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An association between exposure to Middle East Respiratory Syndrome (MERS) and mortality rate of Coronavirus Disease 2019 (COVID-19)

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Abstract. – OBJECTIVE: Our objective was to find an association between exposure of a population to Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and mortality rate due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) across different countries worldwide.

MATERIALS AND METHODS: To find the relationship between exposure to MERS-CoV and mortality rate due to SARS-CoV-2, we collected and analyzed data of three possible factors that may have resulted in an exposure of a population to MERS-CoV: (1) the number of Middle East Respiratory Syndrome (MERS) cases reported among 16 countries since 2012; (2) data of MERS-CoV seroprevalence in camels across 23 countries, as working with camels increase risk of exposure to MERS-CoV; (3) data of travel history of people from 51 countries to Saudi Arabia was collected on the assumption that travel to a country where MERS is endemic, such as, Saudi Arabia, could also lead to exposure to MERS-CoV.

RESULTS: We found a significantly lower number of Coronavirus disease 2019 (COVID-19) deaths per million (deaths/M) of a population in countries that are likely to be exposed to MERS-CoV than otherwise (*t*-stat=3.686, *p*<0.01). In addition, the number of COVID-19 deaths/M of a population was significantly lower in countries that reported a higher seroprevalence of MERS-CoV in camels than otherwise (*t*-stat=4.5077, *p*<0.01). Regression analysis showed that increased travelling history to Saudi Arabia is likely to be associated with a lower mortality rate due to COVID-19.

CONCLUSIONS: This study provides empirical evidence that a population that was at an increased risk of exposure to MERS-CoV had a significantly lower mortality rate due to SARS-CoV-2, which might be due to cross-protective immunity against SARS-CoV-2 in that population because of an earlier exposure to MERS-CoV.

Key Words:
COVID-19, MERS, SARS-CoV-2, Coronaviruses.

Introduction

The recent pandemic of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that cause Coronavirus disease 2019 (COVID-19) has brought momentous devastation at socioeconomic level worldwide. While we wait for the availability of vaccination, urgent and technically feasible measures are required to interrupt further transmission of the virus. Until now, a comparatively higher mortality rate has been apparently noticed in the countries in the Western hemisphere than the Middle East countries. This could be attributed to the cross-protective immunity provided by exposure to earlier strains of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in the Middle East. Cross-protective immunity can substantially reduce the severity of infection, limit the spread of disease during

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epidemics and is an important factor for the development of vaccines against viral diseases[1-4]. However, no reports for cross-reactivity between MERS-CoV and SARS-CoV-2 exist until now.

Similar to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and MERS-CoV, the two viruses that previously caused Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks, SARS-CoV-2 belongs to the Beta-Coronavirus genus[5]. The three coronaviruses mainly infect lower respiratory tract leading to compromised immune response and respiratory illness that varies from mild symptoms to fatal outcomes[6]. In 2003, after the initial outbreak of SARS in China, the virus spread to 32 countries before it was contained after 4 months[6]. MERS was first reported in Saudi Arabia in 2012[7], the disease spread over 27 countries, and since then, this disease is endemic in Middle East, with the highest incidence being reported in Saudi Arabia, Qatar, Oman and United Arab Emirates (UAE)[8].

COVID-19, MERS, and SARS are zoonotic diseases, and the primary mode of transmission include direct animal-to-human contact[6]. Animals are the main reservoirs of coronaviruses and the three mentioned human coronaviruses are believed to be originated from bats[6]. It is observed that intermediate host is involved in the transfer of these viruses from animal-to-human, such as civet cats in case of SARS-CoV and camels in case of MERS-CoV[9]. Sporadic transmission of MERS-CoV from dromedary camels has been documented in multiple studies, and people who work with camels are at an increased risk of contracting the disease[10,11]. Human-to-human transmission of MERS may occur *via* different routes, such as, through respiratory droplets[6], direct contact with symptomatic MERS patients[12], nosocomial transmission[11], contact with family members of infected people[3], travel-associated spread of the virus[13], and a few studies have also reported secondary transmission of MERS from camel products and asymptomatic MERS cases[3,11]. Healthcare-associated outbreaks of MERS have occurred repeatedly with the largest outbreaks being reported in Saudi Arabia, UAE and the Republic of Korea[13] along with cluster of cases of human-to-human transmission reported in Jordan, Tunisia, Italy, England and France[12]. COVID-19, like other respiratory diseases, can be transmitted through airborne spread or even asymptomatic cases[14].

The coronaviruses infect respiratory cells by establishing virus-host interaction between receptor binding domain of coronaviruses and cell membrane receptors of host cells[15]. This interaction induces immune response, particularly the production of neutralizing antibodies (NAbs) (i.e., IgG and IgM) that are detectable within 19 days after COVID-19 symptoms[15]. NAbs play vital role in the control of viral infections and also offers cross-protection against other viruses. SARS-CoV-2 shares 79% and 50% genome similarity with SARS-CoV and MERS-CoV, respectively[16,17]. Since these 3 viruses share the same genus, protective immune response against one virus may provide passive immunity against heterotypic coronaviruses of the same family[4,18]. It is possible that in regions where earlier outbreaks of MERS have occurred, seroprevalence of NAbs against MERS-CoV is comparatively higher among people in those regions than unexposed regions and might have offered population-based cross-protective immunity against other coronaviruses, such as SARS-COV-2.

This is an observational study and our specific objective was to find an association between prevalence of MERS-CoV and mortality due to SARS-CoV-2. We hypothesized that an earlier exposure to MERS-CoV can illicit cross-reactive NAbs against SARS-CoV-2, and this phenomenon might explain the difference in COVID-19 mortality rate that is being observed across various countries globally. Furthermore, we hypothesized that repeated exposure of a population to areas where MERS is endemic and contact with animals, that are natural reservoirs of MERS-CoV, might explain the difference in COVID-19 mortality rate across various regions due to cross-protective immunity in a certain population.

Materials and Methods

The data for this cross-sectional observational study was collected from World Health Organization (WHO)[19] and Worldometer website[20]. To find an association between mortality due to COVID-19 across different countries and an earlier exposure to MERS, we collected and analyzed data of three possible factors that could increase the risk of an exposure of a population to MERS-CoV.

Firstly, we collected data on mortality due to COVID-19 across 16 countries and divided them into two groups on the basis of number of

MERS cases reported since 2012. The first group included 10 countries that reported zero or negligible MERS cases (less than 10 cases), i.e., UK, USA, China, Japan, Germany, Canada, France, Italy, Spain and Iran. The second group included 6 countries that reported at least 10 MERS cases since 2012 i.e., Saudi Arabia, South Korea, Jordan, Oman, Qatar, and UAE. The data on the prevalence of MERS-CoV was collected from the Food and Agricultural Organization of the United Nations (FAOUN)[8].

Secondly, an important factor that may increase the risk of exposure of a population to MERS-CoV is working with camels, as they are a natural reservoir of the virus and are an important source of community transmission of MERS-CoV[10]. Therefore, in the second part of this study, we compared mortality due to COVID-19 across 23 countries and divided them into two groups depending upon whether MERS-CoV is reported in camels or otherwise. For the data of seroprevalence of MERS-CoV in camels, we searched Google Scholar, PubMed, and Medline using key words "MERS in camels" and "MERS in dromedary". We used the data of MERS-CoV seroprevalence in camels, as reported by Dighe et al[21], for the comparison of mortality due to COVID-19 across 23 countries. The complete list of these 23 countries is provided in the **Supplementary Material**.

Thirdly, travel to a country where MERS is endemic may also increase the risk of exposure of a population to MERS-CoV. MERS is endemic in Saudi Arabia and according to FAOUN, 2129 MERS cases are reported by February 17th, 2020. Therefore, we collected and analyzed data of the number of people visiting Saudi Arabia from 51 countries for 5 years, i.e., 2014-218. The travel data was collected from the United Nations World Tourism Organization (UNWTO)[22]. The complete list of 51 countries is provided in the **Supplementary Material**.

Statistical Analysis

We mainly used two statistical methods to explore the relationship between the three above mentioned factors that may increase the risk of exposure of a population to MERS-CoV. Firstly, we used two-sample independent *t*-test for comparing the number of COVID-19 deaths per million (deaths/M) of a population in the two groups of countries, based on whether the number of reported MERS cases were at least 10 or otherwise. The test checks the null hypothesis that mortality rate will be the same in both groups against the assumption that mortality rate due to COVID-19 will differ across the two groups. As discussed above, it is anticipated that the mortality rate due to COVID-19 will be significantly lower in a group where MERS is prevalent.

Two-sample independent *t*-test was also used for comparison of the number of COVID-19 deaths/M of a population in the two groups of countries, that were divided according to MERS-CoV seroprevalence in camels. As indicated earlier, it is expected that the mortality rate due to COVID-19 will not be the same between the two groups and is likely to be lower in the group where MERS-CoV is reported in camels than otherwise.

Lastly, we used multivariable ordinary least squares (OLS) regression to test our final assumption that countries that have experienced increased travelling to Saudi Arabia are likely to report lower mortality rate due to COVID-19. We used the following regression equation (1):

$$Mortality\_rate_i = a + b_1 Cases_i + b_2 SArabia\_travelling_i + e_i, \quad \text{(equation 1)}$$

Where, the subscript i denotes country, *Mortality_rate* is the number of deaths/M of a population due to COVID-19 in a country, *Cases* is a control variable indicating the total number of COVID-19 cases/M of a population reported in a country and *SArabia_travelling* is the frequency of travelling to Saudi Arabia, e is an idiosyncratic error term. We used log transformation for all variables. Following, we also used the Breusch-Pagan test to check homoscedasticity and the test failed to reject homoscedastic errors at $p < 0.05$. Statistical significance was set at $p < 0.05$ and we used 2-tailed tests[23]. The data were analyzed using Stata/SE version 16.0 (StataCorp, College Station, TX, USA).

Results

The number of reported COVID-19 cases increased worldwide and the highest number of cases were reported in Europe and North America till May 10th, 2020 (Figure 1).

There was a statistically significant difference in the number of COVID-19 deaths/M of

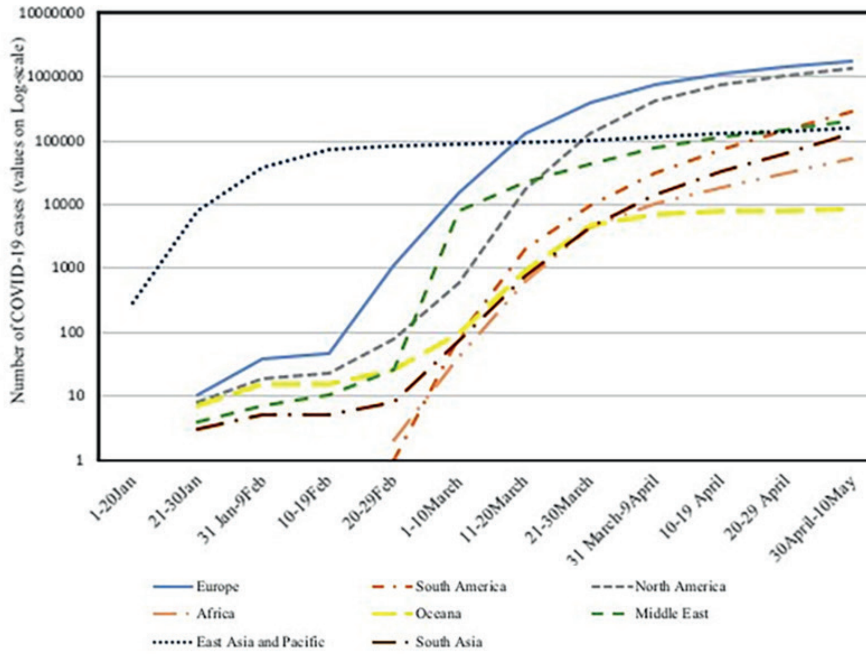

Figure 1. The number of COVID-19 cases, reported by World Health Organization (WHO) until May 10th, 2020 across different regions globally.

a population in the two groups of countries that either reported greater or less than 10 MERS cases since 2012 [p = 0.0024, t-stat=3.686, (95% CI, 0.52%-2.73%)]. The t-test results showed that countries where MERS-CoV is prevalent have a statistically significantly lower number of COVID-19 deaths/M of a population (1.63) than COVID-19 deaths/M of a population (4.74) in the group of countries with no or negligible MERS cases. Figure 2 compares the number of COVID-19 cases per million of a population and the number of COVID-19 deaths per million of a population with the number of MERS cases reported across a few countries.

There was also a statistically significant difference in the number of COVID-19 deaths/M of a population in the two groups of countries where MERS-CoV is reported in camels or otherwise [p=0.0002, t-stat=4.507, (95% CI, 0.74%-2.13%)]. It can be seen from Figure 3 that MERS-CoV is prevalent in camels across the Middle East countries, with the highest MERS-CoV seroprevalence percentage being reported in Qatar and Oman. As of May 17th, 2020, mortality rate of COVID-19 was much lower in the Middle East countries (with high seroprevalence of MERS-CoV in camels) than USA and UK (Figure 4).

The relationship between travel history to Saudi Arabia across five regions globally (i.e. Europe, America, Africa, Asia and Pacific and South Asia) with respect to the Middle East and the number of COVID-19 deaths per million of a population reported across the five regions is shown in Figure 5. It can also be seen from Figure 6 that the number of people visiting Saudi Arabia from Europe and America was comparatively lower than the Middle East, and the number of COVID-19 deaths/M of a population were markedly higher in Europe and America than the other regions as reported by May 17th, 2020. The OLS regression estimates showed that there was a negative relationship between travel history to Saudi Arabia and the number of COVID-19 deaths/M of a population (p<0.001, SE=0.066, t-stat = -3.83, [95% CI, -0.386 to -0.120, adjusted R-squared=0.7705). Also, the regression results of a control variable indicated that the mortality rate of COVID-19 is probable to increase as the total number of COVID-19 cases increase in a population.

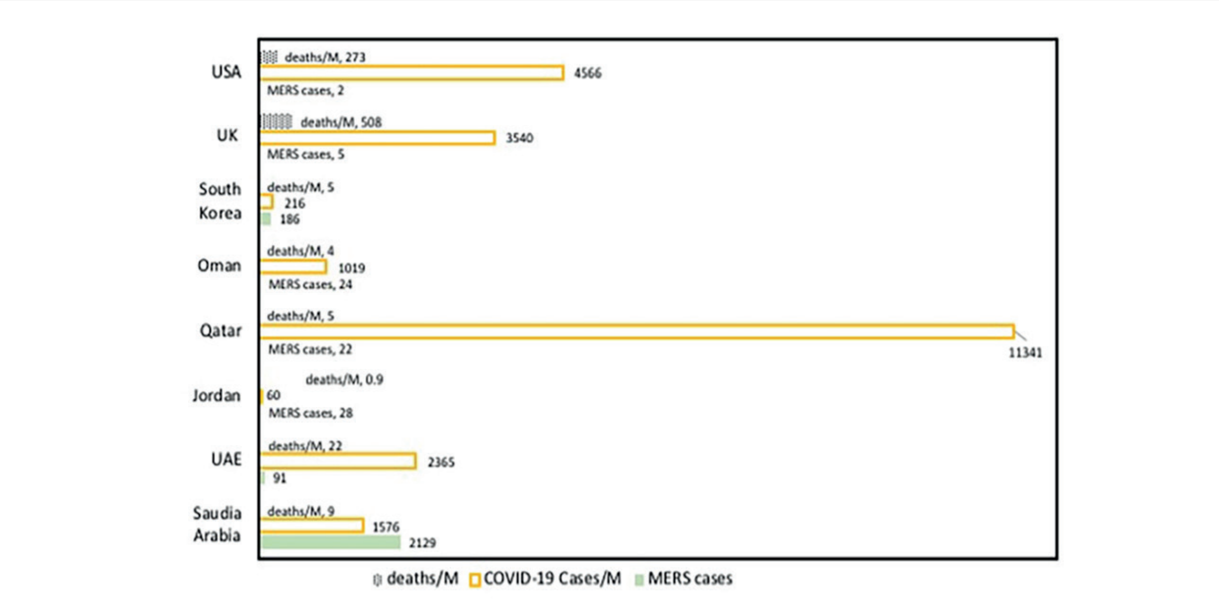

Figure 2. Comparison of the number of COVID-19 cases per million of a population (cases/M) and the number of COVID-19 deaths per million (deaths/M) of a population (until May 17th, 2020) with the number of MERS cases reported across a few countries until February, 2020.

Discussion

Much is still unknown about the illness, recovery, and mortality associated with COVID-19. The Middle East has been the epicenter for the earlier epidemics of MERS. As observed in this study, mortality due to COVID-19 was much lower in the Middle East than Europe and USA; cross-protective immunity from previous endemics of MERS-CoV might have offered a huge benefit. Similarly, MERS have been reported frequently in South Korea (186 MERS cases by

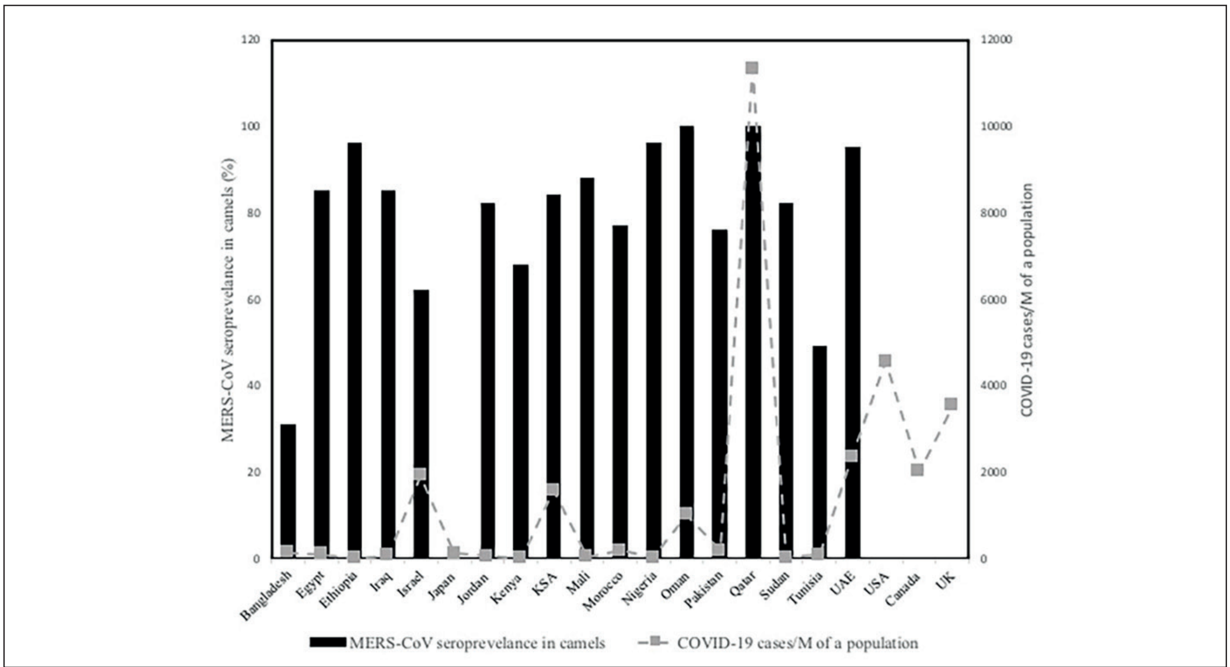

Figure 3. Comparison of the number of COVID-19 cases per million (cases/M) of a population with seroprevalence of MER-CoV in camels across a few countries.

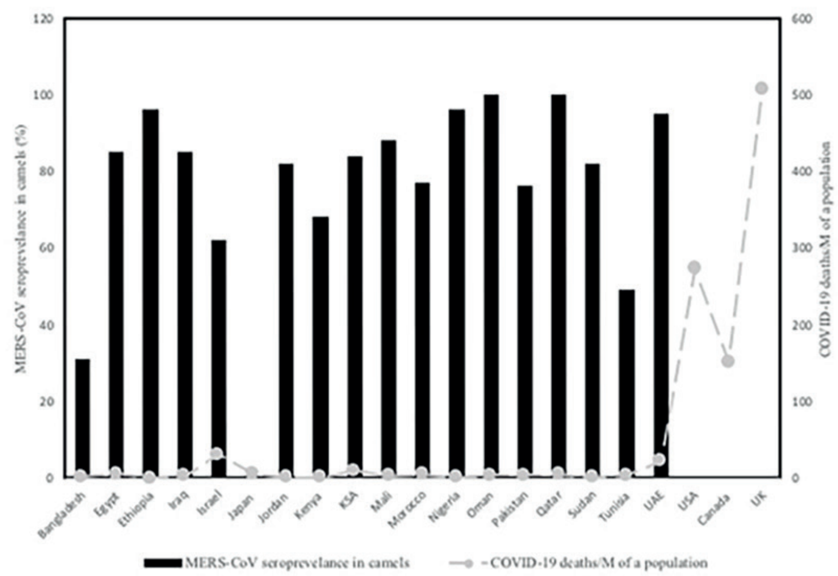

Figure 4. Comparison of the number of COVID-19 deaths per million (deaths/M) of a population with seroprevalence of MER-CoV in camels across a few countries.

2018) and mortality rate of COVID-19 was much lower in South Korea than UK and USA, i.e., total number of COVID-19 cases/M of a population were 216 in South Korea, 4566 in USA and 3540 in UK and total number of COVID-19 deaths/M of population were 5 in South Korea, 273 in USA and 508 in UK, as reported by May 17th, 2020. The mode of infection is remarkably similar among SARS-CoV-2, SARS-CoV and MERS-CoV, i.e., after invading host cells, these viruses

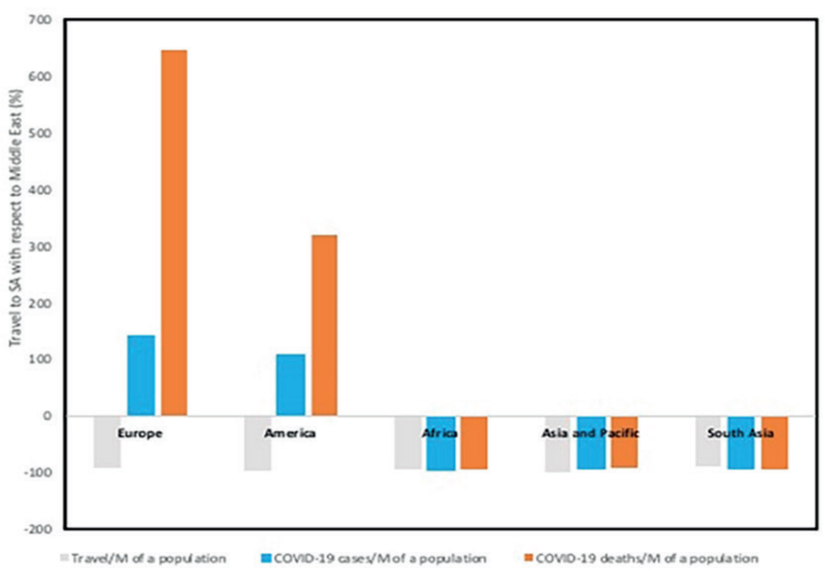

Figure 5. Relationship between travel history to Saudi Arabia from five regions worldwide with respect to the Middle East, the number of COVID-19 cases per million (cases/M) of a population and the number of COVID-19 deaths/M of a population reported across the five regions (until May 17th, 2020). Travel/M of a population shows the total travel to Saudi Arabia across a region for five years (i.e., 2014-2018).

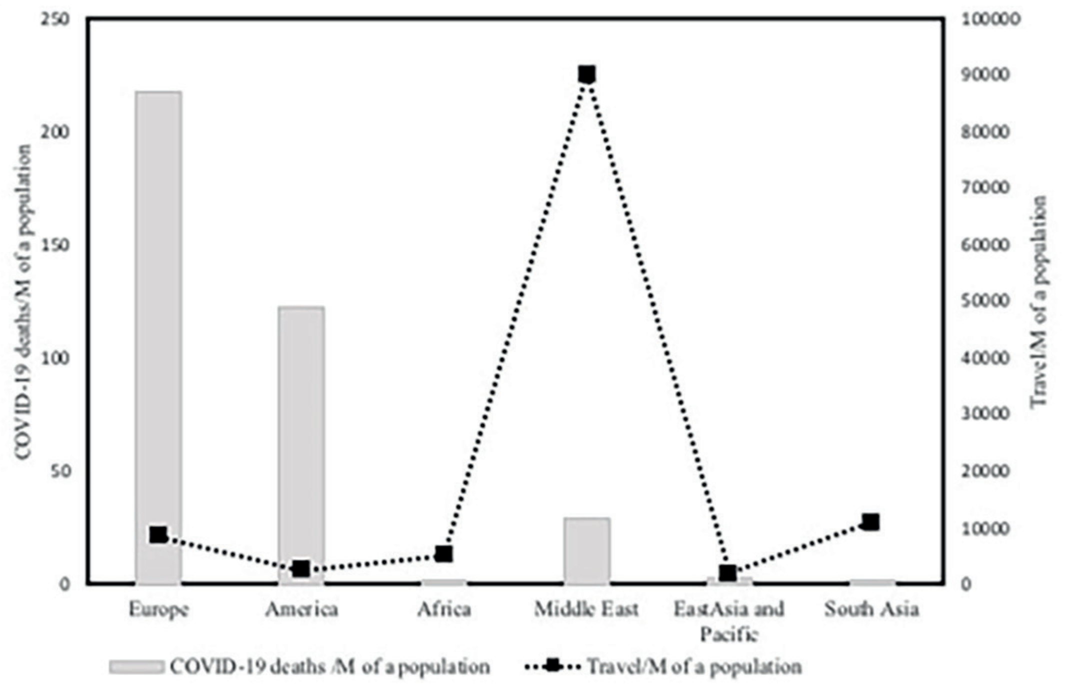

Figure 6. Relationship between death rate due to COVID-19 across six regions worldwide and travel history to Saudi Arabia. Travel per million (travel/M) of a population represents total travel to Saudi Arabia from a region for five years (i.e., 2014-2018).

interfere with antiviral type 1 interferons production pathways through multiple mechanisms compromising the first line of defense against viruses, leading to viremia, increased neutrophils and macrophages at the site of infection, production of proinflammatory cytokines, Th1/Th17 dependent activation of the B cells and production of NAbs[3,4,24].

Neutralizing antibodies can persist up to 34 months and 24 months after MERS-CoV and SARS-CoV infections, respectively[4,25], and may protect from reinfection or infection from a similar strain of other coronaviruses, such as SARS-CoV-2. Previous studies[1,4,25] have demonstrated that NAbs against one virus may also provide cross-protection against viruses of the same genus. Seroprevalence of antibodies against human coronaviruses that cause common cold increases with age until adolescence[26], and it has been observed that prevalence of SARS-CoV-2 is much lower in children and it mainly affects older people[27]. This might be due to cross-reactivity between NAbs against human coronaviruses that cause common cold and SARS-CoV-2. Chan et al[2] found that convalescent plasma from patients with SARS might contain cross-reactive antibodies against MERS. In a recent investigation, Walls et al[24] showed that antibodies response against SARS-CoV potently cross-react and neutralize the effect of SARS-CoV-2. Our results suggest the possibility of cross-reactivity between NAbs against MERS-CoV and SARS-CoV-2. Furthermore, the seroprevalence of NAbs depends on the severity of the infection, and mild asymptomatic infections are associated with low levels of NAbs[25]. These asymptomatic cases often go unrecognized and have the potential to transmit the disease to other persons.

We also found that mortality due to COVID-19 was much lower in countries with a high seroprevalence of MERS-CoV in camels. High seroprevalence of MERS-CoV have been reported in dromedary camels across Africa and the Middle East[21,28]. MERS-CoV is capable of transmission from camels-to-humans and humans-to-humansm[10,11]. This community transfer of MERS-CoV is repeatedly reported in Saudi Arabia and close contact with camels is considered as a risk factor for contracting the disease[10]. For example, Azhar et al[10] demonstrated high seroprevalence of MERS-CoV among people who were in close contact with camels than general population of Saudi Arabia. Moreover, these camel workers may or may not develop symptoms of the disease but can transmit the disease to high risk susceptible people with comorbidities in which MERS can be fatal. It is interesting to note that although the number of COVID-19 cases/M of a population, as reported by May 17th, 2020, were markedly higher in Qatar than UK and USA (Figure 3), but COVID-19 deaths/M of a population were markedly lower in Qatar than UK and USA, i.e., deaths/M of a population was 5 in Qatar *vs.* 273 and 508 in USA and UK respectively (Figure 4). The highest MERS-CoV seroprevalence in camels was reported in Qatar. This significant difference in mortality due to COVID-19 might be due to community transfer of MERS-CoV from camels-to-humans and persistence of cross-reactive NAbs against SARS-CoV-2 among people of Qatari, leading to a comparatively lower mortality rate of COVID-19 in Qatar.

The transmission of COVID-19 seems to be highly associated with the travel-related spread of the virus. Basic reproductive number (which is a measure of transmissibility of viral diseases) of COVID-19 is 2.2[5] and travel associated spread of the virus led to the global pandemic. The reproductive number of MERS-CoV can be as high as 8.1 (as reported in South Korea) than 0.45 (as reported in Saudi Arabia)[11]. In 2015, a single person infected with MERS-CoV travelled to South Korea from the Middle East and led to MERS outbreak in South Korea[11]. By April 29th, 2020, Europe and America were hard hit by the disease and the mortality rate due to COVID-19 in these two regions was remarkably higher than the Middle East. We found that among 51 countries, the number of people visiting Saudi Arabia from the Middle East was comparatively higher than Europe and USA, and there was a significant difference in the number of deaths/M of a population and travel history to Saudi Arabia. Frequent travel to Saudi Arabia may have an increased risk of contracting MERS among people of the Middle East, leading to a high seroprevalence of NAbs against MERS-CoV, and population-based cross-protective immunity against SARS-CoV-2 may have led to lower mortality rate due to COVID-19 in the Middle East countries.

There is a lack of data on the seroprevalence of MERS-CoV in countries other than Saudi Arabia. Although, high seroprevalence of MERS-CoV in camels is reported in a number of countries, such as Pakistan and Kenya[21], camels-to-human transfer of MERS-CoV is reported mainly in Saudi Arabia only. This might be due to phylogenetic variations that exist between different strains of MERS-CoV[28,29]. It is possible that one particular strain is more transmittable and virulent than other strain of MERS-CoV. Chu et al[28] compared the virulence of MERS-CoV isolated from camels of Africa and Arabian Peninsula, and they demonstrated that MERS-CoV isolated from camels in Africa had lower virus replication potential in human lung cell cultures than MERS-CoV isolated from camels in Arabian Peninsula. The genetic mutations are frequently observed in coronaviruses[28,29]. For example, SARS-like strain was detected in civets in China with limited pathogenicity and transmission potential in humans[30]; however, a few changes in amino acid sequence in the SARS-CoV spike protein enabled the virus to cause deadly SARS disease among humans[29]. Furthermore, MERS is likely to be overlooked in developing countries across Africa and Asia due to lack of awareness about the disease, limited healthcare facilities than Saudi Arabia, lack of surveillance and seroepidemiological studies involving population pool, and lack of research resources in developing countries.

This research has some limitations. We did not include the number of people tested for COVID-19 across different countries and it may have influence results. Other factors that may have influenced the spread of SARS-CoV-2 include temperature variation across countries, mean age of population in countries, healthcare infrastructure, influence of extent of lockdown and social distancing measures that were being implemented by governing bodies. Furthermore, it is an observational study and future cohort seroepidemiological studies for the detection of NAbs are required to confirm the role of cross-protective immunity in a population.

Conclusions

We compared the mortality rate of COVID-19 between countries that are likely to be exposed to MERS-CoV and those that are unexposed or with very negligible exposure to MERS-CoV. We found that the mortality rate due to SARS-CoV-2 was statistically significantly less across countries where people are at an increased risk of exposure to MERS-CoV than otherwise. The three factors (i.e., number of MERS cases, MERS-CoV seroprevalence in camels and travel to Saudi Arabia) that were assumed to increase the risk of exposure of a population to MERS-CoV were associated with lower mortality rate due to SARS-CoV-2. Our study indicates an important factor that might explain disparities in the COVID-19 mortality rate that are being observed across different countries globally. For example, we found that despite having a high number of COVID-19 cases/M of a population, the mortality rate due to SARS-CoV-2 was much lower in the countries where high seroprevalence of MERS-CoV was reported in camels than otherwise, such as Qatar. This might be due to community transfer of MERS-CoV from camels-to-humans, and it is possible that high seroprevalence of NAbs against MERS-CoV exists among Qatari population, and these NAbs might have offered population-based cross-protective immunity against other coronaviruses, such as SARS-CoV-2, leading to comparatively lower mortality due to COVID-19 in Qatar. These results strongly suggest the possibility of cross-reactivity between MERS-CoV neutralizing antibodies and SARS-CoV-2. Our study highlights the importance of serological cohort studies to stratify a population that is immune and is less likely to be infected by SARS-CoV-2. This study strongly supports the growing body of research that emphasizes the role of serological response in diagnosis, treatment and prevention of COVID-19. Future population-based seroepidemiological studies are required to confirm our findings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Chan KH, Cheng VCC, Woo PCY, Lau SKP, Poon LLM, Guan Y, Seto WH, Yuen KY, Peiris JSM. Serological responses in patients with severe acute respiratory syndrome coronavirus infection and cross-reactivity with human coronaviruses 229E, OC43, and NL63. Clin Diagn Lab Immunol 2005; 12: 1317-1321.
2) Chan KH, Chan JFW, Tse H, Chen H, Lau CCY, Cai JP, Tsang AKL, Xiao X, To KKW, Lau SKP, Woo PCY, Zheng BJ, Wang M, Yuen KY. Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests. J Infect 2013; 67: 130-140.
3) De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14: 523-534.
4) Liu WJ, Zhao M, Liu K, Xu K, Wong G, Tan W, Gao GF. T-cell immunity of SARS-CoV: implications for vaccine development against MERS-CoV. Antiviral Res 2017; 137: 82-92.
5) Chakraborty C, Sharma AR, Sharma G, Bhattacharya M, Lee SS. SARS-CoV-2 causing pneumonia-associated respiratory disorder (COVID-19): diagnostic and proposed therapeutic options. Eur Rev Med Pharmacol Sci 2020; 24: 4016-4026.
6) Eo SA, Alhowikan AM, Khlaiwi TAL, Meo IM, Halepoto DM, Iqbal M, Usmani AM, Hajjar W, Ahmed N. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur Rev Med Pharmacol Sci 2012; 24: 2012-2019.
7) Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012; 367:1814-1820.
8) FAO MERS situation update – MERS Corona virus – FAO Emergency Prevention System for Animal Health (EMPRES-AH). Available at: http://www.fao.org/ag/againfo/programmes/en/empres/mers/situation_update.html.
9) Meyer B, Müller MA, Corman VM, Reusken CBEM, Ritz D, Godeke GJ, Lattwein E, Kallies S, Siemens A, van Beek J, Drexler JF, Muth D, Bosch BJ, Wernery U, Koopmans MPG, Wernery R, Drosten C. Antibodies against MERS coronavirus in dromedaries, United Arab Emirates, 2003 and 2013. Emerg Infect Dis 2014; 20: 552-559.
10) Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, Hashem AM, Madani TA. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med 2014; 370: 2499-2505.
11) Killerby ME, Biggs HM, Midgley CM, Gerber SI, Watson JT. Middle east respiratory syndrome coronavirus transmission. Emerg Infect Dis 2020; 26: 191-198.
12) Cotten M, Watson SJ, Kellam P, Al-Rabeeah AA, Makhdoom HQ, Assiri A, Aal-Tawfiq J, Alhakeem RF, Madani H, AlRabiah FA, Hajjar S Al, Al-Nassir WN, Albarrak A, Flemban H, Balkhy HH, Alsubaie S, Palser AL, Gall A, Bashford-Rogers R, Rambaut A, Zumla AI, Memish ZA. Transmission and evolution of the Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive genomic study. Lancet 2013; 382: 1993-2002.
13) Swerdlow DL, Finelli L. Preparation for possible sustained transmission of 2019 Novel coronavirus: lessons from previous epidemics. JAMA 2020; 323: 1129-1130.
14) Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Contact tracing assessment of COVID-19 transmission dynamics in taiwan and risk at different exposure periods before and after symptom

onset. JAMA Intern Med Published online 2020; e202020. doi: 10.1001/jamainternmed.2020.2020. Online ahead of print.

15) Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, Liao P, Qiu JF, Lin Y, Cai XF, Wang DQ, Hu Y, Ren JH, Tang N, Xu YY, Yu LH, Mo Z, Gong F, Zhang XL, Tian WG, Hu L, Zhang XX, Xiang JL, Du HX, Liu HW, Lang CH, Luo XH, Wu SB, Cui XP, Zhou Z, Zhu MM, Wang J, Xue CJ, Li XF, Wang L, Li ZJ, Wang K, Niu CC, Yang QJ, Tang XJ, Zhang Y, Liu XM, Li JJ, Zhang DC, Zhang F, Liu P, Yuan J, Li Q, Hu JL, Chen J, Huang AL. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020; 26: 845-848.

16) Zhou P, Yang X Lou, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang R Di, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.

17) Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pacific J Allergy Immunol 2020; 38: 1-9.

18) Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 2020; 11: 1-12.

19) COVID-19 situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

20) Worldometer. Coronavirus Cases. Worldometer. Available at: https://www.worldometers.info/coronavirus/

21) Dighe A, Jombart T, Van Kerkhove MD, Ferguson N. A systematic review of MERS-CoV seroprevalence and RNA prevalence in dromedary camels: implications for animal vaccination. Epidemics 2019; 29: 100350.

22) (UNWTO) UNWTO. Saudi Arabia: Country-specific: Basic indicators (Compendium) 2014 - 2018 (01.2020). Available at: https://www.eunwto.org/doi/abs/10.5555/unwtotfb0682011120142018201907.

23) Lyu W, Wehby GL. Comparison of estimated rates of coronavirus disease 2019 (COVID-19) in border counties in Iowa without a stay-at-home order and border counties in Illinois with a stay-at-ome order. JAMA Netw open 2020; 3: e2011102.

24) Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020; 181: 281-292.e6.

25) Payne DC, Iblan I, Rha B, Alqasrawi S, Haddadin A, Al Nsour M, Alsanouri T, Ali SS, Harcourt J, Miao C, Tamin A, Gerber SI, Haynes LM, Al Abdallat MM. Persistence of antibodies against Middle East respiratory syndrome coronavirus. Emerg Infect Dis 2016; 22: 1824-1826.

26) Shao X, Guo X, Esper F, Weibel C, Kahn JS. Seroepidemiology of group I human coronaviruses in children. J Clin Virol 2007; 40: 207-213.

27) Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; 323: 1775-1776.

28) Chu DKW, Hui KPY, Perera RAPM, Miguel E, Niemeyer D, Zhao J, Channappanavar R, Dudas G, Oladipo JO, Traoré A, Fassi-Fihri O, Ali A, Demissié GF, Muth D, Chan MCW, Nicholls JM, Meyerholz DK, Kuranga SA, Mamo G, Zhou Z, So RTY, Hemida MG, Webby RJ, Roger F, Rambaut A, Poon LLM, Perlman S, Drosten C, Chevalier V, Peiris M. MERS coronaviruses from camels in Africa exhibit region-dependent genetic diversity. Proc Natl Acad Sci U S A 2018; 115: 3144-3149.

29) Li F. Structural analysis of major species barriers between humans and palm civets for severe acute respiratory syndrome coronavirus infections. J Virol 2008; 82: 6984-6991.

30) Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, Luo SW, Li PH, Zhang LJ, Guan YJ, Butt KM, Wong KL, Chan KW, Lim W, Shortridge KF, Yuen KY, Peiris JSM, Poon LLM. Isolation and characterization of viruses related to the SARS coronavirus from animals in Southern China. Science 2003; 302: 276-278.