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.

demonstration of longevity of response and of empiric protection from this candidate will be important, even using a two-dose regimen.[6]

Two lessons arise from this study. First, we can use existing tried and tested platforms to produce vaccines. We know their limitations, but we also know that in previous incarnations they are usually acceptably safe. And second, unexpected things can happen in science as in life. A change in manufacturing process to scale up production can change the performance of a vaccine. It can also affect reactogenicity, although reactogenicity does not seem to have been affected in this study. We should expect the unexpected when considering vaccine safety, and vigilantly observe for unanticipated harms. Like all phase 2 trials, the results must be interpreted with caution until phase 3 results are published. But even then, after phase 3 trial completion and after licensure, we should prudently remain cautious. Pharmacovigilance will be needed long into phase 4 studies, and we should recall that COVID-19 vaccine harms could occur in any of the following ways: real direct harms from adverse events or from disease enhancement; perceived direct harms temporally but not causally associated with receipt of the vaccine (eg, in an older population or among those with excess comorbidities who are already at risk for adverse health events);[7] and suboptimal vaccine deployment and unrealistic expectations or inadequate safety communication (eg, a vaccine that reduces disease [the primary outcome in all phase 3 COVID-19 vaccine trials] but not transmission [an unpowered secondary outcome], and that works less well in older individuals or is not taken up by high-risk groups, could allow unmitigated transmission to paradoxically worsen population outcomes for groups at risk, especially if vaccination leads to lower adherence to physical distancing and use of masks). Global and national regulators have declared licensure would be approved for efficacy against disease of 50% with bounds well below that, and unknown efficacy against transmission. Therefore, should such a vaccine be licensed, and without clear protective correlates to allow bridging studies, early licensure could stymie developments of better future candidates, and pose ethical challenges for other trials commencing or that are ongoing.[8–10] Regardless, the trust of the global community is hardwon and achieved through total transparency and realism of expectation, both during and long after vaccine development and deployment.

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Estimating the COVID-19 *R* number: a bargain with the devil?

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The deeper understanding Faust sought
Could not from the Devil be bought.
But now we are told
By theorists bold
All we need know is R_0.[1]

Robert May, 1936–2020

Bob May's limerick alludes to both the promises and dangers of characterising epidemic control by a single number. The basic reproduction number (R_0) is the average number of infections produced by a single infectious person in a population with no immunity. R_0 has a close relative named the effective reproduction

number (*R*), which is the average number of infections produced by a single infected person in a population with partial immunity. In *The Lancet Infectious Diseases*, You Li and colleagues[2] estimate how the imposition and lifting of non-pharmaceutical interventions (NPIs) changed the *R* number for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 131 countries in the first half of 2020.

If the *R* value is less than 1, an epidemic eventually dies out because each infected person generates less than one new infection. Ending an epidemic by keeping the *R* value below 1 could take a long time if there are currently many infections, like the proverbial small rudder on a big ship. However, when the *R* value is higher than 1, the epidemic could continue to grow. *R* can also change over time: NPIs such as closing schools, physical distancing, and mask use can reduce *R*. Hence, *R* is often used to gauge whether pandemic mitigation is working.

Li and colleagues compared daily estimates of *R* at the country level against a database describing which NPIs each country applied and when. Generally, they found that imposing NPIs reduced *R*, and lifting them later on increased *R*. School closure, a public events ban, requirements to stay at home, and internal movement limits—both when being imposed and when lifted—had the biggest individual effects, changing *R* between 3% and 25%.

NPIs in combination were even more effective. The combined effect of school and workplace closure, a ban on public events and gatherings of more than ten people, internal movement limits, and a stay at home requirements reduced *R* by 52% (95% CI 29–68) 28 days after they were introduced. The R_0 value for SARS-CoV-2 lies somewhere between 2 and 3.[3] Hence, early pandemic interventions must reduce *R* by between 50% and 67% to bring it below 1. Li and colleagues' estimates do not include the effects of contact tracing and isolation. Despite this omission, the estimate suggests that it might have been exceedingly difficult to flatten the curve in spring, 2020, had the R_0 for SARS-CoV-2 been a little higher.

But *R* is not without shortcomings. Just as our body-mass index does not tell us everything about our state of health, a single number cannot provide a complete picture of the state of a pandemic. National-level estimates can hide local heterogeneity. Seasonal differences in contact patterns from spring to autumn are not captured by the short time windows used in many epidemiological studies. Reporting delays, stochastic effects, and superspreading can also bias *R*. Moreover, *R* does not tell us what proportion of infections are caused by an infected individual before symptom onset. This crucial distinction for infection control might explain why severe acute respiratory syndrome coronavirus did not cause a pandemic, whereas SARS-CoV-2 did, despite their comparable R_0 values.[4,5]

Li and colleagues discuss some of these limitations and also raise the issue of behavioural inertia. Timelines of decision making lend the perception that governments can turn NPIs on and off like a switch. But in fact, populations can take weeks to adjust their mobility patterns in response to imposition of NPIs.[2,6] This effect probably contributes to the authors' finding that NPIs did not exhibit their maximal effect on *R* until up to 28 days later.

R promises crystal clarity in a time when there are no crystal balls. Hence, the allusion to R_0 as a bargain with the devil. Statistician George Box has been widely paraphrased as writing "All models are wrong, but some are useful."[7] I like to re-paraphrase this as some models are useful precisely because they are wrong. A model including all the real-world details of a study system would no longer be a model, because it would be the system itself.

Despite *R*'s imperfections, the findings of Li and colleagues tell us that NPIs work and which ones work best. This information is crucial, given that some NPIs have massive socioeconomic effects. In a similar vein, transmission models that project COVID-19 cases and deaths under different NPI scenarios could be highly valuable for optimising a country's portfolio of NPIs.[8–10] Moreover, I think *R* provides a social utility that epidemiologists can easily overlook. The success of large-scale NPIs requires population adherence. *R* can stimulate populations to act and gives them useful feedback on the fruits of their labour. Perhaps this is one reason that *R* has entered our vernacular in 2020.

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Cefiderocol: the Trojan horse has arrived but will Troy fall?

The global public health crisis of multidrug-resistant Gram-negative organisms underscores the need for antibiotics with novel bacterial targets. Cefiderocol, the first siderophore-conjugated antibiotic to progress beyond phase 1 human trials, was designed to overcome challenges presented by common carbapenem-resistance mechanisms. The drug enters bacterial cells using active iron transporters (ie, a Trojan horse), overcoming drug resistance from porin channel mutations and upregulated efflux pumps; it also has intrinsic stability from hydrolysis by carbapenemases. By contrast with other novel agents, cefiderocol is active against a variety of drug-resistant pathogens, including both serine and metallo-β-lactamase (MBL) carbapenemases, as well as problematic non-fermenting Gram-negative organisms, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex, and *Stenotrophomonas maltophilia*. In *The Lancet Infectious Diseases*, the APEKS-NP study by Richard Wunderink and colleagues[1] and the CREDIBLE-CR study by Matteo Bassetti and colleagues[2] offer insights into the role of cefiderocol for the treatment of challenging Gram-negative infections.

In APEKS-NP,[1] patients with Gram-negative nosocomial pneumonia were randomly assigned to receive 3-h infusions of either cefiderocol 2 g or meropenem 2 g every 8 h for 7–14 days. Cefiderocol was non-inferior to meropenem for the primary endpoint of all-cause mortality at day 14 (adjusted treatment difference 0·8%, 95% CI −6·6 to 8·2; non-inferiority was concluded if the upper bound of the 95% CI for the treatment difference was <12·5%). The study population was reasonably ill, with approximately 70% of participants in an intensive care unit (ICU) at randomisation. High-dose, extended-infusion meropenem was a robust comparator, and its selection was in contrast with other prominent phase 3 pneumonia trials.[3–5] Moreover, the prohibition of additional systemic or inhaled drugs with Gram-negative activity limited the confounding that is inherent in many pneumonia trials wherein additional antibiotics confuse the interpretation of results.[3,4]

CREDIBLE-CR[2] was a randomised, open-label trial in which adult patients with serious infections caused by carbapenem-resistant Gram-negative bacteria were randomly assigned to receive either cefiderocol (given as described for the APEKS-NP study[1]) or best available therapy, 66% of which consisted of colistin-based regimens. 78 (47%) of 150 patients were in the ICU at randomisation, 67 (45%) had pneumonia, 47 (31%) had bloodstream infection (BSI). A high frequency of patients had non-fermenting organisms and 142 (95%) had recently received antibiotics. Clinical cure at test of cure, the primary endpoint for patients with nosocomial pneumonia or BSI, was similar in both treatment groups. However, mortality at day 14 was higher in patients treated with cefiderocol than in those treated with best available therapy for pulmonary infections (25% *vs* 11%) and BSI (22% *vs* 7%), but not in patients with complicated UTI (12% *vs* 40%). Mortality differences persisted at day 28 and at the end of the study.

How do we reconcile the seemingly conflicting mortality data from these studies? In CREDIBLE-CR, cefiderocol—regardless of whether it was administered as monotherapy or combination therapy—appeared to do no better than colistin: clinical cure was reported in 53% and 50% of patients who received cefiderocol monotherapy and combination therapy, respectively, and in 67% and 42% of patients who received colistin

Dr Barry Slaven/Science Photo Library

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