Middle East respiratory syndrome coronavirus (MERS-CoV): Summary of Current Situation, Literature Update and Risk Assessment–as of 5 February 2015

As of 5 February 2015, 971 laboratory-confirmed cases of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO, including at least 356 deaths (Figure 1). Overall, 63.5% of cases reporting gender (n=949) are male and the median age is 48 years (range 9 months–99 years; n=964).

To date, the affected countries in the Middle East include Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia (SAU), United Arab Emirates (UAE) and Yemen; in Africa: Algeria, and Tunisia; in Europe: Austria, France, Germany, Greece, Italy, the Netherlands, Turkey and the United Kingdom; in Asia: Malaysia and Philippines; and in North America: the United States of America (USA). The majority of cases (>85%) have been reported from SAU. Since June 2014, two new countries (Austria and Turkey) have been affected.

Since June 2014, WHO was made aware of 272 laboratory-confirmed cases of MERS-CoV, including 113 cases that were reported by SAU with onset of symptoms before 12 June 2014. Among the other 159 cases, 2 cases were reported by Iran (Kerman Province), 2 cases by Qatar (Doha), 2 cases by UAE (Abu Dhabi), 3 cases by Oman (Dakhelyia Region), 1 case each reported by Austria, Jordan and Turkey (Figure 2) and 147 cases reported by SAU (including cases from Asir, Al Bahah, Al Hudud ash Shamaliyah, Al Jawf, Jubail, Meccah, Medina, Najran Al Quassim, Riyadh, Ash Sharqiyah, Tabuk and Taif).

The number of laboratory-confirmed MERS-CoV cases in SAU and UAE, where several large healthcare-associated outbreaks occurred in April and May 2014, had decreased sharply by June 2014. However, cases continue to be reported from SAU, including several hospital-associated clusters involving healthcare workers and patients in Taif city, Jubail city, and Riyadh. This suggests that hospital infection control measures may not be adequately adhered to in order to prevent healthcare-associated transmission. In addition, the increased case count includes 16 retrospective MERS-CoV cases with onset of symptoms before 9 June 2014, as reported to WHO by SAU in September 2014.

Since the last update (June 2014), three exported cases with exposure in SAU have been reported by Turkey (1 case), Jordan (1 case) and Austria (1 case). The case reported by Jordan sought treatment in Jordan but was subsequently repatriated to SAU for treatment. The case reported by Turkey was working in Jeddah, SAU, and initially sought treatment in SAU but then travelled to Hatay, Turkey, for medical treatment. No additional cases were reported by Jordan or Turkey. Austria reported one case, a female citizen of SAU, who had respiratory symptoms before entry into Austria. Follow-up of passengers on her flights and contacts in Austria identified no further cases.

Five cases of MERS-CoV were reported by Iran in May and June (including 2 additional cases since the last WHO update). All five cases were connected to a single hospital in Kerman, Iran, and were believed to be healthcare-associated transmissions. Following increased surveillance and

preparedness activities in Kerman province and across the country, there have been no reports of further cases in the affected hospital or in the province or the country to date.

In July 2014, UAE reported two cases of MERS-CoV infection from Abu Dhabi. The first case was an elderly man who owned and had frequent contact with camels. The second case was identified during contact tracing on a farm where a camel tested positive by PCR for MERS-CoV. No additional cases were reported from UAE.

In October 2014, two unrelated cases were reported from Doha, Qatar. The first case owned a camel farm and developed symptoms while traveling by car from Doha to Al Hasa, SAU. The second case reported frequent contact with camels.

In January 2015, a household cluster of MERS-CoV infection was reported in Dakhelyia region by Oman. The initial fatal case, a 32-year-old man, a farm owner, reported contact with camels, goats and sheep. Contact tracing of household members identified two additional cases; one was mildly symptomatic and the other was asymptomatic. Neither case reported direct contact with camels. At the time of writing, contact tracing is continuing among household and healthcare worker contacts. These are the first cases reported by Oman since January 2014.

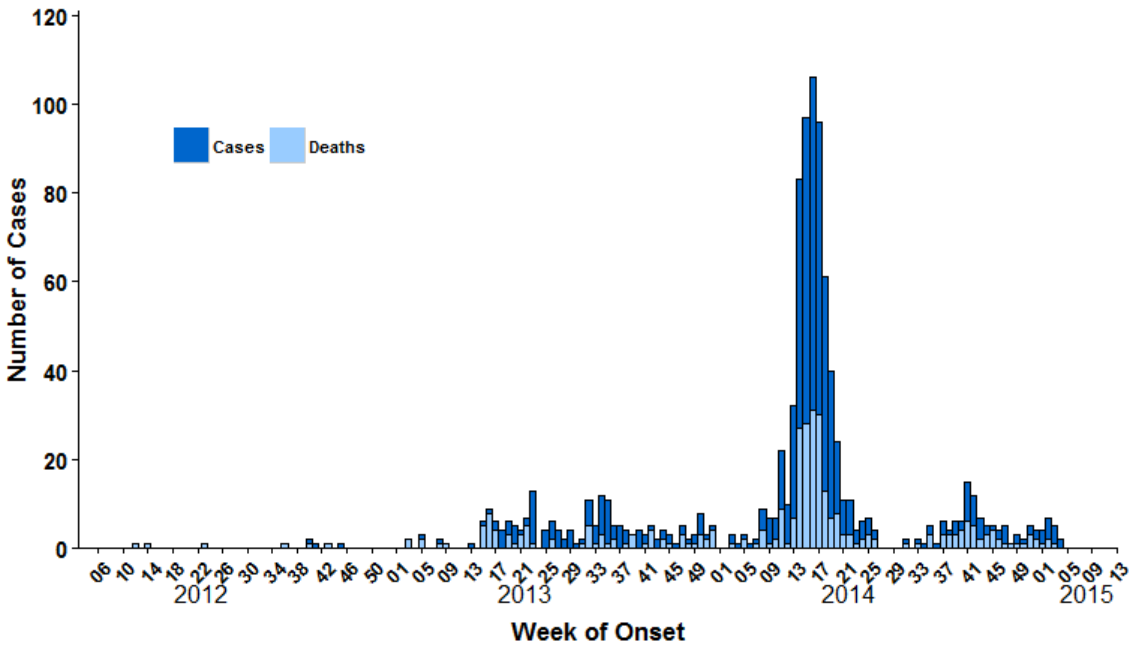

Figure 1. Epidemic curve of MERS-CoV human cases as of 5 February 2015 (n=971)

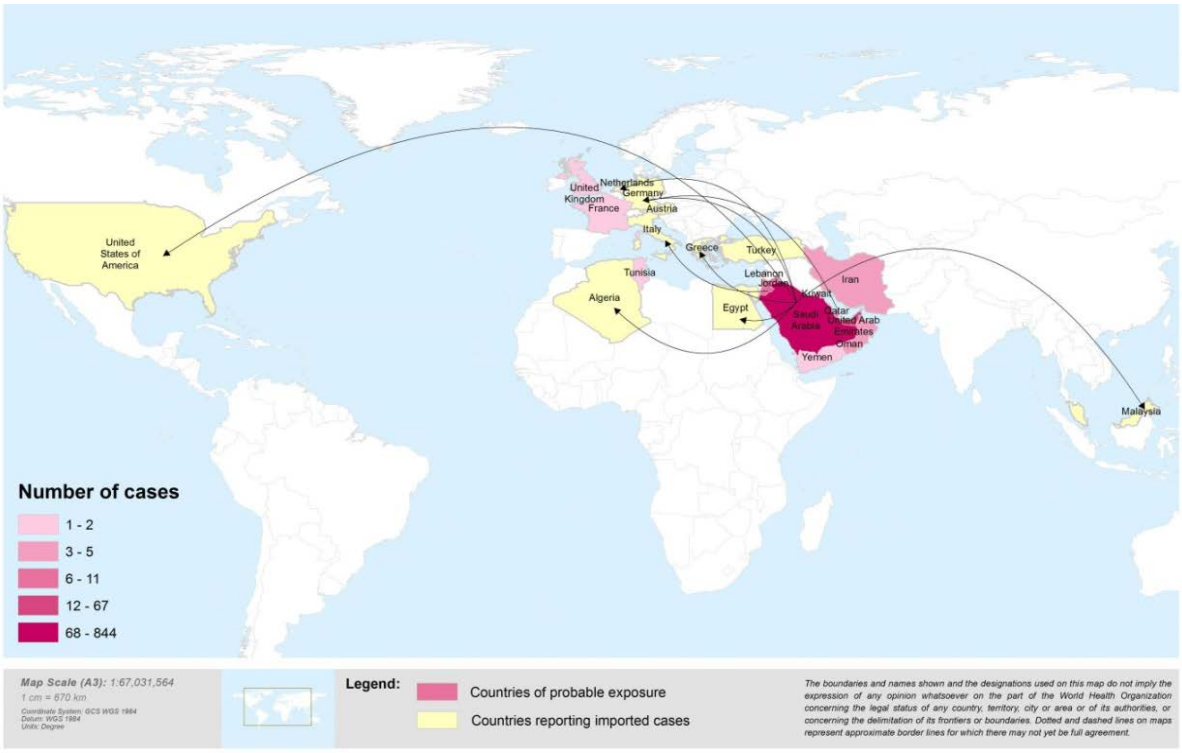

Figure 2. Countries reporting MERS-CoV infection as of 5 February 2015

WHO MERS-CoV Activities and Guidance

- Following discussions held between WHO and SAU, during the last World Health Assembly in May 2014, WHO and SAU strengthened collaboration for international response to MERS-CoV in SAU under the International Health Regulations (2005). After these discussions, a WHO team was deployed to SAU from 21 May to 30 June 2014. WHO has offered further support to the Ministry of Health and the Command and Control Centre (CCC) in Jeddah in coordination of the international response to the outbreak.

- A technical mission was also conducted during June and July 2014 to assess the five SAU regional laboratories of the Ministry of Health. The purpose of this mission was to set up reliable and consistent laboratory diagnostic standards and capabilities for MERS-CoV across all reference laboratories in the country, with a focus on biosafety and quality assurance.

- During July and August, a team from WHO coordinated and worked closely with the risk communication platform of the CCC in Jeddah, SAU. This team verified and reviewed the risk communication products and materials developed for MERS-CoV and Ebola in preparation for the Hajj.

- On 16-17 September 2014, WHO organized a meeting in Jeddah with medical missions of the top 10 countries sending pilgrims to Mecca for the Hajj. The participants reviewed and discussed overall preparedness measures for MERS-CoV during and after Hajj and identified better ways to enhance surveillance and exchange of information. A WHO team was deployed to Jeddah and Mecca during the Hajj to oversee the preparedness and surveillance activities related to MERS-

CoV. This team provided support for coordination and information sharing between WHO, the SAU Ministry of Health and other countries sending large numbers of pilgrims.

- WHO has prepared MERS-CoV risk communication materials for Umrah and Hajj, healthcare workers and the general public in three languages (Arabic, English and French). The materials, including animated videos for protection against MERS-CoV during the Hajj, are posted at http://www.emro.who.int/entity/surveillance-forecasting-response/index.html.

- A WHO team, including experts from GOARN technical partners, conducted a 5-day mission in Iran in August 2014 to follow up on the Kerman outbreak of 5 laboratory-confirmed cases of MERS CoV reported between May and July 2014.

- A meeting of the OIE ad hoc group on MERS-CoV Infection in Animals was held at OIE Headquarters, Paris, from 15 to 17 July 2014. The group reviewed the WHO current interim general recommendations on MERS-CoV transmission from animals to humans and the interim recommendations for at risk groups. The group was supportive of the recommendations and suggested they should apply to countries where there was a risk of transmission of MERS-CoV from camels to humans. The group reviewed the current state of knowledge and made a series of recommendations with regard to animal health management, need for further studies, surveillance activities and on revising the OIE Q&A. The OIE Q&A have been amended accordingly.

- WHO has published revised case definitions and surveillance guidance for MERS-CoV:

    a. Revised case definitions for MERS-CoV: Revised interim case definition for reporting to WHO – Middle East respiratory syndrome coronavirus (MERS-CoV) Interim case definition as of 14 July 2014

    b. MERS-CoV surveillance: Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus - As of 14 July 2014

- Following the 10-11 June 2014 laboratory meeting held in Lyon, France, in-depth discussions on the use of molecular and serological tests for MERS-CoV informed changes to the WHO interim recommendations on laboratory testing, which now include guidance on laboratory confirmation of cases using serology alone. Revised laboratory recommendations are available here: Laboratory Testing for Middle East Respiratory Syndrome Coronavirus Interim recommendations (revised) September 2014

- WHO has published a new epidemiologic field protocol for investigating populations at risk for MERS-CoV infection: Cross-sectional seroprevalence study of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in presumed high risk populations

Summary and Risk Assessment

WHO is continuing to work with Ministries of Health in affected countries and with international partners to better understand the reasons for the increase in cases reported in the Spring of 2014. As previously reported, WHO/GOARN missions to SAU and UAE found that the upsurge in cases in both countries was due to several hospital-acquired outbreaks that resulted from a lack of systematic implementation of infection prevention and control measures.

Since mid-May, the numbers of cases in SAU and UAE have sharply declined. However, cases continue to be reported from SAU, some of which reflect nosocomial transmission in hospitals in Taif city, Jubail city, Eastern Region and Riyadh. Although the number of cases reported from SAU has been relatively small, the cases occurred in several regions across SAU, suggesting that zoonotic transmission is allowing the virus to infect humans residing in several locations across the country, and that human-to-human transmission in healthcare settings continues. The risk of exported cases from SAU remains. Since the last update, three cases with exposure in SAU have been reported by Austria, Jordan and Turkey. No onward transmission has been observed in these three countries.

The WHO team concluded that the cluster of MERS-CoV cases in Kerman, Iran, in May and June 2014, showing epidemiological evidence of healthcare-associated transmission, could possibly have been caused by a combination of factors. These included inconsistent application of infection prevention and control measures in a healthcare setting at the beginning of the outbreak, as well as weakness in the surveillance system to actively follow and identify cases. Surveillance has been enhanced and preparedness activities have been implemented in Kerman province and other parts of the country and there have been no reports of further cases in the affected hospital, in Kerman province, or the rest of the country.

Also in October, two cases were reported by Qatar. One case became ill while travelling from Qatar to SAU and sought medical treatment in Al-Hasa, SAU, and the other case had reported recent contact with camels and camel milk in Qatar.

An estimated 1.4 million people travelled to SAU for Hajj in October 2014. Enhanced surveillance during Hajj, upon exit from the country and in the countries of the returning pilgrims did not identify any MERS-CoV cases.

Investigations in SAU and UAE took place in 2013-2014 to evaluate the role of asymptomatic PCR-positive cases in human-to-human transmission. It has been suggested that there may have been human-to-human transmission from asymptomatic cases in the UAE and SAU; however, in these instances, not all other potential sources of transmission have been ruled out. It is also currently not clear whether asymptomatic cases were asymptomatic at the time of reporting and remained asymptomatic, or later developed symptoms, as the follow-up of a number of recently reported asymptomatic cases have documented mild symptoms. Until more is known, and when resources allow, close monitoring and investigation of all contacts, including asymptomatic contacts, should be conducted.

Risk Assessment

Has the transmission pattern of MERS-CoV changed?

Based on available information from recent cases, there is neither evidence of sustained human-to-human transmission in the community nor evidence of airborne transmission. Therefore, the overall transmission patterns previously observed remain unchanged. WHO bases this assessment on the evidence that:

I. The clinical picture appears to be similar to that observed previously; secondary cases tend to present with milder disease than primary cases, and many of the recently reported secondary cases have been mild, or were people whose tests were positive for MERS-CoV but were asymptomatic;
II. The cases recently exported to other countries have not resulted in sustained onward transmission to persons in close contact with these cases on airplanes or in the respective countries outside the Middle East ;
III. Intensive screening of MERS-CoV contacts revealed very few instances of household transmission; and
IV. There has been no increase in the size or number of observed household clusters.

Can we expect additional cases of MERS-CoV infection in the Middle East? And can we expect additional cases exported to other countries?

WHO expects that additional cases of MERS-CoV infection will be reported from the Middle East, and it is likely that cases will continue to be exported to other countries by tourists, travellers, migrant workers or pilgrims who might acquire infection after exposure to an animal (for example, while visiting farms or markets) or human source (possibly in a health care setting). Until more is understood about mode of transmission and risk factors for infection, cases resulting from zoonotic transmission will continue to occur, and will eventually lead to limited community transmission within households and possibly significant hospital-associated outbreaks. Among the recently exported cases who reported performing Umrah in SAU, investigation into their activities while in SAU revealed that they had either visited a healthcare facility or had come into contact with camels or raw camel products while in SAU.

Recommendations

Urgent epidemiologic investigations are required to better understand the transmission patterns of MERS-CoV. The most urgent needs include understanding how humans become infected from animal or environmental source(s), through case-control studies, identifying risk factors for infection in health care settings, and enhancing community studies and surveillance for community-acquired pneumonia. Collaboration between human and animal health sectors in the affected countries is essential to understand the risk of transmission of MERS-CoV between animals and humans, whether there is any seasonal variation in the circulation of the virus in animals, and the natural reservoir(s) of MERS-CoV.

In addition, a better understanding of how healthcare workers are infected in healthcare settings is urgently needed.

WHO guidelines and tools on investigations can be found here:

- WHO guidelines for investigation of cases of human infection with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
  pdf, 359kb
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Initial Interview Questionnaire of Cases
  pdf, 114kb
- Case-control study to assess potential risk factors related to human illness caused by Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
  pdf, 257kb
- Seroepidemiological Investigation of Contacts of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Patients

WHO understands that detailed epidemiologic investigations are underway in Qatar, SAU and UAE.

Enhancing infection prevention and control awareness and implementation measures is critical to prevent the possible spread of MERS-CoV in healthcare facilities. It is not always possible to identify patients with MERS-CoV early because some have mild or unusual symptoms. For this reason, it is important that healthcare workers apply standard precautions consistently with all patients, regardless of their diagnosis, in all work practices all the time. Droplet precautions should be added to the standard precautions when providing care to any patient with symptoms of acute respiratory infection.

Healthcare facilities that provide care for patients suspected or confirmed to be infected with MERS-CoV infection should take appropriate measures to decrease the risk of transmission of the virus from an infected patient to other patients, healthcare workers and visitors. Contact precautions and eye protection should be added when caring for probable or confirmed cases of MERS-CoV infection, and airborne precautions should be applied when performing aerosol-generating procedures.

Until more is understood about MERS, people at high risk of developing severe disease (those with diabetes, renal failure, chronic lung disease, and immunocompromised persons), should take precautions when visiting farms and markets where camels are present. These precautions include: avoiding contact with camels; not drinking raw camel milk or camel urine; and not eating meat that has not been thoroughly cooked.

Preliminary results from recent studies in Qatar indicate that people handling or working with camels are at increased risk of infection with MERS-CoV compared with people who do not have contact with camels. Until more evidence is gathered, it is prudent for camel farm workers, slaughterhouse workers, market workers, veterinarians and those handling camels at racing facilities to practice good personal hygiene, including frequent hand washing after touching animals. They should wear facial protection where feasible and wear protective clothing, which should be removed after work and washed daily.

Workers should also avoid exposing family members to soiled work clothing, shoes, or other items that may have come into contact with camel excretions. It is therefore recommended that these clothes and items remain at the workplace for daily washing and that workers have access to and use shower facilities at their workplaces before leaving the premises.

Camels infected with MERS-CoV may not show any signs of infection. It is therefore not possible to know whether an animal on a farm, in a market, race track or slaughterhouse is excreting MERS-CoV that can potentially infect humans. However, infected animals may shed MERS-CoV through nasal and eye discharge, faeces, and potentially in their milk and urine. The virus may also be found in the organs and meat of an infected animal. Therefore, until more is known about infection in animals, the best protection is to practice good hygiene and avoid direct contact with all of these. Obviously sick animals should never be slaughtered for consumption; dead animals should be safely buried or destroyed.

Unless protected, people should avoid contact with any animal that has been confirmed positive for MERS-CoV until subsequent tests have confirmed that the animal is free of the virus.

Countries outside the affected region should maintain a high level of vigilance, especially those with large numbers of travellers or migrant workers returning from the Middle East. Surveillance should continue to be enhanced in these countries according to WHO guidelines, along with infection prevention and control procedures in healthcare facilities. WHO continues to request that Member States report all confirmed and probable cases along with information about their exposures, testing, and clinical course to inform the most effective international preparedness and response.

WHO does not advise special screening at points of entry with regard to this event nor does it currently recommend the application of any travel or trade restrictions.

Selected MERS-CoV Literature

- MERS-CoV has been shown to be phylogenetically related to bat coronaviruses but the origins of MERS are still unclear. A recent study by Wang et al. showed that a bat coronavirus has a similar hCD26-biding mode to MERS-CoV. hCD26 are the human binding site that initiate the processes of viral entry into human cells. This study supports a bat origin for MERS-CoV.

  Wang Q, et al. Bat Origins of MERS-CoV Supported by Bat Coronavirus HKU4 Usage of Human Receptor CD26. Cell Host Microbe. 2014 Sep 10;16(3):328-37. doi: 10.1016/j.chom.2014.08.009.

- Previous epidemiologic investigations have identified dromedary camels as the likely source of zoonotic transmission of MERS-CoV. In this study, Adney et al. inoculated three dromedary camels with MERS-CoV. The three camels developed benign upper respiratory tract infections, but each of the camels shed large quantities of virus from the upper respiratory tract. The pattern of virus shedding was essentially identical in all three animals and supports the available epidemiologic data indicating that camels are likely a major reservoir host for MERS-CoV.

  D Adney et al. (2014) Replication and Shedding of MERS-CoV in Upper Respiratory Tract of Inoculated Dromedary Camels. Emerging Infectious Diseases *DOI: 10.3201/eid2012.141280.*

- In the October 2014 issue of *Lancet Infectious Diseases*, researchers from SAU and elsewhere published a series of articles of MERS and emerging respiratory diseases. A few of these articles are detailed below. The full papers can be found on the *Lancet Infectious Diseases* website:

(http://www.thelancet.com/journals/laninf/issue/vol14no10/PIIS1473-3099%2814%29X7074-X).

- In October, researchers from the Netherlands published results from a study evaluating the exposures of persons who had travelled to SAU with two laboratory-confirmed MERS-CoV cases identified in the Netherlands in May 2014. They found that there were multiple potential sources of exposures among this group.

  Fanoy EB et al., (2014) Travel-related MERS-CoV cases: an assessment of exposures and risk factors in a group of Dutch travellers returning from the Kingdom of Saudi Arabia, May 2014. Emerg Themes Epidemiol. 11:16. doi: 10.1186/1742-7622-11-16. eCollection 2014. http://www.ete-online.com/content/11/1/16

- A two-stage serologic study of MERS-CoV in equids (192 samples from adult horses from UAE, 861 samples from 697 horses, 82 donkeys, and 82 mules from Spain) found no evidence of infection with MERS-CoV. None of the samples showed reactivity in either the recombinant immunofluorescent or microneutralization assays.

  Meyer et al (2014). Serologic Assessment of Possibility for MERS-CoV infection in Equids. EID 21 (1) 181-182 http://wwwnc.cdc.gov/eid/article/21/1/14-1342_article

- A transgenic mouse line was generated, which exhibited constitutive global expression of hCD26/DPP4, the functional MERS CoV receptor, normally absent in mouse species. The transgenic mice were shown to be fully permissive to MERS CoV infection following intra-nasal inoculation of EMC-2012. The lung and brain were found to be the prime sites for viral replication and both viral RNA (PCR) and infectious virus (recovered in cell culture) was detected in these sites. Viral RNA was also detected in the spleen, heart and intestines of infected transgenic mice but no infectious virus was recovered from these PCR-positive tissues. No viral RNA was detected in the liver or kidneys of these mice despite both organs expressing hCD26. Both lung and brain tissue showed significant cytokine and chemokine responses consistent with those expected during an acute inflammatory response to infection. This transgenic mouse model could therefore prove useful as a small animal model for studying MERS CoV pathogenesis and for evaluating intervention strategies to reduce or prevent disease.

  Agrawal AS et al (2015). Generation of Transgenic Mouse Model of Middle East Respiratory Syndrome-Coronavirus Infection and Disease. J Virol. 2015 Jan 14. pii: JVI.03427-14. [Epub ahead of print]

- Three strains of MERS coronavirus were isolated from dromedary camels in Saudi Arabia (Dromedary/Al-Hasa-KFU-HKU13/2013[AH13] and Dromedary/Al-Hasa-KFU-HKU19D/2013[AH19D]) and Egypt (Dromedary/Egypt-NRCE-HKU270/2013[NRCE-HKU270]). The replication kinetics of the three dromedary strains were compared with those of the prototype human MERS-CoV strain EMC2012 (hMERS-CoV EMC 2012) in both cell culture (VERO E6 cells) and in ex-vivo human respiratory tract tissues. In cell culture, all four strains replicated to similar levels, with NRCE-HKU270 being slightly faster than the others over 48 hours (at moi=0.01) but having a comparable final titre at 72 hours post infection. All four strains were able to infect the ex-vivo human bronchial and lung tissues, suggesting the dromedary strains

would be competent to cause human infection. The paper concludes that dromedary MERS-CoV strains from both the Gulf States and genetically diverse viruses from Egypt can pose a risk of infection in humans. Therefore, unexplained viral pneumonias in Africa, as well as across the Middle East, should be investigated for MERS-CoV involvement.

Chan et al (2014). Tropism and replication of Middle East respiratory syndrome coronavirus from dromedary camels in the human respiratory tract: an in-vitro and ex-vivo study. Lancet Resp Medicine, 2 (10) 813-812.

- A serologic study of MERS-CoV antibodies in 350 stored human (300 animal workers and 50 non-animal worker controls in Saudi Arabia) serum samples from 2012. No evidence of infection, as analysed by pseudoparticle MERs-CoV spike protein neutralization assay, was identified in any of the samples.

  Memish ZA et al. Sparse evidence of MERS-CoV infection among animal workers living in Southern Saudi Arabia during 2012. Influenza Other Respir Viruses. 2014 Dec 3. doi: 10.1111/irv.12287. [Epub ahead of print]

- Eighty-one percent of 189 stored serum samples from dromedary camels from Egypt, Sudan and Somalia were found to have neutralizing antibodies to MERS-CoV. The samples were collected between 1983-1984 (samples from Sudan and Somalia), and 1997 (samples from Egypt), suggesting that MERS-CoV has been circulating for decades in dromedary camels in northeast Africa.

  Muller et al. MERS coronavirus neutralizing antibodies in camels, Eastern Africa, 1983-1997. Emerg Infect Dis. 2014 Dec;20(12):2093-5. doi: 10.3201/eid2012.141026.