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Editorial

Middle East respiratory syndrome coronavirus – The need for global proactive surveillance, sequencing and modeling

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1. Introduction

Over the past 20 years, three zoonotic coronaviruses have jumped the species barrier to cause lethal infections in humans: the Severe acute respiratory syndrome (SARS) coronavirus-1, (SARS-CoV-1), first reported from Guangdong province China in 2002 [1]; the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) was first reported from Jeddah, Kingdom of Saudi Arabia (KSA), in 2012 [2] and SARS-CoV-2 was first reported in December 2019 from Wuhan, Hubei province in China [3]. SARS-CoV-2 has spread rapidly worldwide resulting in the ongoing pandemic of Coronavirus Disease-2019 (COVID-19). There have been over 170 million COVID-19 cases with 3.5 million deaths reported to the WHO as of June 1st, 2021 [4]. Over time several genetic variants of concern (VOC) of SARS-CoV-2 have emerged [5] such as the South Africa variant B.1.351 (spike mutations K417 N, E484K, N501Y, D614G, A701V), Brazil variant B.1.1.28 (K417T, E484K, N501Y, D614G, H655Y), UK variant B.1.1.7 (E484K, N501Y, D614G, P681H) and the India variant B.1.617.2 (L452R, T478K, D614G, P681R). SARS-CoV-2 variants has led to significantly higher potential rate of transmission (R0), impact on severity.

The unprecedented COVID-19 pandemic with associated lockdowns, and huge death tolls, has riveted political and scientific attention and overshadowed attention on all other important communicable diseases with epidemic potential. Whilst COVID-19 is now the top cause of death globally from an infectious disease, it is important that global attention is not lost on the evolution and circulation of other WHO priority R&D Blueprint pathogens, including MERS-CoV [6].

1.1. MERS-CoV, camels and continuing circulation

Whilst in 2002, SARS-CoV-1 emerged as a new zoonotic pathogen and spread worldwide, causing over 8,000 infections and 800 deaths, it disappeared within 18 months, never to be seen again [7]. The MERS-CoV continues to circulate and cause sporadic human infections and outbreaks in the Middle East, 8 years after first discovery [8]. According to the World Health Organization (WHO), at the end of April 2021, there were a total of 2574 laboratory-confirmed MERS cases, including 886 associated deaths (case-fatality ratio: 34.4%) [9] reported from 27 countries. Of these 2121 out of 2564 cases were reported from Saudi Arabia with 788 deaths (a case-fatality rate of 37.1%) [10]. MERS cases continue to be sporadically reported from the Middle East. The natural host reservoir of MERS-CoV remains elusive. Exposure to dromedary camels has been recognized by WHO as a risk factor in primary human MERS cases, but the exact source and mechanisms of transmission of MERS-CoV from animals to humans remain clear. Only a proportion of reported MERS human cases have reported direct camel exposure. Several studies have shown a high prevalence of MERS-CoV antibodies and MERS-CoV has been isolated from dromedary camels in the Arabian Peninsula and across North, East, West and Central Africa [11]. MERS-CoV antibodies have been found to be present in stored camel sera as early as early 1980s, suggesting the presence of MERS-CoV in dromedaries well before its first detection in humans in 2012 [12,13].

1.2. MERS-CoV models and Middle East outbreaks

Several MERS modelling studies have addressed the differences

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between primary and secondary cases. One study found that index cases transmit more effectively than secondary cases with $R_i = 0.84$ (0.58–1.20) vs $R_s = 0.36$ (0.24–0.51) and that the average R of the 2013 outbreak was <1 [14]. In a subsequent analysis based on the incidence decay with exponential adjustment (IDEA) method, it was calculated that the R_0 in Jeddah (3.5–6.7) was higher than in Riyadh (2.0–2.8) [15]. Earlier studies showed that the MERS R_0 was near or below the critical pandemic threshold of 1 [16,17]. Differences in the modeling estimates of R might also be related to the variable account of outbreaks, use of sporadic cases, or the combination of these parameters [15–17]. This is illustrated by the R in Jeddah that was shown to be much higher than that of Riyadh as a large outbreak had occurred in Jeddah during the study [18]. This suggested that the R_0 will be influenced by super-spreading events which occur in crowded environments. MERS-CoV modelling was helpful in the description and development of mitigation measures for controlling the spread of MERS-CoV in nosocomial settings where hospital-based transmission was found to be 4.3–4.6 times higher than community-based transmission [19], and where use of two or more R_0 factors were more accurate predictors for achieving control.

1.3. Risk of spread outside Middle East

A mathematical model of importation of MERS-CoV into countries outside the Middle East, utilizing the arrival time of each imported MERS case into different countries and publicly available airline transportation network data showed that the effective distance derived from airline transportation network data predicted the risk of importing MERS-CoV at the country level [20]. Out of 30 countries predicted to be at risk, 17 (56.7%) reported at least one imported MERS cases [20]. Another study utilized the time-line of reported MERS cases (June 7, 2012 and June 30, 2014) and modeled three scenarios. An expected/Low Incidence (weekly risk of infection matching the risk among foreign Umrah pilgrims from June 1, 2014 to August 28, 2014), a High Incidence (weekly risk matching age-adjusted average risks in residents of Makkah- January 1 and June 30, 2014) and *very High Incidence* (weekly risk of infection matching age-adjusted average for Makkah, April 10 to May 7, 2014) [21].

1.4. South Korean outbreak and pandemic potential

MERS-CoV transmission appears heterogenous, and there remains substantial potential for outbreaks and super-spreading events outside KSA such as the one in South Korea. The largest outbreak of MERS outside the Middle East occurred in the Republic of Korea in 2015 resulting in 186 laboratory-confirmed cases (185 in Republic of Korea and 1 in China) and 38 deaths [22]. This highlighted the pandemic potential of MERS-CoV especially in light of 10 million pilgrims who visit Saudi Arabia for the hajj and umrah pilgrimages annually. The Korean outbreak was unique because it represented a single point source without continuous zoonotic transmission. Estimates of MERS-CoV modeling in relation to occurrence of super-spreading events in South Korea of 82 individuals during his course of illness [23] showed that the index case resulted in 27 secondary cases, and, one of these cases infected an additional 24 tertiary cases, and a third patient caused 73 tertiary cases [24]. Based on the occurrence of such events, it was found that cluster sizes >150 cases are not unexpected for MERS-CoV infection [25]. The estimation of South Korea MERS-CoV outbreak showed an R_0 of 7.0–19.3 [26] and that expected number of secondary cases following an imported index case to be less than 1 [27]. The major MERS outbreak in South Korea in 2015 was due to several super-spreading events in the hospital and highlighted the pandemic potential of MERS-CoV.

1.5. Need for global proactive surveillance, sequencing and modelling

Of concern is recent data from Nigeria which shows for the first time

the presence of MERS-CoV infection in humans in Africa [28] and now adds to the increasing number of zoonotic infections in Africa. The study highlights the threat of spread of human MERS infections in African regions areas where large number of MERS-CoV infected dromedaries are present, which with time may lead to MERS-CoV adapting and transmitting more efficiently in humans [29,30]. Alternatively, a camel-derived virus more distantly related to MERS-CoV and with the ability to replicate in the human upper airway efficiently may emerge, and similarly to SARS-CoV-2, would have immediate pandemic potential, especially with over 10 million pilgrims visiting Saudi Arabia from 182 countries annually. Whilst the umrah and hajj pilgrimages have recently been scaled down [31] in light of the COVID-19 outbreak, local and international travel to and from Middle East continues, and there are plans to re-open the Hajj to international pilgrims [32–34].

MERS-CoV binds to the receptor dipeptidyl peptidase 4 (DPP4) [35] and SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) [36]. One shared characteristic of the MERS-CoV with SARS-CoV-2 is genetic variation. In a study of 8 isolates from South Korea outbreak of MERS-CoV, these isolates, whilst 99% had nucleotide homology with the strain from Riyadh, Saudi Arabia, there were 13 variant nucleotides [37, 38].

Coordinated sequencing of emerging viruses such as MERS-CoV and SARS-CoV-2 has a major role to play on the surveillance of these novel coronavirus infections of humans [39]. Sequencing allows delineation of transmission dynamics and introductions of novel genetic variants; definition of the relationship between clades/lineages, transmissibility, disease severity or risk groups to guide public health action; assessment of the impact of mutations on the performance of molecular, antigen detection or serological diagnostics; assessing relatedness SARS-CoV-2 strains in epidemiological clusters during contact tracing; confirming reinfections; study of the relevance of observed mutations in the pathogenesis of the COVID-19; study of the impact of mutations on the performance of antiviral drugs; and assessment of the impact of mutations and modelling of the antigenic properties of SARS-CoV-2. A vital component of sequencing is having meaningful, non-stigmatizing nomenclatures to the sequence data. This is also required for streamlining communication between different molecular epidemiology stakeholders worldwide, who in turn need to provide more simplified tabulation of the genomic data for epidemiological analysis and public consumption without attributing stigma by naming after the country of first detection [40]. . Viral sequencing also allows the tracking of the transmission pattern and facilitate the development of vaccines [41]. Further enhancement of the tracking of these mutations require the development of enhanced bioinformatics in order to have a fast and detailed phylogenetic analysis [42].

2. Conclusions

Early detection of new outbreaks and monitoring the evolution of MERS-CoV will require accurate surveillance, real-time sequencing and accurate modelling of spread in humans and camels in, and outside of the Middle East. As Saudi Arabia starts staged opening up of umrah and hajj [43] to millions of pilgrims from 182 countries, it is vital that in addition to monitoring of SARS-CoV-2, global attention must now be refocused on other pathogens with pandemic potential, including MERS-CoV.

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Jaffar A. Al-Tawfiq^{a,b,c,1,*}, Eskild Petersen^{d,e}, Ziad A. Memish^{f,g,h}, Stanley Perlmanⁱ, Alimuddin Zumla^{i,1}

^a Infectious Disease Unit, Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia

^b Infectious Disease Division, Indiana University School of Medicine, Indianapolis, IN, USA

^c Infectious Disease Division, Johns Hopkins University, Baltimore, MD, USA

^d Institute for Clinical Medicine, Faculty of Health Sciences, University of Aarhus, Denmark

^e European Society for Clinical Microbiology and Infectious Diseases [ESCMID] Task Force for Emerging Infections, Basel, Switzerland

^f King Saud Medical City, Ministry of Health, Riyadh, Saudi Arabia

^g Al-Faisal University, Riyadh, Saudi Arabia

^h Hubert Department of Global Health, Rollins School of Public Health,
Emory University, Atlanta, GA, USA

ⁱ Department of Microbiology and Immunology, And Department of
Pediatrics, University of Iowa, Iowa City, IA, USA

^j Department of Infection, Division of Infection and Immunity, University
College London and NIHR Biomedical Research Centre, UCL Hospitals NHS
Foundation Trust, London, United Kingdom

^{*} Corresponding author. Infectious Disease Unit, Specialty Internal
Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia.
E-mail addresses: jaffar.tawfiq@jhah.com, jaltawfi@yahoo.com (J.A. Al-
Tawfiq), eskild.petersen@gmail.com (E. Petersen), zmemish@yahoo.com
(Z.A. Memish), stanley-perlman@uiowa.edu (S. Perlman), a.zumla@ucl.ac.uk (A. Zumla).

¹ contributed equally.