HUMAN EXPOSURE TO MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS FROM LIVESTOCK OR WILDLIFE SPECIES

A Qualitative Risk Assessment (Exposure)

SUMMARY
The likelihood of humans being exposed to MERS-CoV in affected areas through:

- Direct contact with dromedary camels can be considered
  - Moderate to high (occupational exposure) in MERS-CoV-endemic* regions;
  - Negligible in other regions.
- Handling or consumption of dromedary products (meat and milk), body fluids and excreta can be considered
  - Negligible to low (contamination) for raw milk;
  - Negligible to low (contamination) for raw meat;
  - Negligible for urine or faeces;
  - Nil for pasteurized milk or thoroughly cooked meat.
- Contact with other domestic species can be considered
  - Negligible to low (incidental hosts) for alpacas and llamas;
  - Negligible for goats, swine and rabbits;
  - Nil for cattle, buffalo, chickens, ducks, sheep, Bactrian camels, bank voles, shrews, mice, hamsters and ferrets.
- Contact with bats and other wildlife species can be considered
  - Negligible through direct contact with bats (absence of scientific evidence of MERS-CoV in bats);
  - Negligible through direct contact with non-human primates (lack of evidence of naturally occurring infection; replication restricted to the lower respiratory tract).
- The environment and fomites at the animal-human interface can be considered
  - Negligible.

* Endemicity is defined here as the constant presence of a zoonotic pathogenic agent or health condition affecting animals and/or humans within a given geographic area or population.
INTRODUCTION

Recurrent outbreaks of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in humans have been reported, mainly from the Arabian Peninsula, since 2012, with a notable outbreak in Republic of Korea from May through July 2015.

To evaluate the role of domestic and wild animals, in particular dromedary camels and bats, and assess the likelihood of human exposure¹ to MERS-CoV (i) through direct contact with these animals, (ii) while handling and consuming their products (milk, meat, urine) and (iii) from the environment at the animal-human interface (e.g. farms, households, slaughterhouses, markets, etc.), FAO prepared the following qualitative release assessment.

This assessment is based on information available as of 19 May 2017 and will be revised as circumstances change. It focuses on livestock-related aspects² and is therefore restricted to an exposure assessment at the animal-human interface (i.e. a description of biological pathways necessary for exposure of humans to MERS-CoV released from animals and the estimation of its probability). For further aspects of the human infection and detailed consequence assessments, please refer to risk assessments by the World Health Organization (WHO)³.

The reader should note that the overall uncertainty in the assessment is considered high, since many data gaps remain (See Annex 2). Our understanding of MERS-CoV epidemiology still requires improvement in order to be able to provide a more precise assessment of risk to human health.

The detailed background information used to conduct this qualitative risk assessment can be found in Annex 1.

RISK QUESTIONS ADDRESSED

What is the likelihood of humans being exposed to MERS-CoV in affected areas through⁴:

a. Direct contact with dromedary camels;
b. Handling or consumption of dromedary products (meat and milk), body fluids and excreta;
c. Contact with other domestic species;
d. Contact with bats and other wildlife species;
e. The environment and fomites at the animal-human interface?

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¹ Exposure: to come into contact with a pathogen, in this case MERS-CoV.
² Please note that aspects of human-to-human transmission are not considered in this assessment.
³ WHO updates and other material (e.g. maps and epicurves) can be accessed at: http://www.who.int/emergencies/mers-cov/en/
⁴ Because of current knowledge gaps on the existence of seasonal patterns in the transmission of MERS-CoV in the animal reservoir, we did not include any time reference regarding the likelihood of humans being exposed to the virus in affected areas.
Results of studies currently available indicate contact (direct or indirect) with infected dromedary camels as the main probable source of primary infection for humans (Gossner et al., 2014).

According to current knowledge and based on the scientific evidence available, dromedary camels are considered the primary reservoir hosts of MERS-CoV (Mohd et al., 2016; Nowotny and Kolodziejek, 2014). The role of other species including bats in the reservoir system is not fully known but is considered to be minor (see section c. on contact with other species).

Events that involve increased human exposure to dromedary camels (e.g. camel racing, religious gatherings, festivals, camel shows, etc.) have not been thoroughly investigated.

MERS-CoV viral nucleic acids are more frequently detected in juvenile than in adult animals. Calves may be a source of infection for humans after the fourth month of life, when MERS-CoV specific antibodies begin to wane, and during the first year of life in endemic regions. This is the period when calves appear to be more susceptible to MERS-CoV infections due to their naïve immunological systems (Alagaili et al., 2014; Meyer et al., 2016).

The exact route(s) of transmission is (are) not well understood. However, based on findings from epidemiological studies and surveillance to date, it can be assumed that MERS-CoV spills over to humans through direct contact with infected dromedary camels (Mohd et al., 2016).

Environmental conditions are thought to affect MERS-CoV transmission from dromedary camels to humans as suggested by environmental niche models for MERS-CoV transmission risk (Reeves et al., 2015).

The livelihoods of pastoralists are entirely dependent on camels, implying a close interaction (i.e. direct and prolonged contact) on a day-to-day basis. Therefore, the likelihood of humans being exposed to MERS-CoV in affected areas through contact with dromedary camels can be considered:

- **Moderate to high** in MERS-CoV-endemic\(^5\) regions, with higher risk for people in regular close contact with these animals (e.g. occupational exposure);
- **Negligible** in regions where no positive samples have been detected through serological or virological testing in dromedary camels.

\(^5\) Endemicity is defined here as the constant presence of a zoonotic pathogenic agent or health condition affecting animals and/or humans within a given geographic area or population.
More than half of the reported human cases result from secondary human-to-human transmission in health care settings, as multiple nosocomial outbreaks have been identified since the emergence of MERS-CoV (Kahn et al., 2016; WHO, 2016).

b. Handling or consumption of dromedary products (meat and milk), body fluids and excreta

Considering that:

- As described in section a., the absence of systemic replication and viremia, and the concentration of the virus in the upper respiratory tract indicate that there is unlikely to be hematogenous spread of MERS-CoV in dromedary camels to extra-respiratory tissues, and therefore infectious virus is unlikely to be found in other body compartments or products such as meat, milk and urine.
- No infectious virus or viral ribonucleic acid (RNA) was detected in any serum or whole blood samples (Adney et al., 2014).

Milk

- Most camel milk in Saudi Arabia is produced for own consumption and small-scale commerce, and is mainly consumed raw or fermented (Faye, 2016) (Calistri, personal communication, 2017).
- MERS-CoV RNA was demonstrated in dromedary camel milk samples from dams shedding the virus. However, it is not clear if the virus was excreted in the milk or if the milk was contaminated through the milking process or by an infected suckling calf (Gossner et al., 2014; Reusken et al., 2014).
- Milk contaminated with MERS-CoV (camel, goat or cow), can survive for prolonged periods (72 hours when stored at 4 °C or 48 hours at 22 °C) (van Doremalen et al., 2014).
- Since camels are milked under less-than-optimal hygienic conditions (i.e. the udder is rarely cleaned before milking, so the source of virus could be through secondary infections), raw milk could be a medium for human infection following contamination.
- In order to stimulate milk production, the newborn calf is often left to suckle the dam. If the calf is infected with MERS-CoV, it can be considered a potential source of contamination of milk (Reusken et al., 2014).
- Pasteurized milk is safe to handle and consume. Virus particles are destroyed by heat treatment at 63 °C for 30 minutes (van Doremalen et al., 2014; WHO, 2015a).

Meat

- Camel meat is an important animal product and is mostly consumed in North Africa, the Arabian Peninsula and China (Faye and Bonnet, 2012).
• While there is no evidence to date of MERS-CoV in camel meat, by extrapolation from what is known about other similar viruses like Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), it is possible that the fall in pH of meat with maturation inactivates the virus (Rabenau et al., 2005) and that proper cooking kills the virus, given that virus particles are destroyed by heat treatment (van Doremalen et al., 2014; WHO, 2015a; Gossner et al., 2014).6

Urine

• Camel urine is considered as having medicinal properties, especially among Bedouins and camel-herding people. It is used to wash the hands, face and hair and is also consumed, sometimes mixed with fresh milk (Gossner et al., 2014).
• Low titres of MERS-CoV virus RNA have been found in the urine samples of an infected human (Drosten et al., 2013; Gossner et al., 2014).
• In experimentally inoculated dromedary camels, none of the camels shed viral RNA through urine (Adney et al., 2014).

Faeces

• Livestock faeces (including those from camels) are used as fertilizer in MERS-CoV-endemic regions (Bhakat and Sahani, 2006).
• To date, MERS-CoV RNA has not been detected in faeces or rectal swabs using reverse transcription polymerase chain reaction (RT-PCR) (Haagmans et al., 2014; Hemida et al., 2014; Meyer et al., 2014; Reusken et al., 2014; Sabir et al., 2015).

Therefore, the likelihood of humans being exposed to MERS-CoV in affected areas through handling or consumption of dromedary products (meat and milk), body fluids and excreta can be considered:

• negligible to low for raw milk when considering the possibility of milk contamination with the virus through calves (i.e. suckling), udder contamination or through milkers’ hands in pastoral regions; negligible for milk collected under hygienic conditions, considering that virus shedding through milk is unlikely to occur;

• negligible to low for raw meat due to cross-contamination while handling the carcasses and preparing the meat in slaughterhouse and non-slaughterhouse facilities;

• negligible for urine, which could be cross-contaminated like raw milk and meat;

• negligible for faeces;

• nil for pasteurized milk, if following FAO’s recommendations on food preparation and consumption, avoiding cross-contamination;

• nil for thoroughly cooked meat, if following FAO’s recommendations for food preparation and consumption, avoiding cross-contamination (as with Salmonella sp. or E. coli).

This risk evaluation is associated with a high degree of uncertainty due to the limited studies conducted in this area to date (Annex 2).

c. Contact with other domestic species

Considering that:

• No antibodies were found during field surveys in: goats (Perera et al. 2013, Hemida et al., 2013, Reusken et al., 2013, Buchholz et al., 2013); cattle, sheep (Perera et al., 2013, Hemida et al., 2013, Reusken et al., 2013); chickens (Hemida et al., 2013); swine, ducks, buffalo (Perera et al., 2013) and equids (Meyer et al., 2015).

• Experimentally infected young goats showed seroconversion to MERS-CoV (Adney et al., 2016b).

• MERS-CoV specific Immunoglobulin G (IgG) antibodies were also found in alpacas (Vicugna pacos) in the Al-Shahaniya region of Qatar (endemic region) (Reusken et al., 2016). However, no human cases were shown to be related to exposure to alpacas.

• Presence of virus shedding and neutralizing antibodies against MERS-CoV was confirmed in experimentally infected alpacas (Crameri et al., 2016), as well as in alpacas in close contact with them (Adney et al., 2016). Also, in vitro replication (Eckerle et al., 2014) and virus excretion (Vergara-Alert et al., 2017) were observed in experimentally infected llamas (Llama pacos).

To date, MERS-CoV specific antibodies have mostly been detected in dromedary camels (Mohd et al., 2016). Surveys conducted on MERS-CoV in Bactrian camels (Camelus bactrianus) in Kazakhstan have demonstrated absence of the virus. A total of 550 camels (455 dromedaries and 95 bactrians) were sampled from four different regions. The representativeness of the sample size in the camel population in this area is not indicated in this study. Sera samples were analysed using the MERS-CoV spike protein pseudoparticle neutralization test and no positive results were found (Miguel et al., 2016).

• No neutralizing antibodies against MERS-CoV have been detected so far in camelids outside Africa or the Middle East, i.e. the United States and Canada (Alexandersen et al., 2014; n=6), Europe (except the Canary Islands) (Meyer et al., 2014; n=16; Reusken et al., 2013) Kazakhstan (Miguel et al., 2016; n=550) and Australia (Hemida et al., 2014); n=25).

• The virus was shown not to replicate in vitro using sheep, bank voles (Myodes glareolus), shrews (Crocidura...
suaveolens), cattle (Eckerle et al., 2014); mice (Coleman et al., 2014); hamsters (de Wit et al., 2013) and ferrets (Mustela putorius furo) cells (Raj et al., 2014), nor was it shown to replicate in vivo in studies conducted on ferrets (Raj et al., 2014).

- In vivo replication was observed in goats (Eckerle et al., 2014) and rabbits (Haagmans et al., 2015).
- Experimentally infected rabbits (Haagmans et al., 2015) and pigs (Vergara-Alert et al., 2017) excreted infectious virus from the upper respiratory tract; however, it remains to be investigated if rabbits and pigs in MERS-CoV-endemic areas have sufficient opportunity for exposure to camels in order to become infected and, further, if they could be a source of infection for humans.
- So far, no research has been carried out for non-livestock domestic animals (i.e. cats and dogs).
- It is highly unlikely that other animal species act as maintenance hosts for MERS-CoV due to the lack of serological and virological findings.

Therefore, the likelihood of humans being exposed to MERS-CoV in affected areas through contact with other domestic species can be considered:

- negligible to low for alpacas and llamas as they can be incidental hosts;
- negligible for goats, swine and rabbits;
- nil for cattle, buffalo, chickens, ducks, sheep, Bactrian camels, bank voles, shrews, mice, hamsters and ferrets.

For assessing the risk from non-livestock species (cats, dogs) the information available is insufficient due to the fact that there is no further research about prevalence of the virus in these species.

d. Contact with bats or other wildlife species
Considering that:

- There are over 900 species of bats around the world, making up about one quarter of all mammal species. They live in very diverse ecosystems, with different ecobehaviours and food preferences.
- Bats are known to host a wide diversity of coronaviruses (Munster et al., 2016).
- Bats have been found to carry coronaviruses with genetic similarity to MERS-CoV (de Wit et al., 2013). MERS-related CoVs RNA have been found in roost faeces, faecal pellets and rectal swab samples of the following bat families: Emballonuridae (Taphozous perforatus), Pteropodidae (Eidolon helvum), Rhinopomatidae (Rhinopoma hardwickii), Vespertilionidae (Pipistrellus kuhlii) (Memish et al., 2013; Anthony et al., 2017; Chan et al., 2011).
- Findings of MERS-related CoVs were obtained in regions without confirmed human or animal MERS-CoV infections (ten different species from Ghana and Pipistrellus spp from European countries) (Mohd et al., 2016).
- MERS-related CoVs microscopic lesions were also found in the respiratory tract during bat necropsies. None of the animals showed clinical signs (Munster et al., 2016); there is no clinical disease in infected bats reported to date (Shehata et al., 2016).
- Novel lineage C betacoronavirus closely related to human MERS-CoV and camel MERS-CoV was identified in Vespertilio superans bats (Yang et al., 2015).
- To date, no infectious MERS-CoV has been isolated from bats. The first and only identification of MERS-CoV in one Egyptian tomb bat (Taphozous perforatus) presented total nucleotide identity with the virus from a linked human index case patient after PCR amplification in Saudi Arabia. However, MERS-CoV was not successfully cultured (Memish et al., 2013).
- MERS-CoV has not been detected in bats in China (Du et al., 2016), Saudi Arabia (Memish et al., 2013), Lebanon and Egypt (Shehata et al., 2016). Only alpha-CoV genera were found in eastern bent-wing bats (Miniopterus fuliginosus) through PCR assays in different regions in China (Du et al., 2016).
- Experimentally infected Jamaican bats (Artibeus jamaicensis) demonstrated MERS-CoV replication and shedding through the respiratory tract (Munster et al., 2016).
- Laboratory models using African green monkeys (Chlorocebus sabaeus) (Eckerle et al., 2014), rhesus macaques (Macaca mulatta) (de Wit et al. 2013) and common marmosets (Callithrix jacchus) (Falzarano et al., 2014; Johnson et al. 2015) showed in vivo replication.
- Non-human primate experimental models to date do not mimic naturally occurring disease (de Wit et al. 2013). Therefore, the likelihood of humans being exposed to MERS-CoV in affected areas through contact with bat or other wildlife species can be considered:

  - negligible through direct contact with bats due to the absence of scientific evidence of MERS-CoV in bats;
  - negligible through direct contact with non-human primates due to lack of evidence of naturally occurring infection and replication restricted to the lower respiratory tract.

e. The environment and fomites at the animal-human interface
Considering that:

- MERS-RNA, related to human cases, was detected in: anterooms, medical devices, bed sheets, air-ventilating equipment, radiographic devices, bedrails, and intravenous fluid hangers in hospital facilities in Republic of Korea (WHO, 2016). Findings matched with MERS-CoV RNA retrieved from patients through virus sequencing (Seo et al.,
2016). MERS-CoV RNA was also detected on two surfaces in a hospital’s intensive care unit in Saudi Arabia (Khan et al., 2016).

- There is limited data available on how long the MERS-CoV survives on objects and environmental surfaces. One experiment showed longer MERS-CoV survival on surfaces (up to 48 hours) when compared with influenza A (H1N1) viruses (less than four hours), but shorter survival when compared to SARS-CoV (up to five days) (van Doremalen et al., 2013).

Therefore, the likelihood of humans being exposed to MERS-CoV in affected areas through the environment and fomites can be considered:

- negligible for fomites, depending on the level of disinfection.

This risk evaluation is associated with a high degree of uncertainty due to the limited studies conducted in this area to date (Annex 2).

GAPS
To increase precision of the assessment, our understanding of MERS-CoV epidemiology needs to be improved. It is important to note that the uncertainty associated with each of the qualitative risk estimates in this assessment remains high because of significant current information gaps (see Annex 2 for an inventory of gaps and suggestions on how to address them).

EVALUATION OF CONSEQUENCES
As MERS-CoV-infected camels present minimal or no clinical signs, infection may not lead to any negative effects on camel husbandry or production, or to veterinary expenses. Restrictions on camel trade and/or transboundary movements may be applied by affected countries on a case-by-case basis.

The disease in humans can range from no, or mild, respiratory symptoms, to severe acute respiratory syndrome in individuals with co-morbidities. If severe, the disease can lead to respiratory failure requiring intensive care and mechanical ventilation support, which implies high treatment costs. Over 677 human deaths due to MERS-CoV were reported to WHO between April 2012 and February 2017. Absence of patients from their workplace due to disease can be considered a loss, which may be aggravated when nosocomial outbreaks include health care workers.

Camels act as the reservoir for MERS-CoV from which humans can be exposed to the virus, leading to human infection under favourable conditions (environmental and host factors).
Even though the majority of human cases acquired the disease through human-to-human transmission, especially in health care settings, primary human infections (through camel-to-human transmission) do happen regularly.

Camel-importing countries, such as Egypt, therefore implement a testing and quarantine policy to identify active shedders, and camels can be held at border points in Egypt. Animals are kept in public and private quarantine stations between 3 and 14 days. In private quarantine stations, about ten percent of camels are also sero-tested for MERS-CoV. If positive animals are detected within this sample, the rest of the animals are then also tested. Negative animals are released for sale in markets while positive camels are sent to slaughter, which implies direct economic losses to camel traders owing to business being halted, as well as premature slaughtering of seropositive animals.

Some countries also run an active surveillance programme in native camel herds to determine MERS-CoV sero-prevalence and/or identify active shedders. While active surveillance combined with quarantine or elimination of positive animals helps reduce circulation of the virus in dromedary populations, which consequently lowers opportunities for human infection, it involves costs for the veterinary services. These costs include logistics and manpower, sampling equipment, testing materials, transport of samples, laboratory analysis, etc. Control measures may also imply socio-economic costs to camel owners due to standstill of animals until shedding has ceased and additional public health measures taken, such as testing of owners and their family members.

Since no food-borne pathway has been documented for MERS-CoV to date, negative effects on consumer behaviour, such as avoidance of certain camel or livestock products, are not expected unless as a result of consumer misinformation or negative propaganda.

This consequence assessment needs to be further elaborated as research gaps are being filled.

**MITIGATION MEASURES AVAILABLE**

The following mitigation measures should be considered to reduce the risk of human exposure to MERS-CoV from animals:

- Test dromedary camels prior to transport for slaughter and, if found virus-positive (or PCR-positive), do not slaughter but isolate them to avoid virus dissemination until shedding has ceased. A sampling strategy should be utilized to ensure that positive animals are not sent to slaughter (i.e. either with a robust sub-sample that confers a high degree of confidence in a zero-positive herd, or by testing all animals). Once entering the slaughter facilities, animals should be slaughtered and not released alive to farms or

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To date, the duration of shedding is still unknown. Also, if and when intermittent shedding may occur still needs to be confirmed.
markets. As a general public health rule, never slaughter feverish or sick animals for consumption.

- Screen prized camels for the absence of MERS-CoV, or other high-impact disease agents, prior to gatherings (i.e. competitions or shows). Camel identification can be introduced as a practice for facilitating camel movement, traceability and sanitary control.

- For camel-importing countries: strengthen screening of camels at ports of entry, in particular for dromedary camels coming from infected areas, and quarantine virus-positive animals until infection has cleared.\(^7\)

- Isolate PCR-positive animals from other animals and humans until infection has cleared. Positive findings should be reported from farmers, animal markets and slaughterhouses to competent veterinary and public health authorities.

- Implement disinfection protocols in facilities where infected animals were held. As infected camels may not show any clinical signs, general hygiene, with regular cleaning and disinfection, is recommended for any camel holding, live animal market, slaughterhouse or similar facility.

WHO provides a MERS-CoV factsheet which advises on methods to prevent human infection (WHO, 2015a):

- Wash hands with soap often to inactivate and remove any virus. This should always be done after handling dromedary camels.

- For camel farms, slaughterhouse, racing and market workers: wear protective clothing, which should be removed after work and washed daily. Avoid exposure of people to soiled work clothing, shoes, or other items that may have come into contact with camels or camel excretions.

- In MERS-CoV enzootic areas, implement enhanced hygiene and biosecurity procedures for juvenile camels (<2 years of age) which seem to be most at risk of active infection. Also, personal protection of people in regular close contact with this camel age-class should be considered, such as wearing face masks and gloves.

- Promote public health services to people showing clinical signs of fever or respiratory symptoms after being in contact with dromedary camels.

- As zoonotic transmission pathways have yet to be elucidated, the possibility of food-borne transmission cannot, to date, be excluded. Eat only well-cooked camel products, prepared under hygienic conditions, and avoid consumption of raw meat, milk or urine.

- The Codex Alimentarius provides General Principles of Food Hygiene (Codex, 2003).

- Develop communication strategies to ensure appropriate and science-based messages to the public on MERS-CoV and associated risks.

- Engage with the private sector (racing associations, breeding enterprises, meat packing, etc.) to ensure input, improved communication, and compliance with the measures suggested.

### Annex 1

**BACKGROUND INFORMATION USED**

- In 2012, a newly emerged human pathogenic coronavirus (CoV) caused a still-ongoing human epidemic in the Arabian Peninsula. The novel coronavirus, designated Middle East Respiratory Syndrome (MERS-CoV), belongs to the lineage C beta coronavirus, closely related genotype with bat CoVs from the same lineage (Mohd et al., 2016).

- MERS-CoV in humans was first reported in September 2012 in Saudi Arabia. Retrospectively, health officials identified the first known cases in Jordan in April 2012.

- Coronavirus is a family in the order Nidovirales, enveloped and RNA-positive stranded virus. They possess a spike protein on the surface and can be classified in subfamilies: alpha, beta, gamma and delta.

- The clinical presentation of MERS-CoV infection in humans ranges from asymptomatic to very severe pneumonia with acute respiratory distress syndrome, septic shock and multi-organ failure resulting in death.

- The clinical presentation of MERS-CoV in camels is usually asymptomatic or is marked by mild respiratory signs.

- The number of human cases reported by the World Health Organization was 1 980, including 699 deaths, as of 8 June 2017. Around 157 of all reported human cases were estimated to be primary cases. Considering the high case fatality rate of MERS-CoV in human patients and the non-availability of preventive vaccines or viral treatments, the disease remains a public health concern (Mohd et al., 2016).

- MERS-CoV has spread to many countries but most of the human cases are linked to the Arabian Peninsula, where new outbreaks continue to occur. The countries presenting human cases are: Algeria*, Austria*, Bahrain, China*, Egypt*, France*, Germany*, Greece*, Iran, Italy*, Jordan, Kuwait, Lebanon*, Malaysia*, Netherlands*, Oman, Philippines*, Qatar, Republic of Korea, Saudi Arabia, Thailand*, Tunisia, Turkey, United Arab Emirates, United Kingdom*, United States of America* and Yemen.

- The origin of the virus remains under research but epidemiological studies show that dromedary camels are likely to be the main reservoir of infection.

- Antibodies against MERS-CoV have been detected in dromedary camels in:

- Canary Islands (Reusken et al., 2013)

\(^7\) (*) denotes cases with travel to/through the Middle East/Arabian Peninsula.
- Egypt (Chu et al., 2014; Perera et al., 2014; Muller et al., 2015)
- Ethiopia (Reusken et al., 2014)
- Jordan (Reusken et al., 2013)
- Kenya (Deem et al., 2015; Corman et al., 2014)
- Kuwait (OIF, 2014)
- Nigeria (Reusken et al., 2014; Chu et al., 2015)
- Oman (Reusken et al., 2013)
- Pakistan (Saqib et al., 2017)
- Qatar (Reusken et al., 2014; Haagmans et al., 2014; Miguel et al., 2016)
- Saudi Arabia (Hemida et al., 2014; Alagaili et al., 2014; Hemida et al., 2013; Memish et al., 2014)
- Tunisia (Reusken et al., 2014)
- United Arab Emirates (Wernery et al., 2015; Alexandraen et al., 2014; Meyer et al., 2014)
- Somalia (Muller et al., 2015)
- Sudan (Muller et al., 2015).

• Animals from the United States of America and Canada (Alexandraen et al., 2014), Europe (except from Canary Islands) (Reusken et al., 2013; Meyer et al., 2013), Kazakhstan (Miguel et al., 2015) and Australia (Hemida et al., 2014) have not presented antibodies against MERS-CoV:
  - (Alexandraen et al., 2014): sequential serum samples from dromedary camels (11), sheep (3) and horses (3) collected in Dubai (2005) and from dromedary camels (6) for export/import testing between Canada and USA in (2000-2001) were tested. Nine out of 11 dromedary camels from Dubai tested positive for MERS-CoV through neutralization test and ELISA. None of the dromedary camels tested in North America showed positive findings. These animals were imported from Australia around the 1990s when import was allowed. A geographic separation between Australian, Middle Eastern and Asian dromedary camel populations can be noted.
  - (Hemida et al., 2014): sera collected from 25 adult dromedary camels in Australia (17 feral dromedaries from central Australia transported to an abattoir in Caboolture, Queensland, and eight from a dromedary farm in Coominya, Queensland) in 2014; slaughterhouses in Egypt in 2014; and archived sera from the King Faisal University collected in 1993 from different provinces in Saudi Arabia (Al Hasa, Eastern Province (27); As Sulayyil, Ar Riyadh province (30); Hafar Al-Batin, Eastern Province (45) and Medina, Al Medinah (29)). No positive findings were found in Australian samples.
  - Virological evidence of MERS-CoV in dromedary camels has been detected in:
    - Egypt (Chu et al., 2014)
    - Oman (Nowotny et al., 2014)
    - Qatar (Haagmans et al., 2014; Raj et al., 2014)
    - Saudi Arabia (Hemida et al., 2015; Hemida et al., 2014; Alagaili et al., 2014; Meyer et al., 2014; Sabir et al., 2016; Memish et al., 2014)
    - United Arab Emirates (Wernery et al., 2015).

• Considering epidemiological patterns, when it comes to:
  - Age distribution: i. dromedary camel infection probably between Australian, Middle Eastern and Asian dromedary camel populations can be noted.
  - Epidemiological factors: no statistical effect observed considering prevalence (Deem et al., 2015) in different production systems (commercial herds, commercial/pastoralist herds or nomadic herds) or based on herd isolation (high, intermediate and low isolation levels).

• No antibodies were found in: goats (Perera et al., 2013, Hemida et al., 2013, Reusken et al., 2013, Buchholz et al., 2013); cattle, sheep (Perera et al., 2013, Hemida et al., 2013, Reusken et al., 2013); chickens (Hemida et al., 2013); swine, ducks, buffalo (Perera et al., 2013) and equids (Meyer et al., 2015):

Goats
- No positives found during screening of sera collected from goats in Egypt with micro-neutralization test (Perera et al., 2013);
- No positives found during screening of 45 animal sera in Saudi Arabia with pseudoparticle neutralization test (Al-Ahsa = 15, Taif = 10, Madinah = 10 and Qatif = 10) (Hemida et al., 2013);
- No antibody reaction against IgG MERS-CoV antibodies in sera samples from 150 goats sampled in Zarqa and Mafraq, Jordan (Reusken et al., 2013).

Equids
- A total of 1053 sera samples were collected from equids in MERS-CoV- endemic and non-endemic areas in United Arab Emirates (192 horses) and Spain (697 horses, 82 donkeys and 82 mules) were analysed and submitted to ELISA test using spike protein S1-domain as antigen: all showed similarities between the amino acid residues critical for virus entry between humans and horses DPP-4 (Meyer et al., 2015).
- No reactivity observed in recombinant immunofluorescent or micro-neutralization assays, suggesting no precedent exposure to MERS-CoV in the countries studied. The 50 most reactive tests were confirmed by micro-neutralization and recombinant immunofluorescent assays (Meyer et al., 2015).

Cattle
- No positives found during screening of sera collected from cows in Egypt with micro-neutralization test (Perera et al., 2013);
• No positives found during screening of sera collected from 50 animals in Saudi Arabia with pseudoparticle neutralization essay (Al-Ahsa = 17, Taif = 13, Madinah = 10 and Qatif = 10) (Hemida et al., 2013);
• No IgG antibody reactivity in sera of 91 cows sampled in Jordan (Zarqa and Mafraq) (Reusken et al., 2013).

Buffalo
• No positives found during screening of sera collected from water buffalo in Egypt with a micro-neutralization test (Perera et al., 2013).

Chickens
• No positives found during screening of sera from 240 chickens sampled in Saudi Arabia with pseudoparticle neutralization assay at 1:20 dilution (Al-Ahsa = 120, Dammam and Alkhober = 80, Abqaiq = 40) (Hemida et al., 2013).

Swine
• No neutralizing activity for MERS-CoV in micro-neutralization assays used on swine sera collected in Hong Kong (Perera et al., 2013).

Ducks
• No neutralizing activity for MERS-CoV in micro-neutralization assays used on wild northern pintails (Anas acuta) or Eurasian wigeon (Anas Penelope) sera collected in Hong Kong (Perera et al., 2013).

Sheep
• No positive results when screening sera collected from sheep in Egypt with a micro-neutralization test (Perera et al., 2013).
• In Saudi Arabia (Al-Ahsa) a total of 100 sheep were sera-sampled and none were positive for pseudoparticle neutralization test (Hemida et al., 2013).
• A total of 126 Awassi-breed sheep were sampled in Jordan in the regions of Zarqa and Mafraq from June to September 2013. The study presented males and females from all ages and sera, and faecal samples were collected from all animals. Samples were tested for the presence of IgG antibodies against MERS-CoV. Six out of 126 sera presented antibodies against MERS-CoV S1 antigen. However, no neutralizing activity was observed on the positive samples in neutralization assay (Reusken et al., 2013).
• The virus did not replicate in in vitro studies conducted on sheep, bank voles (Myodes glareolus), shrews (Crocidura suaveolens), cattle (Eckerle et al., 2014); mice (Coleman et al., 2014); hamsters (de Wit, et al., 2013) and ferrets (Mustela putorius furo) (Raj et al., 2014). Nor did it do so in in vivo studies conducted due to lack of evidence of naturally occurring infection. Non-human primate experimental models to date do not mimic naturally occurring disease in ferrets.

Although experimentally infected young goats showed seroconversion to MERS-CoV, serological field surveys in goat populations have not revealed any MERS-CoV positive animals to date.
- (Eckerle et al., 2014): cultivation of cell lines from goats, sheep, cattle, camelids (dromedary and alpaca), rodents, insectivores, bats, human and non-human primates and bat and primate cells were used as controls because they are known to be permissive to MERS-CoV. The quantification of the virus replication was done by RT-PCR. Replication was not observed in sheep, cattle, rodent or insectivore cells.

- (Coleman et al., 2014): MERS-CoV (strain HCoV-EMC/2012) was inoculated intranasally into 129 mice (BALB/c, 129S6/SvEv and 129/STAT12/2 species). Infected mouse lungs were tested by TCID assay and no signs of viral replication were identified. The experiment also handled an RT-PCR assay for lung cells with negative results for genomic sequencing.

- (de Wit, et al., 2013): three groups of 40 hamsters each were experimentally infected with MERS-m (HCoV-EMC/2012) with different doses and different means of administration (4x102 TCID50 via aerosols; 103 TCID50 and 106 TCID50 intratracheally). The animals were observed for 21 days for clinical signs, body weight and temperature. All showed disease symptoms, increase of body temperature and weight loss. Swabs (nasal, urogenital, rectal and oropharyngeal) were daily taken until day 11. After histopathological analysis, immunohistochemistry assays in lungs, kidney small intestine, colon and urinary bladder by using an α-DPP4 antibody; RNA extraction; RT-PCR upE assay and ELISA test no cell replication was observed.

- (Raj et al., 2014): in vitro and in vivo experiments were conducted on four ferrets. Animals were intranasally and intratracheally inoculated with MERS-CoV. After infection, RT-qPCR detected low levels of viral RNA inputs and no infectious virus. In vivo bind of recombinant protein spike S1 was observed.

- (Vergara-Alert et al., 2017): virus excretion confirmed through PCR, titration of infectious virus, immunohistochemistry, and in situ hybridization in nasal swabs of pigs and llamas. Pigs showed mild clinical respiratory signs and white mucus excretion. Seroconversion was also detected in both species. Findings show susceptibility of species regarding MERS-CoV infection. Sheep and horses did not have any viral replication in the upper respiratory tract. The study population was composed of eight llamas (6–8 months of age), eight horses (6–8 months), 14 sheep (2–3 months), and 14 pigs (two months). Animals were obtained from Spain and France (private sales). All animals were intranasally inoculated and monitored daily for clinical signs (e.g. sneezing, coughing, nasal discharge, dyspnoea) and body temperature. Sampling
(nasal and faecal swabs and sera samples) were obtained until day 24 post-inoculation and sera samples were tested before and after inoculation.

- **Bactrian camels (Camelus bactrianus)** in Kazakhstan tested negative to MERS-CoV. A total of 550 camels (455 dromedary and 95 bacterian) were sampled in Kyzylorda (105 animals from two herds), Zanakorgan (35 animals from one herd), Sholak-Korgan (110 animals from two herds), and Akshiy (205 animals from four herds). Sera samples were submitted to MERS-CoV spike pseudoparticle neutralization test and no positive results were found (Miguel et al., 2016).

- **Virus neutralization tests (VNT) titres for dromedary camels** were much higher than those for the alpacas. In Australia, three female alpacas from a commercial supplier were experimentally infected with a camel isolate of MERS-CoV passing through challenge and rechallenge. Animals were oronasally exposed and observed for 21 days; for re-exposure another 14 days. RNA extraction and RT-PCR were performed (Crameri et al., 2016).

- **Laboratory models tested:**
  - Marmosets used as an animal model representative of severe human infection with MERS-CoV. Infection and disease after oropharyngeal inoculation, resulting in extensive lesions in lungs, virus replication, seroconversion in surviving marmosets and death (seven out of nine) was reported by one group (Falzarano et al., 2014). However, other groups were unable to repeat this result and reported only limited viral replication and mild or moderate clinical signs (Johnson et al., 2015).
  - Cynomologous macaques (*Macaca fascicularis*) presented mild macroscopic and microscopic lesions in the respiratory tract after intranasal and intratracheal inoculation with MERS-CoV.
  - Rhesus macaques (*Macaca mulatta*) used as animal model representative of mild human infection with MERS-CoV. Infection and disease reported after oropharyngeal inoculation. Virus replication was observed mainly in the lower respiratory tract. Virus shedding predominantly happened through the nose and, to a limited extent, the throat. In macaques, the disease seems to be transient and is more comparable to mild human cases (de Wit, Rasmussen, et al., 2013).

### Bats

- No infectious virus MERS-CoV findings confirmed in bats to date. First and only identification of MERS-CoV in one Egyptian tomb bat (*Taphozous perforatus*) in 1 out of 29 bats sampled in Bisha Ruins (Saudi Arabia). However, MERS-CoV was not successfully cultured (Memish et al., 2013).

- Experimentally infected Jamaican bats (*Artibeus jamaicensis*) showed replication and shedding through the respiratory tract. MERS-CoV-related lesions were also found in the respiratory tract during necropsy. None of the animals showed clinical signs (Munster et al., 2016).

- **MERS-related CoVs have reportedly been found in bat families:** Emballonuridae (*Taphozous perforatus*), Pteropodidae (*Eidolon helvum*), Rhinopomatidae (*Rh. Hardwickeii*), Vespertilionidae (*P. kuhlii*) (Memish et al., 2013; Anthony et al., 2017).

- Detection of MERS-related CoVs in: oral, rectal, lung and liver samples in cave-dwelling bat species in Lebanon and Egypt (Shehata et al., 2016).

- So far, MERS-related CoVs were found in regions with no cases of human or animal infections.

- A total of 5 030 faecal samples from bats (4 758 from ten different species from Ghana and 272 Pipistrellus from European countries) were submitted to RT-PCR for coronavirus RNA detection. In Ghana, 185 Nycteris bats tested positive to 2c betacoronavirus (1 percent of the tested population); as for Europe, 40 bats tested positive for this close-related MERS-CoV (Mohd et al., 2016).

- Only alpha-CoV genera found in *M. fuliginous* bats through PCR assays in different regions in China (Du et al., 2016).

- Like human CoV-229E and SARS-CoV, ancestors of MERS-CoV might exist in Old World insectivorous bats belonging to the family Vespertilionidae. Knowledge of the close relatedness of PML/2011 (a positive specimen with a novel betacoronavirus termed in 2011) and MERS-CoV, which contrasts with the more distant relatedness of CoVs in bats from the Americas and Asia, raises the possibility of an African origin for bat reservoir hosts of MERS-CoV ancestors (Ithe et al., 2013).

- Two MERS-like viruses in bats revealed two mutations in the spike that allow bat viruses to infect human cells (adaptation of human cellular protease). The two mutations were similar to others found to allow the virus that causes SARS to jump from animals to humans (receptor binding). Although MERS-CoV spike might also need to adapt to human DPP4 receptor upon infecting human cells, such adaptations might only have incremental effects on the infectivity of MERS-CoV in human cells. In contrast, the two mutations adaptive to human cellular proteases transformed MERS-CoV spike from completely lacking to fully owning the capacity to mediate viral entry into human cells, and thus they likely played the most critical role in the bat-to-human transmission of MERS-CoV (Yang et al., 2015).

- **MERS-CoV remains viable for 48 hours at 20 °C and 40% relative humidity (comparable to an indoor environment) on plastic and metal surfaces.** The viral particles are sensitive to
heat, lipid solvents, non-ionic detergents, oxidizing agents and ultraviolet light (van Doremalen et al., 2013).

- Considering the outcomes of Meyer et al., (2016), newborn dromedaries can be a source of infection for humans after the fourth month of life, when MERS-CoV specific colostral-derived antibodies wane, and during the first year of life in endemic regions. This period is when calves are most susceptible to MERS-CoV infections due to their naïve immunological systems.

- Dromedary camels are seasonal breeders based on photosensitivity, usually when day length decreases. Different periods are reported in different regions of the world (Al Eknah, 2000):
  - Arabian Peninsula: November-March
  - Egypt: December-May
  - India: November-March
  - Pakistan: December-March
  - Somalia: April-May
  - Sudan: March-August
  - Saudi Arabia: October-April
  - Tunisia: December-March.

- Based on data from Hijmans et al., (2005), in 2015 Reeves et al. developed models related to the ecology and geography of MERS-CoV to explore environmental association patterns and possible implications for the geography of MERS-CoV transmission. Two niche models were developed, one for all cases and another for cases with reported dromedary camel contact only. Real and modelled occurrences were compared. The first model showed a broader distribution across the Arabian Peninsula, Africa and some areas in Asia. As for the second model, a concentration in Saudi Arabia was noticed. Both models were submitted to the annual mean temperature and precipitation levels of the studied region. These models represent and reconstruct the relationship between environmental and occurrence data, showing a restricted set of environmental conditions for the transmission of MERS-CoV in primary cases (those exposed to dromedary camels).

- There remains a lack of studies related to dromedary camel production systems and animal trade in terms of risk of virus introduction or spread. It is known that nomadic production systems tend to have bigger animal movement through different regions. From an epidemiological point of view, as for other diseases, animal trade can be an important point for disease spread when it comes to livestock. Also, camel racing can attract a variety of animals from different regions and increase contact between contaminated and healthy animals.
Annex 2
ADDRESSING INFORMATION GAPS

a. Addressing information gaps related to human exposure from dromedary camels

- Further studies are needed to understand why human cases are reported from the Arabian Peninsula but not from Africa, despite endemic MERS-CoV circulation evidenced in dromedary camels in both areas.
- Conduct serological studies in human populations in areas where MERS-CoV is endemic in dromedary camels.
- Properly investigate and document events that involve increased human exposure to MERS-CoV from dromedary camels.
- Identify critical points in livestock value and supply chains to implement risk reduction measures.
- Further research is needed to better understand risk factors that facilitate human exposure to MERS-CoV from dromedary camels, such as farming systems, human behaviour, agro-ecological factors, climate, etc.

b. Addressing information gaps related to MERS-CoV transmission

- Conduct studies to understand the direction of transmission, potential pathways, and factors that may increase infection risk within dromedary herds and between dromedaries and humans.
- Determine incubation period as well as amount of MERS-CoV shedding in dromedary camels.
- Conduct specific studies to investigate MERS-CoV occurrence and survival in meat (i.e. investigate virus persistence in the environment and virus inactivation in meat) and/or potential MERS-CoV excretion through milk and urine.
- Conduct studies to investigate MERS-CoV occurrence and survival in carcasses, placenta and body fluids.
- Conduct studies to investigate MERS-CoV survival in different climatic conditions, agro-ecological and farming systems (i.e. humidity, ambient temperature, etc.); such factors are important to consider in droplet-transmitted diseases.
• Conduct studies to investigate the transmission of the virus through fomites, water, while handling laboratory specimens or during necropsies.

c. Addressing information gaps related to MERS-CoV host species

• Conduct field studies to investigate other potential host species and relationships between different host populations that may facilitate spillover and/or zoonotic disease transmission. E.g. targeted bat surveys performed to date in MERS-CoV-endemic regions are lacking description of vicinity to dromedary camel and/or human populations and geographical distribution of populations (humans, bats and dromedary camels); differences between camel breeds.

• Conduct controlled infection experiments to understand pathogenesis and immunity in different animal species. Conduct surveillance and screening in different bat species, particularly in MERS-CoV endemic regions. Considering the high number of bat species that have not been investigated yet, more research is warranted to confidently claim MERS-CoV absence.

The following activities should be promoted to help fill knowledge gaps in understanding human MERS-CoV exposure from dromedary camels:

• Develop guidelines for joint outbreak animal/human investigations (see WHO, 2014 and 2015b for guidance on surveillance and outbreak investigation in occupationally exposed populations).

• Understand human behaviour and potential exposure parameters.

• Conduct proper field disease investigations, including molecular studies for further virus characterization, to be able to link suspect primary human cases to infected dromedary camels and collect information on settings where the risk of human exposure from camels may be increased.

• Conduct case-control studies to identify possible risk factors for human exposure from dromedary camels.

• Strengthen active surveillance by engaging camel owners, herders, traders and pastoralists in a participatory disease search through awareness raising of MERS-CoV clinical signs in humans, dromedary camels and other livestock.

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ANIMAL HEALTH RISK ANALYSIS

Human Exposure to Middle East Respiratory Syndrome Coronavirus from Livestock or Wildlife Species


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ANIMAL HEALTH RISK ANALYSIS

Risk analysis is a procedure, which we all do intuitively in our everyday life as we also do in our professional work to assess the risk of any hazard or threat. In animal health, risk analysis has been most widely used as a decision tool about the most appropriate health interventions to support disease control strategies, guide disease surveillance and support of disease control or eradication strategies.

It should be remembered that risk is not equal to zero and never stays static. Risks change as drivers or factors of disease emergence, spread or persistence change such as intensification of livestock production, climate change, civil unrest and changes in international trading patterns. Risk analysis should therefore not be seen as a “one off” activity and should be seen as a good practice of animal health systems to conduct their regular activities. Therefore, risk analysis process should be repeated and updated regularly.

Risk analysis comprises the following components:

**Hazard identification:** the main threats are identified and described.

**Risk Assessment:** risks of an event occurring and developing in particular ways are first identified and described. The likelihood of those risks occurring is then estimated. The potential consequences or impact of the risks if they occur are also evaluated and are used to complete the assessment of the risk.

**Risk Management:** involves identifying and implementing measures to reduce identified risks and their consequences. Risk never can be completely eliminated but can be effectively mitigated. The aim is to adopt procedures that will reduce the level of risk to what is deemed to be an acceptable level.

**Risk Communication:** an integrated processes that involves and informs all stakeholders within the risk analysis process and allows for interactive exchange of information and opinions concerning risk. It assists in the development of a transparent and credible decision-making processes and can instil confidence in risk management decisions.

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