

Evaluating the pandemic potential of MERS-CoV

The emergence in 2012 of a new disease-causing coronavirus has caused significant concern. At the time of writing, Middle East respiratory syndrome coronavirus (MERS-CoV) has been responsible for 77 laboratory-confirmed cases and 40 deaths.¹ The virus is related to the severe acute respiratory syndrome coronavirus (SARS-CoV) that sprang upon the world in 2002-2003. And, like SARS-CoV during its pre-pandemic stage, MERS-CoV has probably been jumping from an unknown animal host to humans repeatedly over the past year.^{2,3} Cases of human-to-human transmission have also been documented in several countries.¹ This raises the question: does MERS-CoV have the potential to cause a pandemic?

In today's *Lancet*, Breban and colleagues address this question.⁴ Mathematical epidemiologists often employ a simple but useful measure called the basic reproduction number (R_0): the average number of infections caused by one infected individual in a fully susceptible population.⁵⁻⁸ If $R_0 > 1$, cases may grow exponentially and cause a full-blown epidemic (Figure 1). In contrast, if $R_0 < 1$, then transmission is guaranteed to fade away. A primary task upon emergence of a new pathogen is estimating its R_0 .⁶⁻⁸

Estimating R_0 during the pre-pandemic stage can be plagued by data uncertainty and variability. The number of secondary infections caused by an index case can be highly variable.⁸⁻¹⁰ Sometimes, an individual carrying a highly infectious disease will only cause a few infections. Conversely, individuals carrying a disease of normally low infectiousness can occasionally cause a large number of infections. This effect is compounded by the small number of confirmed cases during the pre-pandemic stage, and the difficulty of determining whether the earliest cases were infected by other humans or by animals. On top of this, if R_0 is not too much larger than 1 ($1 < R_0 \lesssim 1.5$), there is a significant chance that transmission will sputter out anyway. Hence we cannot conclude that $R_0 < 1$ just because secondary transmission appears to be limited, as for MERS-CoV to date. Our intuition about whether $R_0 > 1$ or $R_0 < 1$ may fail us during the pre-pandemic stage, necessitating statistical methods.

Breban and colleagues apply a specialized statistical method to estimate the R_0 of MERS-CoV.^{4,11} By carefully constructing different scenarios for who infected whom in recent MERS-CoV clusters, Breban and colleagues compute R_0 under best-case and worst-case scenarios for MERS-CoV transmission trees. In the worst-case scenario, R_0 is only 0.69 (95% CI: 0.50-0.92). Despite the small number of confirmed cases to date, the upper 95% confidence interval on the R_0 remains less than 1, meaning that MERS-CoV is unlikely to cause a pandemic. (However, we do find ourselves wondering whether it would be desirable to also report 99.7% CI when estimating a pandemic risk, in addition to the 95% standard.) By comparison, the authors estimate $R_0 = 0.80$ (95% CI: 0.54-1.13) for pre-pandemic SARS-CoV in southeast Asia, 2002-2003.

Breban and colleagues also provide calculations that enable updating the R_0 estimates as more information comes in through new MERS-CoV cases. If the next index patient infects 8 or more individuals, the authors estimate a 5% chance that R_0 is actually above 1, under the worst-case scenario.

Breban and colleagues do a thorough job accounting for how their conclusions may be impacted by: (1) the quality of surveillance systems, (2) the possibility of symptomatic and mild infections, and (3) the network structure of who infected whom within MERS-CoV clusters. Other factors are more difficult to account for because they require a ‘crystal ball’ to anticipate how the situation may change in the future. For example, very recent reports document 6 asymptomatic infections.¹ Additionally, R_0 may change seasonally due to climate, school calendars, or annual gatherings that put individuals in closer proximity to one another.¹² Such gatherings create a coinciding opportunity for more disease introductions from animal populations, if the gatherings involve greater contact between humans and infected animals.

Another potential future development is that MERS-CoV may start evolving, as SARS-CoV did. Evolution is particularly relevant to the problem of estimating R_0 from a series of outbreaks distributed through time. The approach used by Breban and colleagues implicitly assumes that R_0 does not change. Hence, a trend toward increasing cluster sizes would be interpreted by the method as natural variability unrelated to virus adaptation. If cluster sizes were actually growing because the virus is evolving a higher R_0 , the method would underestimate the current, more evolved R_0 . Therefore, the significance of a large, new cluster might be misinterpreted. A method that allows for the estimated R_0 to rise or fall over time might capture movement toward the $R_0=1$ threshold caused by viral adaptation or seasonality, although the amount of data currently available for MERS-CoV probably does not permit this.

A novel and virulent coronavirus continues to circulate in unknown animal populations. If we want to stay on top of MERS-CoV, we need continuing research, including updated R_0 estimates and methodological refinements. However, for the time being, the analysis by Breban and colleagues tells us that MERS-CoV—as we currently know it—is unlikely to cause a pandemic.

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We declare that we have no conflicts of interest.

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Figure1 caption: An illustration of the first few generations of infection transmission for the $R_0 > 1$ case and the $R_0 < 1$ case.

