/ body/person(s)]*
Recruitment, informed consent, enrolment	*[Cite institution/ body/person(s)]*
Data and sample collection from enrolled participants	*[Cite institution/ body/person(s)]*
Laboratory testing and storage of samples	*[Cite institution/ body/person(s)]*
Data and sample collection from dromedary camels enrolled	*[Cite institution/ body/person(s)]*
Laboratory testing and storage of camel samples	*[Cite institution/ body/person(s)]*
Analysis of data and reporting	*[Cite institution/ body/person(s)]*
Data management	*[Cite institution/ body/person(s)]*
IT management	*[Cite institution/ body/person(s)]*
Informing participants of their individual results and the results of their camels (if tested) and communication of overall findings of investigation	*[Cite institution/ body/person(s)]*
[add more roles, as per country context]	*[Cite institution/ body/person(s)]*

Once a study team is identified, a workshop and training should be conducted to familiarize the team with the objectives and organize the implementation of the study.

6. References

1. World Health Organization. Middle East respiratory syndrome: global summary and assessment of risk – 16 November 2022. Available from: https://iris.who.int/handle/10665/364525.

2. Islam MM, Khanom H, Farag E, Mim ZT, Naidoo P, Mkhize-Kwitshana ZL, et al. Global patterns of Middle East respiratory syndrome coronavirus (MERS-CoV) prevalence and seroprevalence in camels: A systematic review and meta-analysis. One Health. 2023;16:100561.

3. Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk Factors for Primary Middle East Respiratory Syndrome Coronavirus Illness in Humans, Saudi Arabia, 2014. Emerg Infect Dis. 2016;22(1):49-55.

4. Madani TA, Azhar EI, Hashem AM. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med. 2014;371(14):1360.

5. Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, Hashem AM, et al. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med. 2014;370(26):2499-505.

6. Drosten C, Kellam P, Memish ZA. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med. 2014;371(14):1359-60.

7. Food and Agricultural Organization of the United Nations. Global technical meeting on MERS-CoV and other emerging zoonotic coronaviruses – meeting summary. 2021. Available from: https://www.who.int/publications/m/item/global-technical-meeting-on-mers-cov-and-other-emerging-zoonotic-coronaviruses-meeting-summary

8. Sikkema RS, Farag E, Islam M, Atta M, Reusken C, Al-Hajri MM, et al. Global status of Middle East respiratory syndrome coronavirus in dromedary camels: a systematic review. Epidemiol Infect. 2019;147:e84.

9. Funk AL, Goutard FL, Miguel E, Bourgarel M, Chevalier V, Faye B, et al. MERS-CoV at the Animal-Human Interface: Inputs on Exposure Pathways from an Expert-Opinion Elicitation. Front Vet Sci. 2016;3:88.

10. Al-Tawfiq JA, Auwaerter PG. Healthcare-associated infections: the hallmark of Middle East respiratory syndrome coronavirus with review of the literature. J Hosp Infect. 2019;101(1):20-9.

11. Guery B, Poissy J, el Mansouf L, Sejourne C, Ettahar N, Lemaire X, et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet. 2013;381(9885):2265-72.

12. World Health Organization. WHO MERS Global Summary and Assessment of Risk. 2019. Available from: https://apps.who.int/iris/handle/10665/326126

13. Omrani AS, Matin MA, Haddad Q, Al-Nakhli D, Memish ZA, Albarrak AM. A family cluster of Middle East Respiratory Syndrome Coronavirus infections related to a likely unrecognized asymptomatic or mild case. Int J Infect Dis. 2013;17(9):e668-72.

14. Health Protection Agency U. K. Novel Coronavirus Investigation team. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. Euro Surveill. 2013;18(11):20427.

15. Abroug F, Slim A, Ouanes-Besbes L, Hadj Kacem MA, Dachraoui F, Ouanes I, et al. Family cluster of Middle East respiratory syndrome coronavirus infections, Tunisia, 2013. Emerg Infect Dis. 2014;20(9):1527-30.

16. Van Kerkhove MD, Alaswad S, Assiri A, Perera R, Peiris M, El Bushra HE, et al. Transmissibility of MERS-CoV Infection in Closed Setting, Riyadh, Saudi Arabia, 2015. Emerg Infect Dis. 2019;25(10):1802-9.

17. Al Hosani FI, Kim L, Khudhair A, Pham H, Al Mulla M, Al Bandar Z, et al. Serologic Follow-up of Middle East Respiratory Syndrome Coronavirus Cases and Contacts-Abu Dhabi, United Arab Emirates. Clin Infect Dis. 2019;68(3):409-18.

18. Alanazi KH, Killerby ME, Biggs HM, Abedi GR, Jokhdar H, Alsharef AA, et al. Scope and extent of healthcare-associated Middle East respiratory syndrome coronavirus transmission during two contemporaneous outbreaks in Riyadh, Saudi Arabia, 2017. Infect Control Hosp Epidemiol. 2019;40(1):79-88.

19. Drosten C, Meyer B, Muller MA, Corman VM, Al-Masri M, Hossain R, et al. Transmission of MERS-coronavirus in household contacts. N Engl J Med. 2014;371(9):828-35.

20. Arwady MA, Alraddadi B, Basler C, Azhar EI, Abuelzein E, Sindy AI, et al. Middle East Respiratory Syndrome Coronavirus Transmission in Extended Family, Saudi Arabia, 2014. Emerg Infect Dis. 2016;22(8):1395-402.

21. Memish ZA, Zumla AI, Al-Hakeem RF, Al-Rabeeah AA, Stephens GM. Family cluster of Middle East respiratory syndrome coronavirus infections. N Engl J Med. 2013;368(26):2487-94.

22. Conzade R, Grant R, Malik MR, Elkholy A, Elhakim M, Samhouri D, et al. Reported Direct and Indirect Contact with Dromedary Camels among Laboratory-Confirmed MERS-CoV Cases. Viruses. 2018;10(8):425.

23. Al-Ahmadi K, Alahmadi M, Al-Zahrani A. Spatial association between primary Middle East respiratory syndrome coronavirus infection and exposure to dromedary camels in Saudi Arabia. Zoonoses Public Health. 2020;67(4):382-90.

24. Hemida MG, Ali AM, Alnaeem A. The Middle East respiratory syndrome coronavirus (MERS-CoV) nucleic acids detected in the saliva and conjunctiva of some naturally infected dromedary camels in Saudi Arabia -2019. Zoonoses Public Health. 2021;68(4):353-7.

25. Hemida MG, Ali M, Alhammadi M, Alnaeem A. The Middle East respiratory syndrome coronavirus in the breath of some infected dromedary camels (Camelus dromedarius). Epidemiol Infect. 2020;148:e247.

26. Hemida MG, Waheed M, Ali AM, Alnaeem A. Detection of the Middle East respiratory syndrome coronavirus in dromedary camel's seminal plasma in Saudi Arabia 2015-2017. Transbound Emerg Dis. 2020;67(6):2609-14.

7. Annexes

Annex 1: Additional information and references

MERS-CoV molecular testing

Currently described tests are an assay targeting upstream of the E protein gene (upE) and assays targeting the open reading frame 1b (ORF 1b) *(1)* and the open reading frame 1a (ORF 1a) *(2)*. 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 *(3)*.

References:

1. Corman VM, Eckerle I, Bleicker T, et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill 2012;17(39):20285.

2. Corman VM, Muller MA, Costabel U, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Euro Surveill 2012;17(49):20334

3. Lu X, Whitaker B, Sakthivel SK, et al. Real-time reverse transcription-PCR assay panel for Middle East respiratory syndrome coronavirus. J Clin Microbiol 2014;52:67-75.

MERS-CoV serological testing

A number of different technical approaches for confirming MERS-CoV infection using serology have been developed. Details of two immunofluorescence assays to detect antibodies to MERS-CoV have been published *(1)* 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 Saudi Arabia *(2–5)*. An assay for detection of MERS-CoV antibodies using protein microarray technology has also been developed and its details published *(6,7)*. 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 neutralization has also been described *(8)*. Details of a neutralization test based on retroviral pseudoparticles which also demonstrates high levels of specificity to MERS-CoV have also been published *(9)*. A commercial ELISA assay based on the spike S1 region is available for screening. Positive ELISA results should be confirmed by neutralization assays.

References:

1. Corman VM, Muller MA, Costabel U, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Euro Surveill. 2012;17(49):20334

2. Corman VM, Eckerle I, Bleicker T, et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill. 2012;17(39):20285.

3. Buchholz U, Muller MA, Nitsche A, et al. Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October–November 2012. Euro Surveill. 2013;18(8):20406.

4. Drosten C, Meyer B, Muller MA, et al. Transmission of MERS-coronavirus in household contacts. N Engl J Med. 2014;371:828-35.

5. Muller MA, Meyer B, Corman VM, et al. Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study. Lancet Infect Dis. 2015;15:559-64.

6. Reusken C, Mou H, Godeke GJ, et al. Specific serology for emerging human coronaviruses by protein microarray. Euro Surveill. 2013;18:20441.

7. Reusken CB, Farag EA, Haagmans BL, et al. Occupational Exposure to Dromedaries and Risk for MERS-CoV Infection, Qatar, 2013–2014. Emerg Infect Dis. 2015;21:1422-5.

8. Trivedi S, Miao C, Al-Abdallat MM, et al. Inclusion of MERS-spike protein ELISA in algorithm to determine serologic evidence of MERS-CoV infection. J Med Virol. 2018;90:367-71

9. Perera RA, Wang P, Gomaa MR, et al. Seroepidemiology for MERS coronavirus using microneutralisation and pseudoparticle virus neutralisation assays reveal a high prevalence of antibody in dromedary camels in Egypt, June 2013. Euro Surveill. 2013;18:pii=20574.

MERS-CoV antibody kinetics

There is currently a lack of generalizable information on antibody kinetics of MERS-CoV in human patients. One study conducted on 42 MERS-CoV infected patients from the outbreak in the Republic of Korea in 2015 found that although all surviving patients seroconverted, none had antibodies 10 months after infection *(1)*. The study employed the use of molecular testing of high-risk health and care worker contacts and serology, in an attempt to capture acute sub-clinical or asymptomatic infection as well as seroconversion. Another study conducted in the Republic of Korea found that although antibody responses may wane, they remain detectable beyond 12 months in patients with severe illness *(2)*. In

a study conducted in Jordan, antibody levels were found to persist and remain detectable for over 34 months in individuals following MERS-CoV infection *(3)*. However, RT-PCR confirmed cases with mild disease failed to seroconvert or developed short-lasted antibody responses. Extensive contact tracing policies recommended by WHO and implemented in Saudi Arabia have identified a substantial number of asymptomatic secondary health and care worker infections *(4)*, however very few of these individuals seroconvert (*personal communication*). These considerations should be accounted for when assessing the ability of the study to capture evidence of seroconversion as a secondary objective of this study.

References:

1. Ko JH, Muller MA, Seok H, et al. Serologic responses of 42 MERS-coronavirus-infected patients according to the disease severity. Diagn Microbiol Infect Dis. 2017;89:106-11.

2. Choe PG, Perera R, Park WB, et al. MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. Emerg Infect Dis. 2017;23:1079-84.

3. Payne DC, Iblan I, Rha B, et al. Persistence of antibodies against Middle East respiratory syndrome coronavirus. Emerg Infect Dis. 2016;22:1824–6.

4. Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013;369:407-16.

Annex 2: Case-control study questionnaire

Comment: This form should be used for all cases and controls included in the investigation.

If the case has died or is otherwise unable to answer questions, a proxy such as person (e.g., family member, friend or co-worker) who knows the person well can answer the questions for him or her.

Before beginning, each case and control included should be allocated a unique identification number.

Implementation tip 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.

Unique Case ID and Cluster number (if applicable):

1. Participant classification

☐ Case ☐ Control

If case, vital status: ☐ Alive ☐ Deceased ☐ Unknown

If control, case ID and cluster number for case on whom control is matched:

If control, have they experienced respiratory symptoms in the last 14 days?
☐ Yes ☐ No
If Yes, it is highly recommended to collect a nasopharyngeal and/or oropharyngeal swab from the participant to test for MERS-CoV and rule out current active infection

2. Data collector and interview information

Name of data collector	
Data collector institution	
Data collector profession	
Data collector telephone number	
Data collector email	
Place of interview (region, city, further details if applicable)	
Interview start date (dd/mm/yyyy)	____/____/____
Form completion date (dd/mm/yyyy)	____/____/____
Language used for interview	

Case-control study questionnaire (continued)

3. Participant personally identifying information *(Note: personally identifying data should be stored securely and separately from other parts of this form)*	
First name	
Family name	
Date of birth (dd/mm/yyyy)	____/____/____ ☐ Unknown
Address (if multiple residences, give addresses for all)	
Telephone (mobile) number	
Email	
National identifier or social number [optional]	
Responsible health centre, if applicable (name, address, contact information):	

4. Interview respondent information (only if the person providing the information is not the case) *(Note: personally identifying data should be stored securely and separately from other parts of this form)*	
First name	
Family name	
Sex	☐ Male ☐ Female ☐ Not known ☐ Prefer not to answer
Date of birth (dd/mm/yyyy)	____/____/____ ☐ Unknown
Relationship to case	
Respondent address	
Telephone (mobile) number	
Email	

Part 1 – Participant Demographic and Clinical Information

5. Participant demographic information and living situation data	
Sex	☐ Male ☐ Female ☐ Not known ☐ Prefer not to answer
Age (years, months)	____ years ____ months ☐ Unknown
Nationality	
Ethnicity [optional, at discretion of study investigators. If using, please input checkbox style options with relevant ethnicities in the right-hand column]	
Country of residence	
Type of dwelling for primary residence(s) [options to the right should to be adjusted to apply to local setting]	☐ Apartment ☐ House ☐ Villa ☐ Other (specify):
Number of people living in the household (including participant, note: a household is defined as having one shared kitchen)	Children less than 18 years of age: ____ Adults 18 years of age and above: ____

Case-control study questionnaire. Part 1 – Participant Demographic and Clinical Information (continued)

Marital status	☐ Single ☐ Married ☐ Divorced ☐ Widowed ☐ Other, specify:
Occupation (select all that apply and specify location and/or facility)	☐ Health and care worker ☐ Health laboratory worker ☐ Working with dromedary camels if Yes, specify in what capacity: ☐ Working with other animals (not dromedary camels) if Yes, specify in what capacity: ☐ Student If Yes, specify current nursery or school or college: ☐ Other, specify: For each occupation, please specify location or facility:
Highest level of education finished	☐ None or not finished primary school ☐ Primary school (approximately 6 years) ☐ Secondary school (total of approximately 12 years) ☐ College or university undergraduate degree or postsecondary diploma ☐ Graduate studies (e.g. Masters, PhD)
Household income level [enter local context specific options in the right-hand column]	☐ Level 1 [specify] ☐ Level 2 [specify] ☐ Level 3 [specify] ☐ Level 4 [specify] ☐ [add or remove as appropriate for local setting]

6a. IF A CASE ONLY – Participant symptoms (from date of onset of symptoms) for this instance of MERS-CoV	
Date of first symptom onset (dd/mm/yyyy)	____/____/____ ☐ No symptoms ☐ Unknown
Fever (≥38 °C) or history of fever	☐ Yes ☐ No ☐ Unknown If Yes, specify maximum temperature: °C
Date of first health facility visit (including traditional care) (dd/mm/yyyy)	____/____/____ ☐ Not applicable (na) ☐ Unknown
Total health facilities visited to date	Specify number, locations, names: ☐ na ☐ Unknown

Case-control study questionnaire. Part 1 – Participant Demographic and Clinical Information (continued)

6b. Respiratory symptoms	
Dry cough	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Productive cough	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Phlegm	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Sore throat	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Runny nose	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Shortness of breath	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Chest pain	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
6c. Other symptoms	
Chills	☐ Yes ☐ No ☐ Unknown
Vomiting	☐ Yes ☐ No ☐ Unknown
Nausea	☐ Yes ☐ No ☐ Unknown
Diarrhoea	☐ Yes ☐ No ☐ Unknown
Headache	☐ Yes ☐ No ☐ Unknown
Rash	☐ Yes ☐ No ☐ Unknown
Conjunctivitis	☐ Yes ☐ No ☐ Unknown
Muscle aches	☐ Yes ☐ No ☐ Unknown
Joint ache	☐ Yes ☐ No ☐ Unknown
Loss of appetite	☐ Yes ☐ No ☐ Unknown
Fatigue	☐ Yes ☐ No ☐ Unknown
Seizures	☐ Yes ☐ No ☐ Unknown
Altered consciousness	☐ Yes ☐ No ☐ Unknown
Other neurological signs	☐ Yes ☐ No ☐ Unknown If Yes, specify:
Other symptoms	☐ Yes ☐ No ☐ Unknown If Yes, specify:

Case-control study questionnaire. Part 1 – Participant Demographic and Clinical Information (continued)

7. Participant medical history	
7a. Pre-existing conditions and chronic illnesses	
Pregnancy	☐ Yes ☐ No ☐ Unknown If Yes, specify number of weeks:
Recent pregnancy – if female and not currently pregnant, was the case pregnant in the last 6 months?	☐ Yes ☐ No ☐ Unknown
Obesity	☐ Yes ☐ No ☐ Unknown
Cancer If Yes, specify (timing and specific cancer): If cancer treatment in the last year:	☐ Yes ☐ No ☐ Unknown ☐ Chemotherapy ☐ Radiation ☐ Other, specify:
Diabetes If Yes, do you use insulin?	☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown
HIV and/or other immune deficiency If Yes, specify:	☐ Yes ☐ No ☐ Unknown
Heart disease If Yes, specify:	☐ Yes ☐ No ☐ Unknown
Asthma (requiring medication) Which medication has been used for treatment of asthma in the past month?	☐ Yes ☐ No ☐ Unknown ☐ Handheld inhalers ☐ Oral medications to open airways ☐ Oral steroids ☐ Home nebulizer treatment to open airways ☐ None in the past month ☐ Other, specify:
Chronic lung disease (non-asthma) If Yes, specify: Specify any medication used for treatment:	☐ Yes ☐ No ☐ Unknown
Chronic liver disease If Yes, specify:	☐ Yes ☐ No ☐ Unknown
Chronic hematological disorder If Yes, specify:	☐ Yes ☐ No ☐ Unknown
Chronic kidney disease If Yes, are you currently receiving dialysis:	☐ Yes ☐ No ☐ Unknown ☐ Yes ☐ No ☐ Unknown
Chronic neurological impairment and/or disease If Yes, specify:	☐ Yes ☐ No ☐ Unknown
Organ or bone marrow recipient	☐ Yes ☐ No ☐ Unknown
Familial hereditary illness If Yes, specify:	☐ Yes ☐ No ☐ Unknown
Other pre-existing condition(s) If Yes, specify:	☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 1 – Participant Demographic and Clinical Information (continued)

7b. Other medical history	
Participant currently smokes tobacco (e.g. cigarettes, cigars, shisha)	☐ Daily ☐ A few days a week ☐ Not at all ☐ Unknown
If participant currently smokes tobacco, do they share their tobacco (e.g. shisha)	☐ Yes ☐ No ☐ Unknown ☐ Not applicable (does not smoke)
If participant does not currently smoke tobacco daily, have they smoked tobacco daily in the past?	☐ Yes ☐ No ☐ Unknown ☐ Not applicable (currently smokes daily)
If participant smoked tobacco in the past (but not currently),at that time was it:	☐ Daily ☐ A few days a week ☐ Unknown
Participant takes medications regularly (within the last 6 months)	☐ Yes ☐ No ☐ Unknown
If Yes, taking corticosteroids:	☐ Yes ☐ No ☐ Unknown
If Yes, list medications:	
Participant has taken traditional medications within the last 6 months	☐ Yes ☐ No ☐ Unknown ☐ If Yes, list traditional medications:

Case-control study questionnaire. Part 1 – Participant Demographic and Clinical Information (continued)

8a. Molecular testing methods and results:							
Complete a new line for each specimen collected and each type of test conducted:							
Laboratory identification number	**Date sample collected (dd/mm/yyyy)**	**Date sample received (dd/mm/yyyy)**	**Type of sample**	**Type of test**	**Result**	**Result date (dd/mm/yyyy)**	**Specimens shipped to other laboratory for confirmation**
	____/____/____	____/____/____	☐ Nasal swab ☐ Throat swab ☐ Nasopharyngeal swab ☐ Other, specify:	☐ Polymerase chain reaction (PCR) ☐ Whole genome sequencing ☐ Partial genome sequencing ☐ Other, specify	☐ positive for MERS-CoV ☐ negative for MERS-CoV ☐ inconclusive ☐ positive for other pathogens Please specify which pathogens: Results of phylogenetic analysis: _____	____/____/____	☐ No ☐ Yes If Yes, specify date ____/____/____ If Yes, name of the laboratory: _____ ***Genomic sequencing*** ☐ No ☐ Yes (locally) ☐ Yes (shipped to external laboratory) If Yes to shipped externally, specify date ____/____/____ If Yes to shipped externally name of the laboratory: _____

Case-control study questionnaire. Part 1 – Participant Demographic and Clinical Information (continued)

8b. Serology testing methods and results:							
Complete a new line for each specimen collected and each type of test conducted:							
Laboratory identification number	**Date sample collected (dd/mm/yyyy)**	**Date sample received (dd/mm/yyyy)**	**Type of sample**	**Type of test**	**Result (MERS-CoV antibody titres)**	**Result date (dd/mm/yyyy)**	**Specimens shipped to other laboratory for confirmation**
	____/____/____	____/____/____	☐ Serum ☐ Other, specify:	Specify type (enzyme linked immunosorbent assay – ELISA, indirect fluorescent antibody assay – IFA, neutralization assay, etc.):	☐ positive If positive, titre: ☐ negative ☐ inconclusive	____/____/____	☐ Yes If Yes, specify date ____/____/____ If Yes, name of the laboratory: ____ ☐ No

Part 2 – Participant Exposures

Comment:

The time frame for the exposure questions to cases is the *14-day period before the onset of their illness.* For cases that happened in the past (e.g. a late notification where investigators were informed of the case >14 days *after* the onset of illness), it is useful to use memory prompts such as holidays or other memorable events that occurred around the same time – this may help the interviewee recall the specific time frame of interest.

For controls, the time frame of interest for exposure questions is the same as that of the case to which the control is matched (that is, the same calendar dates).

If the case has died or is otherwise unable to answer questions, a proxy such as person (e.g., family member, friend or co-worker) who knows the person well can answer the questions for him or her.

Date of symptom onset for case (to identify relevant time period for exposures for both cases and controls), dd/mm/yyyy

1. Travel in the 14 days before case's symptom onset

Participant travelled domestically within the last 14 days If Yes, dates of travel and locations (list all, add extra entries as needed)	☐ Yes ☐ No ☐ Unknown D1. Dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Region(s) and cities visited: D1. Dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Region(s) and cities visited: D1. Dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Region(s) and cities visited:
Attended mass gathering (wedding, festival, religious pilgrimage) at this location?	☐ Yes ☐ No ☐ Unknown If Yes, specify event(s) type & location(s):
Participant travelled *internationally* within the last 14 days	☐ Yes ☐ No ☐ Unknown Int1. Dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Country(s) and cities visited: Int2. Dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Country(s) and cities visited: Int3. Dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Country(s) and cities visited:
Attended mass gathering (wedding, festival, religious pilgrimage) at this location?	☐ Yes ☐ No ☐ Unknown If Yes, specify event(s) type & location(s):

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

2. Human MERS-CoV exposures in the 14 days before case's symptom onset	
Participant had contact with anyone with suspected or confirmed MERS-CoV infection	☐ Yes ☐ No ☐ Unknown If Yes, dates of last contact (dd/mm/yyyy): ____/____/____ Specify location of contact:
Participant had direct contact (e.g. touch, share a bed) with a person with respiratory illness, such as cough and fever	☐ Yes ☐ No ☐ Unknown If Yes, dates of last contact (dd/mm/yyyy): ____/____/____ If Yes, location of exposure: ☐ Home ☐ Hospital ☐ Workplace ☐ Tour group ☐ School ☐ Unknown ☐ Other, specify:
Participant attended festival or mass gathering in the past 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify event, approximate number of persons gathered, and location:
Participant was admitted to an inpatient health facility in the 14 days prior to onset of case's illness	☐ Yes ☐ No ☐ Unknown If Yes, specify, name and address of medical facility: Dates of admission (dd/mm/yyyy): ____/____/____ to ____/____/____ Reason for admission:
Participant visited someone in an inpatient health facility in the 14 days prior to onset of case's illness	☐ Yes ☐ No ☐ Unknown If Yes, specify name and address of medical facility: If Yes, specify date(s) of visit (dd/mm/yyyy): ____/____/____ ____/____/____ ____/____/____ Reason for visit: ☐ Caring for a sick person (consistent direct contact) ☐ Visit sick person briefly with direct contact ☐ Visit sick person briefly without direct contact ☐ Visit facility staff member who was not sick ☐ Unknown Was person being visited sick with a respiratory illness? ☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

Participant visited outpatient treatment facility in the past 14 days, prior to onset of case's illness	☐ Yes ☐ No ☐ Unknown If Yes, specify name and address of medical facility: If Yes, specify date(s) of visit (dd/mm/yyyy): ____/____/____ ____/____/____ ____/____/____ If Yes, specify reason for visit:
Participant visited traditional healer in the past 14 days, prior to onset of case's illness	☐ Yes ☐ No ☐ Unknown If Yes, specify name and general location of traditional healer (if participant prefers not to specify, please indicate this): If Yes, specify date(s) of visit (dd/mm/yyyy): ____/____/____ ____/____/____ ____/____/____ If Yes, specify reason for visit:

3. Exposures to dromedary camels and/or their products or excretions

General exposures to dromedary camels

During the last 6 months, how often on average has the participant had direct physical contact with dromedary camels?	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant had direct contact with dromedary camels in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify:
Participant had direct contact with any of the following dromedary camel body fluids and/or body tissues in the last 14 days (Note: contact outside of use for food or medicinal purposes, see further questions below)	☐ Blood ☐ Raw milk ☐ Urine ☐ Saliva ☐ Seminal fluid ☐ Raw meat and/or body tissues ☐ Other (specify):
Persons in the participant's household (either relatives or domestic help) frequently visit at venues where dromedary camels are kept, sold, or slaughtered	☐ Yes, frequently within the last 6 months **including within the 14 days before the case's illness onset** ☐ Yes, frequently within the last 6 months but **not in the 14 days before the case's illness onset** ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

Persons in the participant's household (either relatives or domestic help) frequently work at venues where dromedary camels are kept, sold, or slaughtered	☐ Yes, frequently within the last 6 months including within the 14 days before the case's illness onset ☐ Yes, frequently within the last 6 months but not in the 14 days before the case's illness onset ☐ No ☐ Unknown
Persons in the participant's household (either relatives or domestic help) had direct contact with dromedary camels within the 14 days before the case's onset of illness	☐ Yes ☐ No ☐ Unknown
Regular contact with dromedary camels at either the participant's home or workplace	
Do you or your immediate family (i.e. spouse or parent or child or sibling if living in the same household) own a barn or farm with animals?	☐ Yes ☐ No ☐ Unknown If Yes, location of the barn or farm:
Participant had dromedary camels living in or around their home anytime during the last 6 months	☐ Yes, within the last 6 months and **until the present** ☐ Yes, within the last 6 months but **not the last 14 days** ☐ No ☐ Unknown
Participant had regular exposure to dromedary camels at their workplace anytime during the last 6 months	☐ Yes, within the last 6 months and **until the present** ☐ Yes, within the last 6 months but **not the last 14 days** ☐ No ☐ Unknown
If Yes to participant having dromedary camels living in or around their home or at their regular place of work anytime during the last 6 months, please specify the following:	Number of dromedary camels: ☐ < 10 animals ☐ ≥ 10 animals What are the dromedary camels used for (select all that apply): ☐ Income (i.e. to be sold) ☐ Food ☐ Work (e.g. farm work, transport) ☐ Racing ☐ Pets ☐ Other, specify: _____ Did the participant have direct contact with these camels? ☐ Yes ☐ No ☐ Unknown Did the participant do any of the following activities (select all that apply): ☐ Feed camels ☐ Clean camel housing ☐ Slaughter camels ☐ Assist with camel births ☐ Milk camels ☐ Kiss and/or hug camels ☐ Other, specify: _____ Did any illness affect these camels during this time? ☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

Participant has had regular contact with dromedary camel carcasses, body fluids, secretions, urine or excrement anytime in the last 6 months	☐ Yes, within the last 6 months and **until the present** ☐ Yes, within the last 6 months but **not the last 14 days** ☐ No ☐ Unknown
Participant has had regular contact with dromedary camel bedding (e.g. straw, other) or feed anytime in the last 6 months	☐ Yes, within the last 6 months and **until the present** ☐ Yes, within the last 6 months but **not the last 14 days** ☐ No ☐ Unknown
Occasional and/or indirect contact with dromedary camels in the last 14 days	
During the last 6 months, how often on average has the participant been on a farm that housed dromedary camels	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant visited a dromedary camel farm in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify farm location: _____ If Yes, contact with camels was: ☐ Direct (touched camels) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown
During the last 6 months, how often on average has the participant been on an animal market that housed dromedary camels	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant visited an animal market that sells dromedary camels in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify market location: _____ If Yes, contact with camels was: ☐ Direct (touched camels) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

During the last 6 months, how often on average has the participant visited abattoirs that slaughter dromedary camels	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant visited an abattoir that slaughters dromedary camels in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify abattoir location: _____ If Yes, contact with camels was: ☐ Direct (touched camels or camel carcasses) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown
Participant personally participated in the slaughter of dromedary camels in the 14 days before the case's illness onset?	☐ Yes ☐ No ☐ Unknown If Yes, was there any indication that the camel slaughtered had been sick? ☐ Yes ☐ No ☐ Unknown
During the last 6 months, how often on average has the participant visited camel quarantine sites	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant visited a camel quarantine site in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify quarantine location: _____ If Yes, contact with camels was: ☐ Direct (touched camels) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown
During the last 6 months, how often on average has the participant visited dromedary camel racetracks	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

Participant visited a dromedary camel racetrack in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify racetrack location: _____ If Yes, contact with camels was: ☐ Direct (touched camels) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown
During the last 6 months, how often on average has the participant visited dromedary camel beauty pageant	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant visited a dromedary camel beauty pageant in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify beauty pageant location: _____ If Yes, contact with camels was: ☐ Direct (touched camels) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown
During the last 6 months, how often on average has the participant visited any other event involving dromedary camels	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
Participant visited other dromedary camel event in the last 14 days	☐ Yes ☐ No ☐ Unknown If Yes, specify dromedary camel event location: _____ If Yes, contact with camels was: ☐ Direct (touched camels) ☐ Indirect (e.g. consume or handle camel products, touch items used for camels or on camels such as bedding) ☐ No contact with camels or camel products or excretions ☐ Unknown If Yes, were you aware of any sick camels at this location at that time: ☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

Food or medicinal exposures to dromedary camels	
In the last 6 months, the participant has **regularly** (i.e. multiple times per week, on average) ingested any of the following dromedary camel products	☐ Raw camel milk ☐ Boiled camel milk ☐ Urine ☐ Raw camel meat ☐ Cooked camel meat ☐ Other (specify): ☐ None
In the last 14 days, the participant has ingested any of the following dromedary camel products **at least once**	☐ Raw camel milk ☐ Boiled camel milk ☐ Urine ☐ Raw camel meat ☐ Cooked camel meat ☐ Other (specify): ☐ None
Participant uses camel products for medicinal purposes	☐ Yes ☐ No ☐ Unknown If Yes, which products: ☐ Camel milk (to drink) ☐ Camel urine (to drink) ☐ Medication (e.g. pills, poultice) containing camel products ☐ Other, specify: _____ If Yes, describe further details of use (e.g. method of ingestion and/or other use, illness being treated):

In the last 6 months, how often on average did you consume or handle any of the following:							
	Daily	At least once per week	Less than once a week but more than once a month	Less than once per month but several times in the last 6 months	Never	Unknown	Answer does not apply to the last 14 days (if ticking this, specify)
Unpasteurized camel milk							
Boiled camel milk							
Camel urine							
Raw camel meat							
Cooked camel meat							
Other camel products (specify)							

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

4. Direct and indirect contact with other animals and livestock (not dromedary camels)	
Was the participant aware of any bats living in or around their home, farm, or regular workplace in the last 6 months?	☐ Yes ☐ Yes, but *not* in the last 14 days ☐ No ☐ Unknown If Yes, specify location
Participant has had other livestock living in or around their home in the last 6 months	☐ Yes ☐ Yes, but *not* in the last 14 days ☐ No ☐ Unknown If Yes, which animals: ☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify: _____
Other members of the participant's household (e.g. relatives or domestic help) frequently have had direct contact with other livestock in the last 6 months	☐ Yes ☐ Yes, but *not* in the last 14 days ☐ No ☐ Unknown If Yes, which animals: ☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify: _____
Participant personally participated in the slaughter of any other livestock in the 14 days before the case's illness onset	☐ Yes ☐ No ☐ Unknown If Yes, which animal(s)" ☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify: If Yes, was there any indication that the animal(s) slaughtered had been sick? ☐ Yes ☐ No ☐ Unknown If Yes (sick animal slaughtered) please specify which animal: ☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify:

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

During the last 6 months, how often on average has the participant had direct physical contact with other livestock	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
During the last 6 months, how often on average has the participant visited animal markets that sold other livestock	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
During the last 6 months, how often on average has the participant visited farms that had other livestock	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown
During the last 6 months, how often on average has the participant visited abattoirs that slaughtered other livestock	☐ Daily ☐ At least once per week ☐ At least once per month but less than once per week ☐ At least several times in the last 6 months but less than once per month ☐ Never ☐ Unknown

Exposures to other livestock within the last 14 days (tick all that apply)	Location of venue (town, country)	Animals present	Direct contact?	Contact with animal carcasses, body fluids, secretions, urine or excrement?
Visit an animal farm ☐		☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify:	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Visit an animal market ☐		☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify:	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown
Visit a slaughterhouse ☐		☐ Goat ☐ Sheep ☐ Horse ☐ Cattle ☐ Other, specify:	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

5. Other food exposures	
In the 14 days before the onset of the case's illness, did you eat any fresh fruits?	☐ Yes ☐ No ☐ Unknown If Yes, specify which fruits:
In the 14 days before the onset of the case's illness, did you eat any dried fruits?	☐ Yes ☐ No ☐ Unknown If Yes, specify which dried fruits:
In the 14 days before the onset of the case's illness, did you eat any raw dates?	☐ Yes ☐ No ☐ Unknown
In the 14 days before the onset of the case's illness, did you eat any vegetables?	☐ Yes ☐ No ☐ Unknown If Yes, specify which vegetables:
In the 14 days before the onset of the case's illness, did you eat any fresh (not canned or processed) fruit or vegetable juices?	☐ Yes ☐ No ☐ Unknown If Yes, specify type:
In the 14 days before the onset of the case's illness, did you eat any uncooked or partially cooked meat?	☐ Yes ☐ No ☐ Unknown If Yes, specify type of animal consumed: If Yes, specify body part consumed (e.g. flesh, blood, etc):
In the 14 days before the onset of the case's illness, did you eat any uncooked liver of any animal?	☐ Yes ☐ No ☐ Unknown If Yes, specify which animal:
In the 14 days before the onset of the case's illness, did you personally cook or otherwise handle raw meat?	☐ Yes ☐ No ☐ Unknown If Yes, specify which type of meat:
In the 14 days before the onset of the case's illness, did you eat any unpasteurized milk or milk products?	☐ Yes ☐ No ☐ Unknown If Yes, specify what products you consumed and from what kind of animals:
Did the participant chew swack during the 14 days prior to the case's onset of illness?	☐ Yes ☐ No ☐ Unknown

Case-control study questionnaire. Part 2 – Participant Exposures (continued)

During the last 6 months how often on average did you consume any of the following products:							
	Daily	At least once per week	Less than once a week but more than once a month	Less than once per month but several times in the last 6 months	Never	Unknown	Answer does not apply to the last 14 days (if ticking this, specify)
Fresh fruit ☐							
Dried fruits ☐							
Fresh salad or vegetables ☐							
Fresh (not canned or processed) fruit or vegetable juices ☐							
Uncooked or partially cooked meat ☐							
Uncooked liver of any animal ☐							
Unpasteurized milk or milk products ☐							

6. End of questionnaire and status of form completion	
Is participant ok with being contacted again with further questions or clarifications	☐ Yes ☐ No
Form completed	☐ Yes ☐ No or partially If No or partially, reason: ☐ Missed ☐ Not attempted ☐ Not performed ☐ Refusal ☐ Other, specify:

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