10 years later...

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On November 16, 2002, in the city of Foshan in the province of Guangdong (China), a 45-year-old man developed a severe atypical pneumonia and further infected four relatives. This was the first case of severe acute respiratory syndrome (SARS), as demonstrated by epidemiological investigations (1). Almost exactly 10 years later, on November 8, 2012, the first report of a mortal case of acute pneumonia associated with renal failure due to a novel coronavirus in a businessman from Bisha, Saudi Arabia, was published (2). In retrospect, we now know that the first confirmed human cases arose in a cluster of 13 individuals with respiratory symptoms in a hospital in Zarqa, Jordan, in April 2012 (3,4).

Middle East respiratory syndrome coronavirus (MERS-CoV) belongs to the *Coronaviridae* family, a group of large, enveloped, single-stranded RNA viruses. Similar to most RNA viruses, they are known for their genomic plasticity, and infect mammalian and avian hosts. It is the fourth identified beta coronavirus with the ability to infect humans (the others are SARS-CoV, human CoV-HKU1 and human CoV-OC43). It belongs to lineage C, shares similarities with viruses identified in the *Pipistrellus* species of bats (HKU4 and HKU5) and has been demonstrated to replicate in various bat cell lines (4). Consequently, a bat origin for MERS-CoV has been suggested. However, no clear and repetitive exposure to bats has been reported in epidemiological studies, and the search for an intermediate host has led researchers to identify dromedary camels as potential suspects (5). The identification of MERS-CoV-neutralizing antibodies in camels from Oman and the Canary Islands, where no human case has been reported, raises more questions than answers.

It must be recognized that new information is being reported constantly and that the data presented in the present report may soon be outdated. As of October 18, 2013, 139 laboratory-confirmed cases of MERS-CoV have been reported, including 60 deaths, representing a case fatality rate of 43%. All cases have been directly or indirectly linked to travel or residence in four countries: Saudi Arabia, Qatar, Jordan and the United Arab Emirates (6).

According to the WHO, a case is 'probable' when it combines the three following clinical, epidemiological and laboratory criteria (7):

- Febrile illness + evidence of parenchymal pulmonary disease (pneumonia or acute respiratory distress syndrome) AND testing for MERS-CoV is unavailable or negative on a single inadequate specimen AND there is a direct epidemiological link with a confirmed case;
- Febrile illness + evidence of parenchymal pulmonary disease (pneumonia or acute respiratory distress syndrome) AND presence of a positive screening test without confirmation (inconclusive) AND resident or traveller to Middle Eastern countries where MERS-CoV was circulating within 14 days of onset;
- Acute febrile respiratory illness of any severity AND presence of a positive screening test without confirmation (inconclusive) AND direct epidemiological link with a confirmed case.

A case is confirmed when a patient has laboratory documentation of MERS-CoV infection. A testing algorithm for cases under investigation using real-time reverse transcriptase polymerase chain reaction was published in September 2013 (8). For the moment, cases cannot

be confirmed by serological testing only, even if highly specific assays have been described, because they have been validated on a limited number of patients (9-11). A case with a positive serological test in the absence of polymerase chain reaction/sequencing confirmation is, therefore, considered to be 'probable'. It is important to mention that one cannot reliably rule out MERS-CoV on a single negative result because virus shedding (similar to SARS) in the respiratory tract varies according to the specimen and the time since onset of illness (11).

The incubation period of MERS-CoV was measured using data from a well-defined hospital outbreak in Al-Hasa in Eastern Saudi Arabia, and estimated to be 5.2 days (95% CI 2.2 to 12.4 days) (12). This is similar to SARS-CoV, which has an average incubation period of four days (95% CI 1.8 to 10.6 days) (13). The serial interval time is the period of time between analogous phases of an infectious illness in successive cases of a chain of infection that is spread from person to person. In the same report, this was defined as 7.6 days for MERS-CoV (versus 8.4 days for SARS) (12,14).

Well-described clusters have been published. Despite several close family contacts with index cases, only a small number of secondary cases have been identified (12,15). The reproduction number (R_0), defined as the number of cases generated by one infected individual on average in a fully susceptible population, is a very important epidemiological measure. When R_0 is <1 , the infection will usually die out over time, and when R_0 is >1 , there is a clear risk of spreading in the population. Breban et al (16) calculated the MERS-CoV R_0 to be 0.69 (95% CI 0.5 to 0.92) in the worst-case scenario. Comparatively, they estimated the R_0 for SARS during the prepandemic stage in Southern Asia to be 0.80 (95% CI 0.54 to 1.13). It is expected that R_0 will be updated as more data are reported because it may change seasonally according to school calendars and yearly gatherings, such as the Hajj pilgrimage, and if the virus evolves. Recent molecular data support the hypothesis of multiple introductions to explain the origin of cases linked in the same hospital outbreak (17). These data have a clear impact on R_0 estimation, which will probably revise R_0 downward.

At this time, the main mechanism of transmission is not well defined. In some reports, secondarily infected patients were >1 m from the index case, which supports potential airborne transmission (12). For the moment, standard, contact and airborne precautions are recommended by the Centers for Disease Control and Prevention (Georgia, USA) and by Health Canada for health care workers involved in the management of suspected MERS-CoV cases or close contacts of confirmed cases (within 14 days of onset). These recommendations are consistent with those of SARS and were influenced by the high rate of morbidity and mortality in infected patients, unknown modes of transmission, potential human-to-human transmission, and lack of vaccine or chemoprophylaxis (18,19).

Assiri et al (20) recently reported a clinical comparison between patients infected with MERS-CoV and those infected with SARS. It is important to specify that this analysis is preliminary because it was performed on a limited number of subjects ($n=47$) and, consequently, is subject to change. General data were updated from other sources (Table 1). As with preliminary reports of SARS patients, data from cohorts described initially may strongly differ from larger, later cohorts. With SARS, the initial published cohorts included several health care workers ($>50\%$) who were younger and healthier than the hospital

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TABLE 1
Comparison between Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS)

Characteristic	MERS-CoV	SARS
Demographic data		
≥18 years of age*	98	93
Median age (range), years†	50 (2–94)	40 (1–91)
Male:female ratio (n=130)†	1.6:1	1:1.3
Outcomes and clinical features		
Case fatality rate‡	n=60/139 (43%)	0–40
Time from onset to death, days*	16.5	23.7
Symptoms*		
Fever	98	99–100
Cough	83	62–100
Hemoptysis	17	0–1
Shortness of breath	72	40–42
Vomiting	21	20–35
Diarrhea	26	20–25
Comorbidities*		
Any	96	10–30
Diabetes	68	24
Chronic renal failure	49	2–6
Chronic heart disease	28	10
Laboratory and imaging		
Chest x-ray abnormalities*	100	94–100
Leukopenia (<4.0×10 ⁹ cells/L)*	14	25–35
Lymphopenia (<1.5×10 ⁹ cells/L)*	34	68–85
Increased alanine aminotransferase/aspartate aminotransferase level*	11/15	20–30/20–30

Data presented as % unless otherwise indicated. *Data adapted from Assiri et al (20); †Data adapted from Morbidity and Mortality Weekly Report (21); ‡Data adapted from WHO (6)

population. With MERS-CoV, several cases in early reports included patients attending the hemodialysis unit. Ongoing evaluation is required to assess whether chronic renal disease is a true risk factor for the development of MERS-CoV infection.

Although there is an ever-increasing body of evidence being reported, there are many knowledge gaps that need to be addressed (20). The origin and the natural reservoir for MERS-CoV remain obscure. The overall incidence and risk factors for acquisition of symptomatic disease and adverse outcome are not well defined. Our limited understanding of transmissibility of this pathogen challenges our ability to define optimal infection prevention and control procedures. We do not know whether there are any specific therapies beyond supportive treatments that will improve outcome.

Only the future will define whether MERS-CoV will be a limited regional phenomenon or whether a pandemic will ensue. While we cannot be certain of the future of MERS-CoV, we believe that the next decade(s) will inevitably witness the emergence of other novel respiratory viruses that, along with SARS and MERS-CoV, will have a profound influence on the global community.

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