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The emergence in 2012 of a new disease-causing coronavirus has generated substantial concern. As of June 26, 2013, Middle East respiratory syndrome coronavirus (MERS-CoV) had caused 77 laboratory-confirmed cases and 40 deaths.\(^1\) The virus is related to the severe acute respiratory syndrome coronavirus (SARS-CoV) that emerged in 2002–03. And, as SARS-CoV had during its prepandemic stage, MERS-CoV has probably been transmitted from an unknown animal host to human beings repeatedly in the past year.\(^2\)\(^3\) Cases of human-to-human transmission have also been documented in several countries.\(^1\) This raises an important question: does MERS-CoV have the potential to cause a pandemic?

In The Lancet, Romulus Breban and colleagues\(^4\) address this question. Mathematical epidemiologists often use 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.\(^5\) If \(R_0\) is greater than 1, cases could grow exponentially and cause a full-blown epidemic (figure). By contrast, if \(R_0\) is less than 1, then transmission is guaranteed to fade away, other things being equal. A primary task upon emergence of a new pathogen is estimation of its \(R_0.\)\(^6\)\(^4\)

### Assessing the pandemic potential of MERS-CoV

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**Comment**

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I declare that I have no conflicts of interest.

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The number of secondary infections caused by an index case can be highly variable. Sometimes, an individual with a highly infectious disease will only cause a few infections. Conversely, individuals with a disease of normally low infectiousness can occasionally cause many infections. This effect is compounded by the small number of confirmed cases during the prepandemic stage, and the difficulty of identifying whether the earliest patients were infected by other human beings or by animals. Additionally, if $R_0$ is not much larger than 1 (ie, between 1 and about 1·5), there is a fair chance that transmission will fade out anyway. Hence we cannot conclude that $R_0$ is less than 1 just because secondary transmission seems to be low, as is the case for MERS-CoV so far. Using intuition to estimate whether $R_0$ is greater than or less than 1 might not be accurate during the prepandemic stage, necessitating investigation using statistical methods.

Breban and colleagues apply a specialised statistical method to estimate the $R_0$ of MERS-CoV. By carefully constructing different scenarios for who infected whom in recent MERS-CoV clusters, the investigators 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 so far, the upper 95% CI on the $R_0$ is less than 1, meaning that MERS-CoV is unlikely to cause a pandemic, although a 99·7% CI might also have been useful to estimate pandemic risk, in addition to the standard 95% interval. For comparison, the investigators estimate that $R_0$ was 0·80 (95% CI 0·54–1·13) for prepandemic SARS-CoV in southeast Asia (2002–03).

Breban and colleagues also provide calculations that enable the $R_0$ estimates to be updated as more information about new MERS-CoV cases is reported. If the next index patient infects eight or more individuals, the investigators estimate that there is 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 might be impacted by the quality of surveillance systems, the possibility of symptomatic and mild infections, and the network structure of who infected whom within MERS-CoV clusters. Other factors are more difficult to account for because the investigators would have to know how the situation might change in the future. For example, very recent reports document six asymptomatic infections. Additionally, $R_0$ might change seasonally according to climate, school calendars, or yearly gatherings such as pilgrimages that put individuals in closer proximity to one another. If such gatherings involve greater contact between humans and infected animals, they would also create an opportunity for more disease introductions from animal populations.

Another potential future development is that MERS-CoV might start evolving, as SARS-CoV did. In the case of SARS-CoV, several mutations enabled the spike glycoprotein of the virus to bind with the angiotensin-converting enzyme 2 human receptor, making it much easier for the virus to infect humans and thus probably increasing the $R_0$ of the virus. Evolution presents a particularly relevant challenge for 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
towards increasing cluster sizes would be interpreted by their method as natural variability unrelated to virus adaptation. If cluster sizes were actually growing because the virus was evolving a higher $R_\infty$, the method would underestimate the actual, more evolved $R_\infty$. Therefore, the significance of a large, new cluster might be misinterpreted. A method that allows for the estimated $R_\infty$ to rise or fall over time might capture movement toward the $R_\infty=1$ threshold caused by viral adaptation or seasonality, although the amount of data available for MERS-CoV probably does not permit this at present.

To maximise our chances of containing MERS-CoV infection, we need continuing research, including updated $R_\infty$ estimates and methodological refinements. However, the analysis by Breban and colleagues\(^1\) concludes that MERS-CoV—in its current guise—is unlikely to cause a pandemic.

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Antiretroviral therapy: dolutegravir sets SAIL(ING)

Of all the antiretroviral therapy (ART) drugs in recent development, few have generated as much expectation as the HIV integrase strand transfer inhibitor dolutegravir. Raltegravir, the first in this class, has proved to be a very valuable drug, from treatment initiation to late salvage.\(^1\,2\)

However, in an era in which once daily therapy and single tablet regimens dominate the treatment initiation market, raltegravir has the relative disadvantage of twice daily dosing.

In 2012 the second-in-class integrase strand transfer inhibitor, elvitegravir, gained US Food and Drug Administration approval as a component of the new four-in-one single tablet regimen Striivil (Gilead Sciences Inc, Foster City, CA, USA). Elvitegravir requires pharmacological boosting because it does not support once daily dosing in its own right. Although this quadruple regimen has shown non-inferiority versus the first single tablet ART regimen of efavirenz, tenofovir, and emtricitabine (Atripla, Gilead Sciences Inc and Bristol-Myers Squibb Co, Princeton, NJ, USA)\(^3\) and ritonavir-boosted atazanavir, tenofovir, and emtricitabine,\(^4\) the need for boosting is a relative drawback with an increased potential for drug-drug interactions. Elvitegravir is not currently available as a single agent.

The third-in-class integrase strand transfer inhibitor likely to obtain approval, possibly within the next year, is dolutegravir. Dolutegravir’s half-life supports once daily dosing, and it is therefore the first stand-alone once daily drug in this class. Dolutegravir has shown non-inferiority in a double-blind comparison with raltegravir.\(^5\) Results presented at a recent conference were consistent with dolutegravir having superior efficacy in ART-naïve participants when used as a component of a single tablet regimen (combined with abacavir and lamivudine) in a double-blind comparison with Atripla.\(^6\)

In The Lancet, Pedro Cahn and colleagues\(^7\) publish the analysis of a case of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. Lancet Infect Dis 2013; published online July 5. http://dx.doi.org/10.1016/S1473-3099(13)70154-3.