EDITORIAL COMMENTARY

Critical Contribution of Laboratories to Outbreak Response Support for Middle East Respiratory Syndrome Coronavirus

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(See the Major Article by Drosten et al on pages 369–77.)

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Middle East respiratory syndrome coronavirus (MERS-CoV) was first detected in a patient living in the Kingdom of Saudi Arabia (KSA) in September 2012 [1]. As of 20 August 2014, 855 laboratory-confirmed cases of human infection have been reported to public health authorities worldwide, including 333 deaths. Most of the cases (97.5%) have occurred in the Middle East (KSA, United Arab Emirates, Qatar, Jordan, Oman, Kuwait, Egypt, Yemen, Lebanon, and Iran), with 723 cases alone reported from KSA. In all 21 cases that have been reported outside the Middle East (United Kingdom, Germany, France, Italy, Greece, the Netherlands, Tunisia, Algeria, Malaysia, Philippines, United States), the patients had lived in or traveled to the Middle East, or had contact with travelers returning from these areas [2].

Although the definite source of infection and the exact routes of direct or indirect exposure remain unknown, the pattern of transmission pointed early toward an animal reservoir in the Middle East from which humans sporadically become infected through zoonotic transmission. Although the close phylogenetic relation of human MERS-CoV isolates initially suggested bats as a putative natural reservoir [3], there is increasing evidence that dromedary camels serve as the primary source of MERS-CoV infection in humans [4]. MERS-CoV sequences have been identified in dromedary camels' nasal secretions [5, 6], but also in raw milk samples of infected animals [7]. There is serologic evidence for MERS-CoV infection in camels and calves from various regions in the Middle East and beyond [8–10]. Isolated viruses are matching to a high degree to the genomes of the human MERS-CoV [11], and phenotypic characterization of viruses revealed that cell tropism and replication kinetics/competence of human and dromedary MERS-CoV are similar [12]. Recently, virus replication and shedding was confirmed in the upper respiratory tract of experimentally infected camels [13].

Besides the sporadic infections of humans through zoonotic transmission, nosocomial transmissions contribute to the epidemiology. Person-to-person transmission of MERS-CoV was shown to occur in healthcare settings with clusters among healthcare workers and patients in several countries [14–20].

Beginning in mid-March 2014, there was an explosive increase of MERS-CoV case notifications in KSA, with more cases reported in the month of April than during the 2 years following the beginning of the outbreak in March 2012 [21]. This raised important questions: Was this a real increase in cases or simply a surveillance artefact due to reporting of false positives or a change in surveillance practice with a more sensitive case detection? Was this increase caused by an increased number of new introductions from the natural reservoir and/or did this increase indicate a breach in infection control measures that allowed increased nosocomial transmission? One of the most pressing questions, however, was whether there was evidence for a change in transmissibility of MERS-CoV enabling a more efficient human-to-human transmission.

On 26 April 2014, during the ongoing outbreak, an initial sequence analysis was communicated by Drosten and Corman indicating that the 3 MERS-CoV viruses recovered from cases in Jeddah exhibited a high degree of similarity to each other and a large number of known MERS-CoV sequences. This provided preliminary evidence that the virus had not undergone

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major genetic change, and instead pointed to nosocomial transmission [22].

In this issue of *Clinical Infectious Diseases*, Drosten and colleagues [23] describe the detailed laboratory-based investigation of outbreaks in Jeddah and Riyadh, KSA. They reviewed the diagnostic laboratory data of the reference laboratory in Jeddah and assessed the laboratories' proficiency. They also described the molecular epidemiology of the outbreak viruses, and studied virus replication and immune escape of interferon response as well as serum neutralization.

The detailed functional examination of the circulating viruses did not provide any evidence for a biologically changed virus in regard to shedding, replication, and immune escape. The findings also provide evidence against the hypothesis of a laboratory contamination causing this increase in reported cases.

The study revealed notable findings respective to the different transmission patterns of MERS-CoV:

- Nosocomial transmission: The phylogenetic analysis showed that the viruses isolated from patients in Jeddah clustered in 1 clade as well as the viruses associated with 1 specific hospital in Riyadh, suggesting human-to-human transmission in healthcare settings.
- Sporadic introduction of viruses from zoonotic sources: The phylogenetic analysis showed that the viruses isolated from Riyadh were genetically diverse, belonging to 6 different clades, which may indicate sporadic introduction from zoonotic sources.
- Community spread: The number of specimens with low reverse transcription polymerase chain reaction copy number increased over the course of the investigation, possibly indicating early infection identified through contact tracing and community spread.

There are several zoonotic diseases that are amplified in the nosocomial setting (eg, Crimean-Congo hemorrhagic fever, Ebola virus, severe acute respiratory syndrome [SARS]) when infection prevention and control measures are breached. Nosocomial transmission is a particular risk factor for international spread, especially if exposure in healthcare settings is more likely than exposure through enzootic contact. The large outbreaks of MERS-CoV in Jeddah and Riyadh have stressed the importance of infection control strategies and practices, not only when caring for suspected MERS-CoV patients, but for overall patient care. Identification of the specific factors that facilitate transmission in the healthcare setting will be key to inform measures for interruption of transmission as shown with SARS [24]. Up to now, no sustained human-to-human spread has been shown for MERS-CoV in the community setting. The role of super-spreading of MERS-CoV in the hospital setting, however, remains to be further elucidated. In the SARS outbreak in 2003, super-spreading events accounted for >70% of the cases, with SARS-CoV being moderately transmissible [25].

This study illustrates nicely how laboratory studies assist in outbreak investigation, explaining an increase in case notifications without performing a detailed analysis of the transmission chains. In this regard, laboratory studies are essential not only for investigating laboratory proficiency but also for studying virus transmissibility. Phylogenetic analysis provides evidence to distinguishing nosocomial transmission from independently acquired infections from zoonotic sources. Further insights in transmission dynamics might be provided and unnoticed transmission links revealed. Laboratory data can add valuable information on the quality of and/or the adherence to the case definition used. They also can guide effective strategies for contact tracing to avoid an overload of the healthcare system, thus reducing human error.

Although much has been achieved to better understand the epidemiology of MERS-CoV infections, several data gaps for laboratory preparedness exist [26]. An important constraint for laboratories is that often insufficiently detailed data are accompanying the laboratory request. To improve the quality of the laboratory support during outbreaks, it is vital to combine the collected clinical data with epidemiological data and to communicate in a timely manner.

Following the outbreak in spring, only a small number of cases have been reported from KSA with onset dates in July and August 2014 [27]. This overall decline in case numbers follows the seasonal pattern observed in the previous year, but has also occurred subsequent to the strict implementation of standard infection control measures by the Saudi Arabia Ministry of Health, dramatically reducing the number of healthcare-associated infections [28]. This decline in numbers however, should not allow complacency as cases continue to be reported in September, with the first case reported in an expatriate healthcare worker on 22 September 2014, suggestive of nosocomial transmission [27]. Special attention to hospital clusters should be given during the Hajj period, when millions of pilgrims from >180 countries will visit KSA and the health system risks becoming overburdened. During the 2013 Hajj season, >1.2 million pilgrims visited hospitals and healthcare centers [29]. Heightened awareness needs to be maintained during the winter, when the peak calving season for dromedary camels starts, to detect zoonotic introductions.

A timely and structured exchange of information between clinicians, epidemiologists, and laboratory scientists needs to be established to early detect signals and to allow proactive infection control measures and intervention against MERS-CoV, a virus that has the proven potential for nosocomial spread.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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