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A comparative analysis of epidemiological characteristics of MERS-CoV and SARS-CoV-2 in Saudi Arabia

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ABSTRACT

In this study, we determine and compare the incubation duration, serial interval, pre-symptomatic transmission, and case fatality rate of MERS-CoV and COVID-19 in Saudi Arabia based on contact tracing data we acquired in Saudi Arabia. The date of infection and infector-infectee pairings are deduced from travel history to Saudi Arabia or exposure to confirmed cases. The incubation times and serial intervals are estimated using parametric models accounting for exposure interval censoring. Our estimations show that MERS-CoV has a mean incubation time of 7.21 (95% CI: 6.59–7.85) days, whereas COVID-19 (for the circulating strain in the study period) has a mean incubation period of 5.43(95% CI: 4.81–6.11) days. MERS-CoV has an estimated serial interval of 14.13(95% CI: 13.9–14.7) days, while COVID-19 has an estimated serial interval of 5.1(95% CI: 5.0–5.5) days. The COVID-19 serial interval is found to be shorter than the incubation time, indicating that pre-symptomatic transmission may occur in a significant fraction of transmission events. We conclude that during the COVID-19 wave studied, at least 75% of transmission happened prior to the onset of symptoms. The CFR for MERS-CoV is estimated to be 38.1% (95% CI: 36.8–39.5), while the CFR for COVID-19 1.67% (95% CI: 1.63–1.71). This work is expected to help design future surveillance and intervention program targeted at specific respiratory virus outbreaks, and have implications for contingency planning for future coronavirus outbreaks.

1. Introduction

1.1. Epidemiological features of MERS-CoV and COVID-19

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV-2) are three highly transmissible and deadly viruses

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that first appeared in humans around the turn of the twenty-first century (Guarner, 2020). These coronaviruses are capable of transmission from animals to human, and human to human. SARS-CoV, transmitted from bats to civet cats to humans, emerged in February 2003 and resulted in 8000 deaths in 26 countries, followed by MERS-CoV, emerged in June 2012 in Saudi Arabia and transmitted from dromedary camels to humans caused severe symptoms and deaths of more than 828 in 27 countries (Li et al., 2020a; Nassar et al., 2018). A decade later, towards the end of 2019, a new human coronavirus disease (COVID-19) was reported in Wuhan, China (Li et al., 2020b), and swiftly spread around the globe. By April 2022, there had been over 497 million confirmed cases, resulting in the death of almost 6.1 million people (Chaplin, 1843). The economic destruction and health hazards presented by these coronaviruses are enormous, and the situation has become worse as the number of MERS-CoV and SARS-CoV-2 cases and deaths continued to rise. Regrettably, medical interventions for these human coronaviruses (hCoVs) remain challenging in a number of countries around the world (Zhu et al., 2020).

This paper focuses on a comparative study of MERS-CoV and SARS-CoV-2. MERS-CoV was the second major coronavirus in the 21st century. The particular mechanism of transmission, on the other hand, is yet uncertain. Despite the fact that the vast majority of MERS-CoV cases occurred in Saudi Arabia and the United Arab Emirates, there have been cases also in South Korea, parts of Europe, North America, and a total of 27 more countries. According to the World Health Organization, the disease is widespread in Saudi Arabia, with one human fatality reported between January and February 2022. At this time, there is no vaccine or treatment for the disease, and containment techniques such as isolation of suspected or confirmed human cases have been used to limit the transmission risk. It has been shown that in the event of an outbreak, the characteristics of the index case can significantly influence the disease spread pattern and scale, which may be accelerated by the transmission inside hospitals (Chowell et al., 2014; for Disease Prevention EC, 2019). On the other hand, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the infection being commonly referred to as COVID-19, rapidly spread globally, producing a pandemic with approximately 497 million cases and 6.1 million deaths at the time of writing (Vickers, 2017). In Saudi Arabia, the first case was confirmed on March 2, 2020 – an individual who had travelled from Iran via Bahrain. As of July 26, 2021, 518143 cases had been confirmed (ali Salih et al., 2020). Many of the initial cases were imported from Iran, with later cases being caused by the local transmission. Public health interventions included identifying potential contacts of confirmed cases; monitoring close contacts and quarantining for 14 days from their last exposure to an identified case. In addition, low-risk contacts were put under active surveillance and contacted daily to monitor their health status (Huang et al., 2020).

SARS-CoV-2 has several characteristics in common with SARS-CoV and MERS-CoV, while also exhibiting significant distinctions (Zhu et al., 2020). It is critically important to learn from the past SARS-CoV and MERS-CoV outbreaks, and timely update our knowledge on SARS-CoV-2 and MERS-CoV for the control of ongoing COVID-19 pandemic and the ongoing outbreak of MERS-CoV. A comparative study of these hCOVs is important for the design of disease-specific interventions (Hijawi et al., 2013; Zhu et al., 2020). For a comparative study, we analyzed contact tracing data from MERS-CoV and COVID-19 clusters in Saudi Arabia and assessed the fraction of pre-symptomatic transmission using incubation periods and serial interval estimation. The serial interval is defined as the time duration between the onset of symptoms in a primary case (infector) and the beginning of symptoms in a secondary case (infectee), while the incubation period is defined as the time period between exposure and development of symptoms. When the serial interval is shorter than the incubation period, pre-symptomatic transmission may occur and may even be more significant and common than symptomatic transmission (Tindale et al., 2020a). On the other hand, estimates of the case fatality ratio (CFR) may be biased upward by underreporting cases and downward by omitting to account for the time period between confirmation and death. Collecting extensive epidemiological data from the population allows for a more detailed description of asymptomatic and symptomatic cases. We estimated the CFRs of COVID-19 and MERS-CoV in Saudi Arabia using publicly accessible data and data from the Ministry of Health, while taking into consideration the time delay between confirmation and death.

2. Material and methods

2.1. Details of the COVID-19 and MERS-CoV datasets

We obtained the COVID-19 data from the Ministry of Health (MoH) in Saudi Arabia and from publicly available official reports of cases by regional health commissions in Saudi Arabia. The detailed information of each confirmed case include the following: case ID, gender, age, date of symptom onset, date of confirmation, history of traveling to or residing in Iran or cities other than the reporting city, date of arriving at the city where the case is reported. If identified via contact tracing done by centers for disease control and prevention officers, the details also include contact case ID and date of exposure. Moreover, the cases are categorized into different groups based on travel or residency history and chains of transmission of infection.

For the MERS-CoV dataset, we retrieved publicly available data from multiple sources, including the MoH of Saudi Arabia, the WHO and local Saudi news reports to collect a line list of all confirmed cases reported by 19 June 2012. In the case of any data conflict between the different sources, we relied on the most up-to-date information from official reports published by the MoH on a daily basis during the outbreak. The official reports were only available in the English language and included brief information of each confirmed case, including demographic characteristics (e.g. age and sex), date of exposure and onset of symptoms, as well as possible linkage with confirmed cases and the associated cluster.

2.2. Methods

For effective prevention and control, it is necessary to first understand the epidemiological features of both MERS-CoV and COVID-19 in general before concentrating on disease-specific interventions. In this study, we estimated and compared the incubation period, serial interval, pre-symptomatic transmission, and case fatality ratio in the study periods of MERS-CoV and COVID-19 outbreaks in Saudi Arabia. Cases were included in our study if information on the time interval between exposure to MERS-CoV and COVID-19 and the onset of symptoms was available.

The estimation of MERS-CoV and COVID-19 incubation periods was based on the start and end possible exposure times, and on the reported times of symptom onset. It is hard to identify the exact times of exposure and thus we used interval censoring, which uses the likelihood of a time falling in a defined window, (R package icenReg (Anderson-Bergman, 2017)) to make parametric incubation period distribution estimations. We divided the data from all data sets into two groups: those who had symptoms early and those who developed symptoms later. The incubation times were then estimated independently for each group. Three commonly used incubation period distributions were fitted (gamma, Weibull, and Log normal). We estimated median incubation time and important quantiles (2.5th, 25th, 50th 75th, and 97.5th percentiles) for each model. We followed this procedure with the complete MERS-CoV and COVID-19 data on confirmed cases and compared the results with estimates computed from aggregate or cumulative numbers of cases and deaths at different stages of the outbreaks by using parametric models (Cox, 1959; Farewell, 1982).

We calculated the proportion of transmission that happened prior to the onset of symptoms as the fraction of samples with a serial interval less than the incubation period. As follows, we presented a method to account for covariation between the two variables. The difference between the means of two random variables is called the mean difference. The mean serial interval minus the mean incubation periods therefore provides an approximation of the mean time interval between symptoms associated with transmission.

In additionally, we estimated the CFR by modelling the expected mortality rate from COVID-19 and MERS-CoV. We estimated that the duration from onset to death for COVID-19 and MERS-CoV was controlled by a gamma distribution with a mean of 14.8 and 16.7 days, respectively, shape parameters of 2.2 and 1.49, and a rate parameter of 0.1 and 0.089. We calculated CFR for COVID-19 using the maximum-likelihood approach, fitting the model to the data under the assumption that observed death rates are Poisson distributed. For MERS-CoV, we simply calculate the CFR by taking the ratio of reported deaths over reported cases.

3. Statistical analysis

3.1. Incubation period

We utilised contact tracing data and exposure interval censoring to analyse the incubation duration of MERS-CoV and COVID-19 in Saudi Arabia. If infection happened between X and Y and the symptoms showed up at Z. From the relation of X, Y, and Z, we obtain the $c(Z|u) = f(Z-u|u) = f(Z-u)$ then the likelihood of the incubation period can be expressed as

$$\int_{u=X}^{Y} k(u) f(Z-u)\, du$$

$k(u)$ represents the probability of infection at time u, and $f(.)$ is the incubation distribution's density. This simplifies to $F(Z-X) - F(Z-Y)$, where $F(.)$ is the cumulative density of the incubation distribution and $k(u)$ is the uniform density. Therefore, the assumption of constant infection probability over any given exposure interval allows us to "reverse the time axis," since the simplified equation above is identical to the likelihood contribution for survival data censored on the interval $(Z-Y, Z-X)$. This condition should be acceptable in the context of MERS-CoV illness, since each exposure period is relatively short, and inverting the time axis enabled us to use standard methods for interval-censored data (Virlogeux et al., 2016a).

We have taken into consideration the following three parametric models (gamma, lognormal and weibull) for the incubation distribution. We can fit any of these parametric models by maximising (for example, by numerical optimization) the likelihood function using the form

$$L(.|D) = \prod_{i:L_i < R_i} F(R_i) - F(L_i) \prod_{i:L_i = R_i} f(L_i),$$

where $F(.)$ and $f(.)$ represent the corresponding cumulative distribution function and probability density function, respectively (Cowling et al., 2007).

3.2. Serial interval

For the serial interval, we depending on the data on the intervals between the first reports of symptoms in several instances within small group such as households and boarding schools. The index case is the person in a household/boarding school who experiences symptoms initially. We tracked how long it took for symptoms to appear in the other members of the household/boarding school compared to the index case. Mixture models are important and flexibile methods (Klinkenberg & Nishiura, 2011; Vink et al., 2014) for modelling the probability density function as a weighted sum of parametric density functions $g_i(x|\theta_i)$ in multivariate independent observations $Y = (y1, .., yn)$ selected from d densities.

$$g(y) = \sum_{i=1}^{d} w_i g_i(y|\theta_i)$$

where d stands for the number of classes or groups that were formed for the mixing, and where $w_i > 0$ denotes the percentage of observations that came from each class i such that $\sum_{i=1}^{n} w_i = 1$. In other words, the parameter may be determined by measuring the mixture's density $\Theta = (w_i, \theta_i)$ of the model where θ_i is the (vector) parameter from class i. An expression for the log-likelihood of the mixing density is as follows:

$$L(\Theta) = log\left(\prod_{i=1}^{n} g(y_i|\theta_i)\right) = \sum_{j=1}^{n} log\left(\sum_{i=1}^{d} w_i g_i(y_i|\theta_i)\right)$$

the maximum likelihood estimate is

$$max \sum_{j=1}^{n} log\left(\sum_{i=1}^{d-1}\left(w_i g_i(y_i|\theta_i) + \left(1 - \sum_{i=1}^{k-1} w_i\right) g_d(y_i|\theta_i)\right)\right.$$

subject to

$$\sum_{i=1}^{d-1} w_i \leq 1$$

When $d > 1$, the addition of terms that exist inside a logarithm makes it very challenging to do this optimization. With the help of the R software's optim function, it is possible to minimise the log likelihood functions of the various laws that are used as arguments for this function. In addition to the initialization of the parameters to be optimised and the serial interval distributions for which we want the best-fit. The estimate outcomes of the mixture models Gamma, lognormal, and weibull are summarised in Fig. 6 (serial interval).

3.3. Case fatality rate

In addition, we utilise the same methodology that we used when estimating the incubation period in order to take into consideration the time delay from symptom onset to death and to estimate the case fatality rate (CFR). We use

$$g_{death}(t) = \int_0^t = g_{onset}(u) f_{onset-to-death}(t-u) d(u)$$

On day d, the number of new instances (onset) and the cumulative number of cases up until that time are as follows: $\xi_d = \int_{d-1}^{d} g_{onset}(t)dt$ and $\zeta_d = \int_0^d g_{onset}(t)dt$, respectively. The cumulative number of death cases up to time t is $D(t) = \int_0^t g_{death}(u)du$. Let $\xi_d = \sum_{i=1}^{n} \xi_d$, $\zeta_d = \sum_{i=1}^{n} \zeta_d$ and $D(t) = \sum_{i=1}^{n} D(t)$ total of new cases, cumulative cases, and cumulative fatalities to time t. Based on the data, we refer to X as the group of deceased people whose dates of onset are known, and Y as the group that includes all of the other instances. Let us define O_i as the observed time delay between the onset of the condition and the death of the jth patient in case X, and let us define O_i' as the observed time between hospital admission and death (which serves as a lower bound for the delay between the onset of the condition and the death) for the ith patient in case Y. The likelihood function is

$$L(\theta) = \prod_{i \in X} f_{onset-death}(O_i|\theta) \prod_{i \in Y} (1 - F_{onset-seath}(O_i'|\theta))$$

Where $f_{onset-death}$ and $F_{onset-death}$ are the probability density function and the cumulative density function of the time between the onset of symptoms and the death, respectively. We assume that the time between symptoms and death follows a gamma distribution.

4. Results

4.1. Incubation period

Incubation periods were estimated for both MERS-CoV and COVID-19 in Saudi Arabia. The direct estimates were from the time of exposure to symptom onset. For cases without a known earliest possible exposure time, we assume that the case must have been exposed within 21 days for both MERS-CoV and COVID-19 as 21 days was the longest incubation period reported for both covui (Qin et al., 2020; Virlogeux et al., 2016a, 2016b). For cases without a known latest possible exposure time, we assumed that exposure had to have occurred before symptom onset. Some cases had a travel history or contact with a known location or presumed source of the virus and this defined their window for exposure. For both, social distancing measures were implemented from the onset of the outbreaks.

For MERS-CoV, our direct analysis revealed a median incubation time of 6.60 days with the gamma distribution; shape 3.97 (95% CI: 3.11–4.56); and scale 1.811 (95% CI:1.397–1.972). The mean incubation time was determined to be 7.21 (95% CI: 6.59–7.85) days. We estimated the median incubation time for COVID-19 to be 4.94 days; the shape to be 3.69 (95% CI: 2.71–4.32); and the scale to be 1.469. (95% CI: 1.053–1.664). The mean was 5.43 (95% CI: 4.81–6.11) days. Table 1 summarizes these findings and also includes fitted Weibull and log-normal distributions. These are consistent with, or slightly longer than, previous estimates: see Fig. 1 and Fig. 2.

We emphasize that the estimated incubation time varies by person, particularly in the case of MERS-CoV, since only exposure and symptom onset data for the 2014 and 2015 were available. We proposed that we could estimate the incubation time for 2014 (which we characterized as the “early incubation period”) and 2015 (which we defined as the “late incubation period”), enabling us to discover any differences between the two periods under consideration (Fig. 2b). For early and late cases, the mean incubation duration was determined to be 5.20 (95% CI:4.58–5.90) days for early cases and 8.92 (95% CI:8.14–9.75) days for late cases, while the mean incubation period for all cases was calculated to be 7.21 days (95% CI:6.59–7.85). In contrast, the first known cases of COVID-19 had a history of travel to Iran, suggesting that people who visited Iran were exposed to the virus before arriving in Saudi Arabia. As a result, all that is required to calculate the incubation period is travel histories and the dates on which symptoms first appeared. We invented the term “early incubation” to describe this process. In addition, we were able to gather information on both the exposure window and the day when symptoms appeared, which allowed us to estimate late incubation periods. Thus, the mean time for early and late instances was 4.31 (95% CI:3.62–5.08) and 6.17 (95% CI:5.26–7.21) days, respectively, while the mean time for all instances was 5.43 (95% CI:4.81–6.11) days, according to the results in Table 2 and (Fig. 2a).

4.2. Serial interval

Serial intervals are defined in epidemiology as the time period between the development of symptoms in the primary case (infector) and the onset of symptoms in the secondary case (infectee). We observed that once non-pharmaceutical interventions were implemented, the average serial interval for (MERS-CoV and COVID-19) changed. Thus, control methods that minimise interactions between individuals in the population are predicted to have an effect on the serial intervals (Ali et al., 2020). The change in serial interval may not only measure the effectiveness of infection control interventions but may also indicate rising population immunity (Ali et al., 2020).

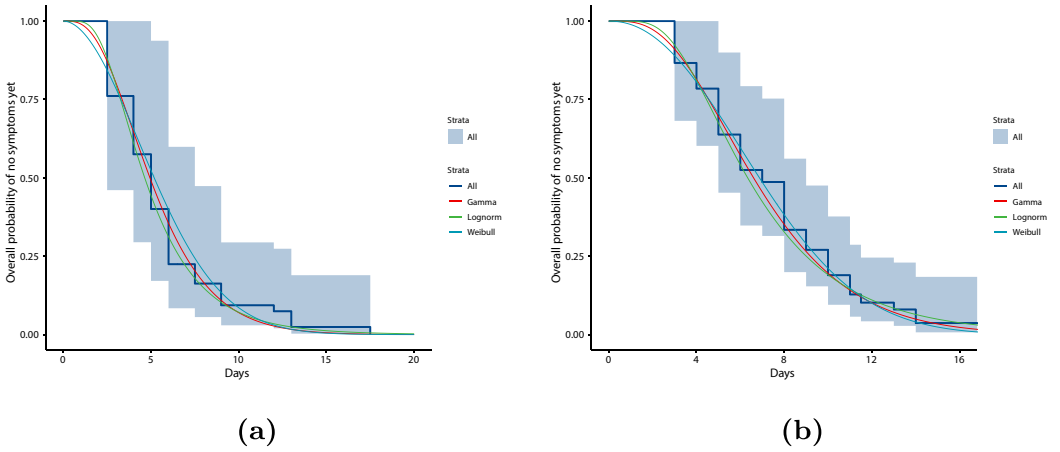


Fig. 1. Comparison of nonparametric and parametric estimations of the distribution of MERS-CoV and COVID-19 infection incubation times in Saudi Arabia. Using data from Saudi Arabia, the panels (a: COVID-19, b: MERS-CoV) compare the nonparametric Kaplan-Meier estimate of the incubation period distribution with the parametric lognormal, Weibull, and gamma distributions.

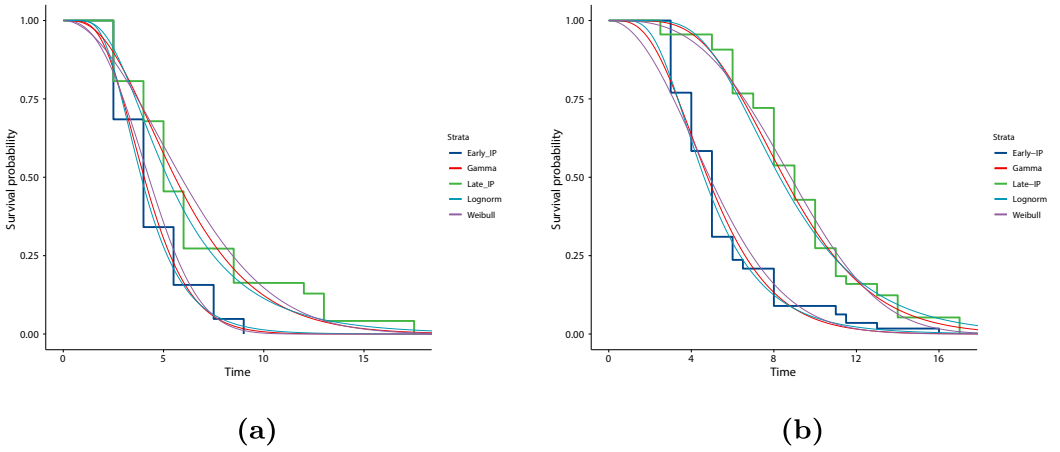


Fig. 2. Comparison of early and late nonparametric and parametric estimates of the distribution of the incubation time for MERS-CoV and COVID-19 infections in Saudi Arabia. Using data from Saudi Arabia, panels (a: COVID-19, b: MERS-CoV) contrast the Kaplan-Meier nonparametric estimate of the incubation duration distribution with the parametric fitted lognormal, Weibull, and gamma, distributions.

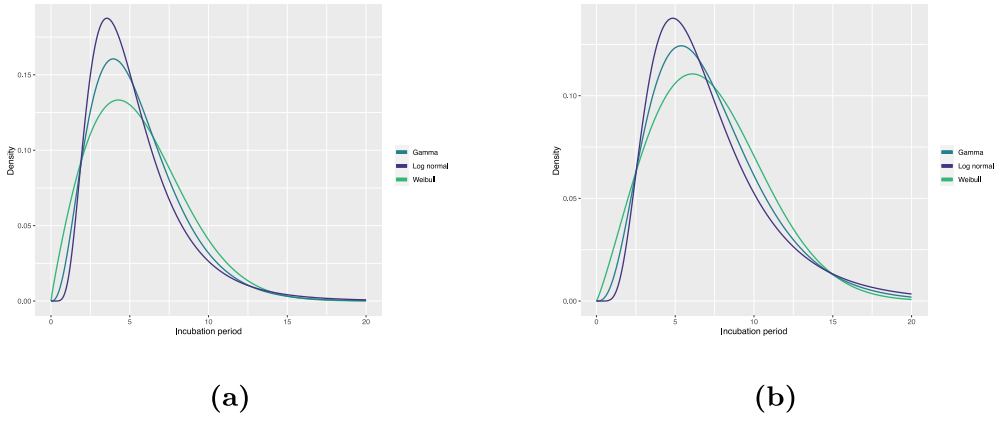


Fig. 3. Incubation period of MERS-CoV and COVID-19 infection outbreak in Saudi Arabia. Panel (a) shows the density estimation of COVID-19 incubation periods with gamma, Weibull and log normal distributions. Panel (b) shows the density estimation of MERS-CoV incubation periods with gamma, Weibull and log normal distributions.

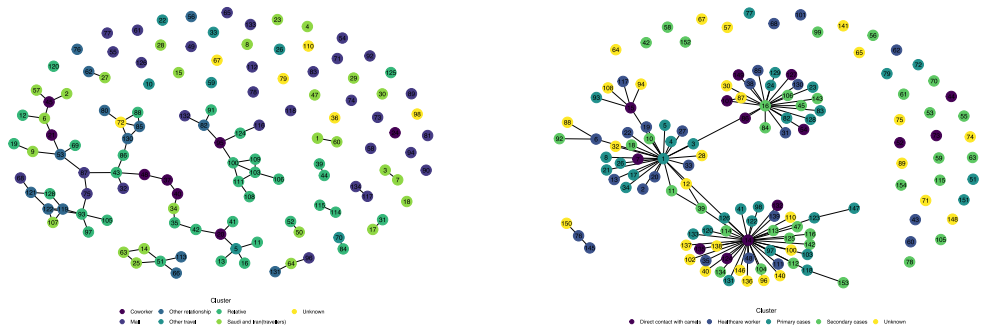
Table 1
The estimated mean incubation period, serial interval and proportion of transmission that is pre-symptomatic. Incubation periods were based on the gamma estimates as it is suitable for taking the covariation of serial intervals and incubation periods into account.

Type	Incubation period	Serial interval	Mean difference	Portion pre-symptomatic(−)
MERS-CoV (all)	7.21 (6.59–7.85)	14.13(13.9–14.7)	−6.92	0
MERS-CoV (early)	5.20 (4.58–5.90)	-	-	0
MERS-CoV (late)	8.92 (8.14–9.75)	-	-	0
COVID-19 (all)	5.43(4.81–6.11)	5.1(5.0–5.5)	0.42	0.758
COVID-19 (early)	4.31 (3.62–5.08)	-	-	0.846
COVID-19 (late)	6.17 (5.26–7.21)	-	-	0.815

In order to estimate the serial interval distributions for both COVID-19 and MERS-CoV, we selected potential transmission pairs from clusters of epidemiologically connected cases in the master database with the goal of estimating the serial interval distributions for both viruses. A potential transmission pair is defined as a pair formed by a primary case and one of their secondary cases. There was definite evidence of contact with an earlier confirmed case in just one of these pairs of cases; however, only the primary case, not the secondary case, had symptom start dates that could be determined for both instances. We estimated the serial intervals between all possible transmission case pairs, which were documented in the data and shown in Fig. 4.

Table 2
Incubation period estimates using gamma, Weibull and log normal distributions. 95% confidence intervals for the shape and scale (logmean and sd for log normal) parameters are shown in brackets.

Gamma	**mean**	**shape**	**rate/scale**
MERS-CoV	7.21(4.3–8.9)	3.97(3.11–4.56)	1.811(1.39–1.97)
COVID-19	5.43(2.8–6.9)	3.69(2.71–4.32)	1.46(1.05–1.60)
Weibull	**mean**	**shape**	**rate/scale**
MERS-CoV	7.23(6.6–7.8)	2.15(1.88–2.47)	8.14(7.48–8.87)
COVID-19	5.58(4.54–5.9)	1.92(1.64–2.25)	5.83(5.08–6.67)
Log normal	**mean**	**mean-log**	**sd-log**
MERS-CoV	7.28(6.4–8.6)	1.85(1.76–1.98)	0.52(0.45–0.59)
COVID-19	5.35(4.5–6.4)	1.54(1.41–1.69)	0.52(0.44–0.62)



(a) (b)

Fig. 4. Network diagram for (a) COVID-19 and (b) MERS-CoV infection in Saudi Arabia, where the source and transmission chain could be determined.

The largest cluster of COVID-19 cases in Saudi Arabia (Fig. 4a) consisted of 55 cases and was traced back to a group of travellers who returned from Iran through Bahrain and the United Arab Emirates. The first case related with this 'travel history' cluster was reported on February 26, 2020 in relation to one traveller who was exposed to COVID-19 during his visit to Iran. Later, on March 9 and 10, five other travelers from the same trip were sick in the Eastern region (confirmed on March 14 and 15, 2020). The second-largest cluster had 12 cases and was associated with family and a prior social event. The other patients were linked via employment and other familial relationships. For MERS-CoV (Fig. 4b), the largest cluster included 60 cases and was linked to a collection of three camel farms in Madinah, Riyadh, and the Eastern region of Saudi Arabia. The first case reported in this 'direct contact with camels' cluster was a man who was exposed to camels on his Riyadh farm on 10 May 2014 and became severely ill on 14 and 15 May. (confirmed on 16 May 2014). The second-largest cluster was associated with health care workers, with cases occurring directly as a consequence of their exposure (including the source case). The remaining clusters were connected by primary and secondary family exposure.

In the MERS-CoV dataset, we found that the mean serial interval in our direct analysis is 14.1 days with the gamma distribution; shape 6.2 (95% CI: 4.8–8.2); and rate 0.43 (95% CI:0.33–0.57). In the COVID-19 dataset, we found a mean 5.1 days; shape 2.78 (95% CI: 2.11–3.96); rate 0.53 (95% CI:0.39–0.77). These results are summarised in Table 3. Furthermore,

Table 3
Serial interval estimates using gamma, Weibull and log normal distributions. 95% confidence intervals for the shape and scale (logmean and sd for log normal) parameters are shown in brackets.

Gamma	**mean**	**shape**	**rate/scale**
MERS-CoV	14.13(13.9–14.7)	6.31(4.88–8.52)	0.43(0.33–0.60)
COVID-19	5.1(5.0–5.5)	2.77(2.09–3.88)	0.53(0.38–0.76)
Weibull	**mean**	**shape**	**rate/scale**
MERS-CoV	14.2(13.3–15.2)	3.07(2.64–3.63)	16.1(15.0–17.1)
COVID-19	5.2(4.6–5.9)	1.74(1.46–2.11)	5.83(5.08–6.67)
Log normal	**mean**	**mean-log**	**sd-log**
MERS-CoV	14.08(13.1–15.2)	2.58(2.50–2.68)	0.44(0.39–0.5)
COVID-19	5.2(4.2–6.5)	1.45(1.31–1.61)	0.63(0.54–0.74)

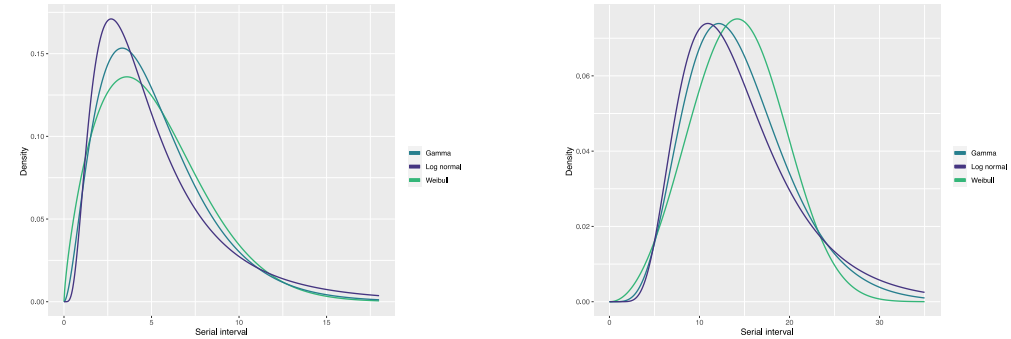


Fig. 5. Fitted serial interval distribution for (a) COVID-19 and (b) MERS-CoV based on reported transmission pairs in Saudi Arabia. We fitted three commonly used distribution, lognormal, gamma, and Weibull distributions, respectively.

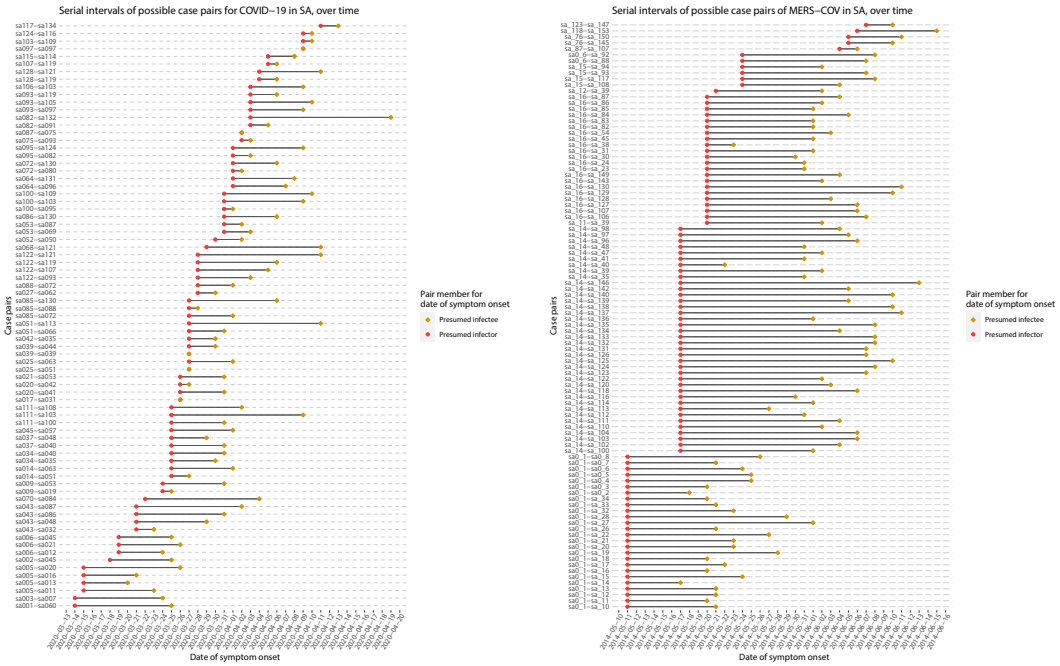


Fig. 6. Serial intervals of possible case pairs in (a) COVID-19 and (b) MERSCoV. Pairs represent a presumed infector and their presumed infectee plotted by date of symptom onset.

Fig. 5 illustrates the three results of the estimated serial interval of both COVID-19 and MERS-CoV infections using the best-fit lognormal, gamma, and Weibull distributions. Meanwhile, Fig. 6 shows the empirical serial intervals between all potential transmission case-pairs as noted in the data, divided into groups according to the date of the first symptom onset for each case-pair. This helps to understand the turnover of case generations and transmissibility of the disease (Nishiura et al., 2020). For each pair, we calculated the number of days between the reported symptom onset date for the infector and the reported symptom onset date for the infectee. We then fit Gamma, Weibull and Log-normal distributions to all observations as in Fig. 5.

We found that the estimated serial interval period varied, particularly in MERS-CoV, due to delays in implementation of measures that have been linked to increased mortality and the need for more stringent measures to minimise the human health risk of the disease. In COVID-19, we found the same effect, but strict local control measures, such as school closures, mosque closures, and border closures, play an important role in controlling the spread of the disease.

4.3. Pre-symptomatic transmission

In our study, we discovered that the serial interval for COVID-19 was less than the incubation duration, suggesting that pre-symptomatic transmission occurs. When compared to the incubation duration of MERS-CoV, the serial interval is longer, indicating that pre-symptomatic transmission is uncommon. The covariance and correlation between the serial interval and incubation period are taken into consideration in order to avoid underestimating presymptomatic transmission. These variables are important in quantifying SARS-CoV-2 transmission and characterizing the effectiveness of public health interventions (Linton et al., 2021). As mentioned in the main text, the proportion of presymptomatic transmission was computed on the basis of the assumption that the serial interval and incubation duration are not independent. According to COVID-19 data from Saudi Arabia, the covariance was 2.61, the correlation was 0.31, and the statistical signal was identical.

Relying on (Tindale et al., 2020a) we estimated the level of pre-symptomatic transmission following the following steps: first, we sampled the incubation period and serial interval parameters using the fitted data. Second, we sampled the shape and scale accordingly (using the gamma distribution). We then generated 100 incubation period and serial interval (shape, scale) pairs (i.e., 100 samples), using a multivariate distributions sampler in R (rmvgamma in the lcmix package), which we used to assess the correlation between the serial interval and incubation period of the infection. Third, we sampled jointly 500 incubation periods and serial intervals, with a correlation of approximately 0.31 for COVID-19 and 0.7 for MERS-CoV. We got $100 * 500 = 50{,}000$ joint samples of incubation period and serial interval. Fourth, we took the difference between the (serial interval minus incubation period) samples as an estimate of the portion of the pre-symptomatic transmission, accounting for covariation. When accounting for correlation, the estimated fraction of pre-symptomatic transmission for COVID-19 was 0.75, 0.84, and 0.81 (regardless of early/late split) and for MERS-C0V is 0 for all (early, late, all), based on the estimates of the incubation periods and serial intervals (see also Fig. 7).

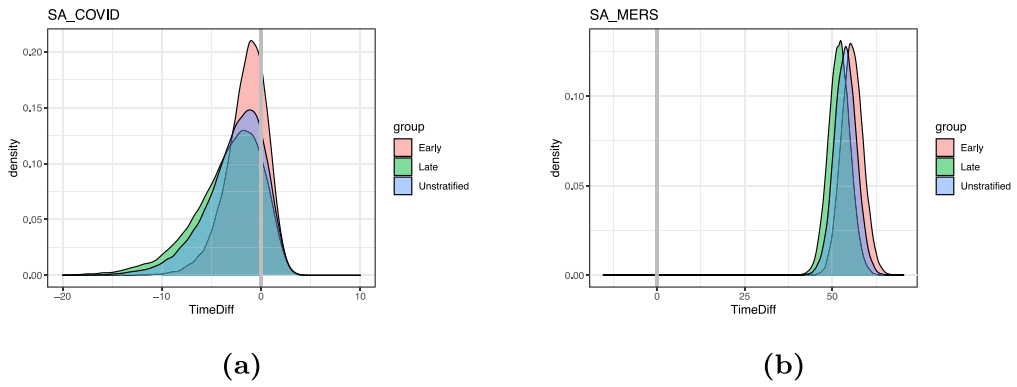


Fig. 7. Pre-symptomatic infection as estimated by samples of (serial interval - incubation period), accounting for covariation. grey vertical line: 0. Samples below zero indicate pre-symptomatic transmission.

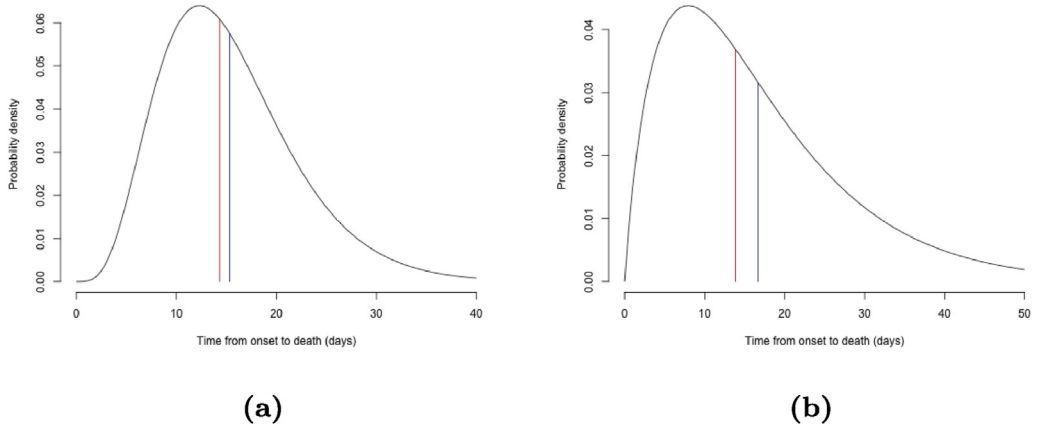


Fig. 8. Using the distributions of onset to death, the updated case fatality rates for MERS-CoV and COVID-19 in Saudi Arabia were derived. The panels a and b show the results of a gamma distribution fit to outbreak data from Saudi Arabia. Mean and median distribution durations for COVID-19 and MERSCoV were (13.4 and 12.7) and (16.6 and 13.8) days, respectively (shown by the red and blue lines).

4.4. Case fatality rate

During an outbreak, the so-called naive CFR (nCFR), defined as the ratio of reported deaths to reported cases, can underestimate the true CFR, since the outcome of each case is uncertain (recovery or death). Thus, if we consider the time period between confirmation and death (see Fig. 8), we may ascertain the CFR's true denominator (the number of instances with known outcomes). As a consequence, the case fatality rate (CFR) of MERS-CoV remained consistently high throughout the epidemic's duration. Meanwhile, the CFR for COVID-19 was high throughout the pandemic's early phases. This is because the majority of patients admitted to hospitals needed critical care support (Chan et al., 2020). Additionally, an increase in fatalities may be attributable to the involvement of linked co-morbidities in comparison to previous coronavirus epidemics (Sorci et al., 2020). We estimated the CFR for MERS-CoV as 38.1% (95% CI:36.8–39.5), and for COVID-19 as 1.67% (95% CI: 1.63%–1.71%). This estimate is in good agreement with other results such as (Ahmadzadeh et al., 2020) and (Organization et al., 2020, p. 82). This shows significantly small case fatality rate for the COVID-19 compared to MERS-CoV.

5. Discussion and conclusion

This study was conducted, based on the data of transmission clusters of MERS-CoV and COVID-19 in Saudi Arabia, where cases have reported links. We estimated the incubation period, serial interval, and case fatality ratio, as these are crucial parameters for informing public health interventions, and are crucial to parametrize transmission dynamics models which remain one of the key policy aids in planning local and global MERS-CoV and COVID-19 responses.

There are few published studies of the incubation period distribution of MERS-CoV infection, despite the fact that Saudi Arabia and South Korea are experiencing the largest outbreaks. However, a median incubation period of 5.2 days (95% CI: 1.9–14.7 days) was estimated across the Middle East (Virlogeux et al., 2016a) to 6.0 days (range of 95% CI: 4–7 days) and 6.3 days (95% CI: 5.7–6.8 days) was seen in the latest epidemic in South Korea (Virlogeux et al., 2016a). To get a better understanding of the previously reported variation, we estimated the incubation duration using the Gamma, Log-normal, and Weibull distributions shown in Table 1. In comparison with (Assiri et al., 2013; Virlogeux et al., 2016a, 2016b), they estimated that the incubation period for MERS-CoV would be 4.9 (95% CI:4.0–6.0), 5.2 (95% CI:1.9–14.7) and 5.0 (95% CI:4.0–6.2) based on gamma, log-normal and Weibull distributions respectively; however, the mean incubation times in South Korean and Saudi Arabian instances were quite different. There were only secondary cases and extended transmission chains associated with the MERS-CoV epidemic in South Korea (Virlogeux et al., 2016b), but the bulk of the patients in Saudi Arabia included in this investigation originated from the same hospital (Azhar et al., 2014). Possible direct transmission may be associated with a greater infecting dosage and greater virulence of the strain, perhaps resulting in a shorter incubation time. Incubation times for MERS-CoV varied in a recent investigation of the virus's spread during the epidemic in Saudi Arabia, the accuracy of which was shown to rely on the duration and severity of the first exposure (Cho et al., 2016).

In contrast, previous investigations have reported an even larger range of (95% CI:3.9–11.2) days for the incubation time of COVID-19 (Ki et al., 2020; Li et al., 2020a; Liu et al., 2020; Tindale et al., 2020b; You et al., 2020). An enormous disparity like this makes it difficult to plan public health measures. The gamma, lognormal and Weibull distributions were estimated to be 5.43 (95% CI: 2.8–6.9), 5.58 (95%: 4.54–5.90) and 5.35 (95% CI: 4.5–6.5), respectively. Estimated parameters are given in Table 2, and the fitted distributions are shown in Fig. 3. COVID-19's incubation duration depends on how it was contracted. Longer-incubating patients were more likely to be infected in public and working environments than at home. Public and professional environments offer greater open space, which reduces exposure intensity compared to domestic settings. In this

investigation, we evaluated imported and locally exposed individuals separately since imported cases reported a longer delay from exposure to symptom onset. The discrepancy might be attributable to natural variability in exposure and immunity between travellers and locals, who are frequently younger (Zhang et al., 2021).

Our estimate of the mean serial interval of MERS-CoV is 14.13 (95% CI: 13.9–14.7), 14.2 (95% CI: 13.3–15.3), and 14.8 (95% CI: 13.1–15.2) for the gamma, Weibull, and lognormal distributions, respectively. These estimates fall within the range of previous studies reviewed by (Cowling et al., 2015), but vary wildly from (Assiri et al., 2013; Cauchemez et al., 2016). Differences in demographics, social interaction, and time periods may account for the given range of estimations. Since the beginning of the epidemic, the introduction of control measures, frequent testing, isolation, and greater understanding of MER-CoV transmission may have decrease the probability that an infected individual would spread the illness for an extended length of time. Multiple studies have reported a reduction in the serial interval and linked it to enhanced control measures (Choi et al., 2018; Oh et al., 2018; Park et al., 2016). Possible explanations for shorter serial intervals include frequent and frequent interaction between household members. This might cause transmissions to occur sooner in the infection's progression, resulting in shorter serial intervals.

The fitted distributions for the serial interval estimate are shown in Fig. 5 and Table 3. Additionally, the serial interval was calculated by making use of the whole dataset. Results from the gamma distribution indicated mean serial interval of 5.1 days (95% CI: 5–5.5), whereas for the weibull distribution the estimated serial interval was 5.2 (95% CI: 4.6–5.9), and for the lognormal distribution the value is 5.2. (95% CI: 4.2–6.5). A slow but steady decrease in the estimated serial interval may be seen between 6.52 and 4.39 (Li et al., 2021). This discovery also helps to explain, to some extent, why previously stated serial intervals in a various of studies are often considerably different from one another. This conclusion also leads us to inquire into the factors that contribute to the occurrence of the serial interval trend. Both (Qian et al., 2020; Wei et al., 2020) pointed out that as the number of infectious cases rises, the probability of a presymptomatic transmission leading to an earlier infection rises as well. It is anticipated that the early infections will shorten the serial interval. Therefore, since the serial gap has been quickly decreasing, we feel compelled to study the potential of pre-symptomatic transmissions.

In most cases, the estimated values of incubation duration and serial interval based on the gamma, lognormal, and Weibull distributions closely match the sample mean and sample standard deviation. This offers confidence that our estimate provides essential information regarding the epidemiological features of MERS-CoV and COVID-19, as well as work that may be used in a range of scenarios, including the planning of interventions and the modelling of epidemics. Additionally, this material may aid in the prevention and management of infectious diseases.

Serial intervals, along with the basic reproduction number, R_0, can be used to infer the form and distribution of epidemic curves (Anderson et al., 2004). These are essential metrics to influence the infection incidence and prevalence, the rate at which an epidemic spreads, and the speed with which public health professionals must deploy intervention strategies to prevent an outbreak and/or mitigate the disease burdens (Anderson et al., 2004). The portion of transmission events that occur before symptom onset is also an important quantity to evaluate the effectiveness of infection control measures (Anderson et al., 2004), and this quantity can impact the efficacy of contact tracing and case finding efforts (Xu et al., 2020).

Saudi Arabia officials responded quickly when MERS-CoV and COVID-19 cases appeared and started implementing contact tracing and other control interventions to control their outbreaks; however, there was a substantial difference between MERS-CoV and COVID-19 in the severity of the measures taken. The first case of MERS-CoV was identified in Jeddah on 23rd Jul 2012 and the first COVID-19 case was reported in the Eastern region on 2nd March 2020. By Jul 2013, Saudi Arabia had reported more than 300 MERS-CoV cases and implemented a series of non-pharmaceutical interventions. Additionally, the government required travellers to monitor their health closely for 2 weeks upon traveling from/to Saudi Arabia and asked the public to adopt precautions, including avoiding close contact with people who were unwell, practising good hygiene and hand washing, and wearing a mask if they had respiratory symptoms. In comparison, by the 23rd of March 2020, in Saudi Arabia there were more than 4000 confirmed cases of COVID-19. All Saudi regions were placed under lockdown. Public gatherings were banned, no one could leave their homes between 6 p.m. and 6 a.m. without an exemption, entrances to Saudi regions were put under control, and all the buses linking nearby provinces and cities were halted.

In this work, we conducted the incubation period analysis for both MERS-CoV and COVID-19 by time of symptom onset (early-late or all) in two different phases. Our estimates of the late-phase incubation period was longer for both MERS-CoV and COVID-19. The reason behind this is unclear, but one possible interpretation is that there were unknown and therefore unreported exposures during the quarantine period.

For both MERS-CoV and COVID-19, we estimated the serial interval and found that the serial interval was longer for MERS-CoV than for COVID-19. Our serial interval findings from COVID-19 mirror those from (Li et al., 2020b), who estimated a serial interval of 4.4 and 4.0 days. For MERS-CoV, we obtained a similar estimate for the serial interval 14.13 as in (Cowling et al., 2015). Furthermore, we found that the serial interval was shorter than the incubation period in COVID-19 clusters, which indicates that pre-symptomatic transmission took place. Based on the available evidence, it appears that these are artefacts of either pre-symptomatic transmission during quarantine/lockdown or of other assumptions made regarding exposures during the collection of the original dataset. We found that, on the basis of this data and acceptable assumptions, at least 75% of transmission occurs prior to the start of symptoms, consistent with previous findings. This suggests that the pandemic was spreading faster than predicted if the transmission was restricted to the symptomatic phase, which brings to light that the spread of COVID-19 is likely to be difficult to stop by isolation of detected cases alone. Although Saudi Arabian authorities were able to keep the MERS-CoV and COVID-19 under control using non-pharmaceutical interventions, contact tracing combined with case finding was one of the keys to limiting symptomatic, asymptomatic and pre-symptomatic spread.

Due to the high fatality rate for MERS-CoV, which is much higher than for COVID-19, there is an urgent need for measures to mitigate risk. Whilst the route to elimination for these viruses, especially MERS-CoV, is still uncertain, public health measures must be sustainable. Improving some of the measures such as detection rate can effectively and rapidly reduce the mortality rate, particularly when medical resources are stretched (Chinazzi et al., 2020).

Some limitations of our study should be noted. First, when it comes to infection, the periods of exposure and the suspected infecting agents are unknown, and the incubation period can vary from person to person. Second, we did not incorporate uncertainty in the dates of symptom onset. Third, we did not account for truncation (i.e., shorter serial intervals are more likely to be noticed first) or the epidemic's growth curve. Serial interval estimates, on the other hand, agree with other studies and are robust to parameter choices, consistently being shorter than anticipated incubation duration's for COVID-19 and the converse for MERS-CoV. In Saudi Arabia, however, there is considerable uncertainty about the case fatality ratio (CFR) of COVID-19 and MERS-CoV. CFR estimates based on reported numbers of confirmed cases and deaths are difficult to evaluate because they may undercount mild cases and right-censor cases depending on the time gap between disease onset and death.

In short, the purpose of this study is to conduct a statistical comparison of the epidemiological characteristics of MERS-CoV and SARS-CoV-2 in Saudi Arabia. It is hoped these estimates may facilitate the development of transmission dynamics models in future studies. Additionally, our results provide some insights of why the estimated values of relevant parameters have varied from studies to studies in the past. The estimated characteristic distinctions of two important diseases may be of some use to design disease-specific interventions and planning, and the design of epidemic modelling and interpretation of modeling results.

Understanding the epidemiological characteristics influencing the transmission patterns of MERS-CoV and COVID-19 is critical for effective public health interventions to mitigate the disease outbreaks. Our study determined the overall average incubation duration, serial interval, case fatality rate, and proportion of pre-symptomatic transmission as well as the case fatility rate in Saudi Arabia. This study provides essential insights and estimates to enable developments of more realistic models in future research to inform intervention design. Our findings also contribute to the understanding of why the values of those estimated parameters vary somewhat across different studies.

Declaration of competing interest

The authors declare that they have no known competing financial interests that could have appeared to influence the work reported in this paper.

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