Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

reasons. First, learning from the South African experience, an important new weapon in the war on smoking-attributed disease is that the smoking status about 5 years before death should be noted when registering causes of death, ideally in every population where underlying causes of death are assigned. Second, it shows that within one country smoking can cause very different risks in different subpopulations, and that smoking is associated with not only lung cancer (which was the first major hazard of smoking to be shown), but also with other cancers and cardiovascular and respiratory disease.

WHO estimates that about 100 million deaths worldwide were caused by tobacco during the past century, and that if current smoking habits persist there could well be about a billion tobacco deaths this century.[12] As well as trying to limit this vast epidemic, the world should monitor it objectively in many different populations and subpopulations. In each population where underlying causes of death are registered, incorporation of this one easy question about smoking 5 years ago into the death notification process would, at little expense, greatly facilitate monitoring of tobacco-attributed mortality. Other countries should now consider following South Africa's example in doing so.

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I declare that I have no conflicts of interest.

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Assessing the pandemic potential of MERS-CoV

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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.[5–8] 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.[6–8]

Estimation of R_0 during the prepandemic stage can be plagued by data uncertainty and variability, however.

The number of secondary infections caused by an index case can be highly variable.[8-10] 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[4] apply a specialised statistical method to estimate the R_0 of MERS-CoV.[11] 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[4] 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[4] 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.[1] 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.[12] 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.[13] 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[4] implicitly assumes that R_0 does not change. Hence, a trend

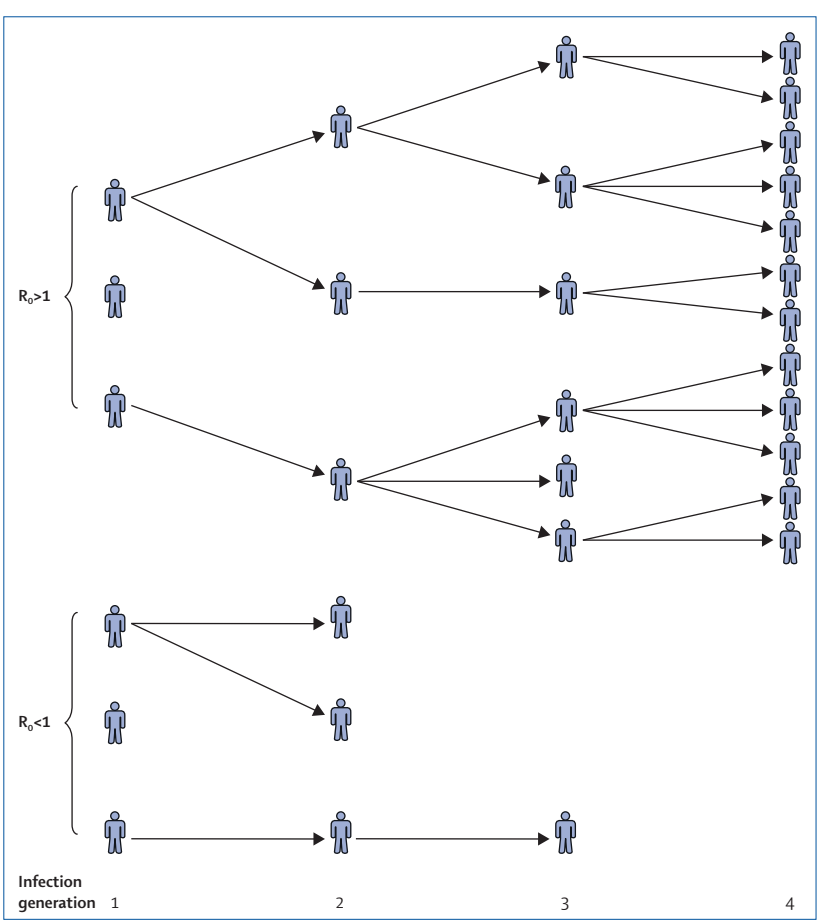

Figure: **Early generations of infection transmission according to whether R_0 is greater than or less than 1**
R_0=basic reproduction number.

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_0, the method would underestimate the actual, 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 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_0 estimates and methodological refinements. However, the analysis by Breban and colleagues[4] concludes that MERS-CoV—in its current guise—is unlikely to cause a pandemic.

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Antiretroviral therapy: dolutegravir sets SAIL(ING)

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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 Stribild (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-naive 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 results of SAILING, a double-blind randomised controlled comparison of dolutegravir versus raltegravir with