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.

variants surge during a new wave of infections, they could hit already overburdened health-care systems, and there will be little capacity to react. Hence, avoiding such a wave is critical to mitigate the impact of potential escape variants.

Is it necessary, then, to have either almost endless restrictions that bring their own detrimental health and economic effects, or accept the surge of another pandemic wave? We would like to propose a midpoint: eating the chocolate cake sufficiently slowly. Lifting restrictions at pace with vaccination allows for increasingly more contact without risking another surge of infections.[3] Alternatively, substantial restrictions would need to be installed at a later point when hospitals are at capacity again. This approach would entail taking the chocolate cake away again after only being allowed one bite. In fact, the progress of releasing restrictions, whether at low or high case numbers, is mainly determined by the pace of vaccination, not on lower or higher levels of infections.[3] The advantage of avoiding another pandemic wave is clear: less so-called long COVID-19, less quarantine, fewer deaths, and reducing the impact of the pandemic on societies and economies.[4] Finally, more infections mean more scope for the spread and evolution of escape variants, which risk a major setback for any vaccination strategy, so avoiding this eventuality will be crucial.

Overall compliance with NPIs has decreased worldwide because of behavioural fatigue.[5] Despite this fatigue, governments and researchers now more than ever should stress the advantages of keeping case numbers low,[5,6] the benefits of high vaccination uptake, and the responsibility that the vaccinated population has to those who are not yet protected, but who are largely expected to keep economies going. As most countries have been much slower at vaccinating their populations than the UK, the country can best support the fight against COVID-19 worldwide by keeping its own national case numbers low. The more progress in vaccination that a country has achieved, the easier it is to maintain low case numbers. This opportunity should be seized.

In every country, we have to decide how to use the protection of vaccines wisely to prevent further waves of SARS-CoV-2. Waves that hit those who have not been offered a vaccine will spread to unprotected people and unprotected countries, which could lead to further evolution of escape variants. Thus, let us enjoy the chocolate cake, responsibly.

We declare no competing interests.

*Sebastian Contreras, *Viola Priesemann*
viola.priesemann@ds.mpg.de

Max Planck Institute for Dynamics and Self-Organization, 37077 Göttingen, Germany

1 Moore S, Hill EM, Tildesley MJ, Dyson L, Keeling MJ. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. *Lancet Infect Dis* 2021; published online March 18. https://doi.org/10.1016/S1473-3099(21)00143-2.

2 Plante A, Mitchell BM, Plante KS, Debbink K, Weaver SC, Menachery VD. The variant gambit: COVID's next move. *Cell Host Microbe* 2021; published online March 1. https://doi.org/10.1016/j.chom.2021.02.020.

3 Bauer S, Contreras S, Dehning J, et al. Relaxing restrictions at the pace of vaccination increases freedom and guards against further COVID-19 waves in Europe. March 10, 2021. https://arxiv.org/abs/2103.06228 (accessed March 15, 2021).

4 Priesemann V, Brinkmann MM, Ciesek S, et al. Calling for pan-European commitment for rapid and sustained reduction in SARS-CoV-2 infections. *Lancet* 2020; **397:** 92–93.

5 Petherick A, Goldszmidt RG, Andrade EB, Furst R, Pott A, Wood A. A worldwide assessment of COVID-19 pandemic-policy fatigue. *SSRN* 2021; published online Feb 1. https://ssrn.com/abstract=3774252 (preprint).

6 Contreras S, Dehning J, Loidolt M, et al. The challenges of containing SARS-CoV-2 via test-trace-and-isolate. *Nat Commun* 2021; **12:** 378.

Inactivated COVID-19 vaccines to make a global impact

Published **Online** February 3, 2021 https://doi.org/10.1016/S1473-3099(21)00020-7

See **Articles** page 803

Many inactivated vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being tested at various clinical stages. Most of these vaccines are formulated with aluminium hydroxide, and one, VLA-2001, has two adjuvants, CpG oligodeoxynucleotides and aluminium hydroxide.[1,2] Because of the ease of production and scale-up and relatively low cost, inactivated vaccines can capture a sizeable portion of the SARS-CoV-2 vaccine landscape. Inactivated vaccines are well established and can provide advantages in a variety of distinct populations, including those with degrees of immune senescence. Given that the risk of more severe COVID-19 increases with age, the clinical evaluation of the responses of older adults to vaccines is essential.[3]

In *The Lancet Infectious Diseases*, Zhiwei Wu and colleagues[4] report the results of a randomised, double-blind, placebo-controlled phase 1/2 clinical trial evaluating an inactivated COVID-19 vaccine, CoronaVac, in healthy adults aged 60 years and older (72 in

phase 1 and 350 in phase 2). The aluminium hydroxide-adjuvanted vaccine was given as two injections (days 0 and 28), and three different doses were tested (1·5 μg, 3 μg, and 6 μg per injection). The vaccine showed good safety and tolerability; adverse reactions, the most frequent being injection site pain (39 [9%] of 421 participants), were all mild or moderate in severity and no serious adverse events related to vaccination were recorded. Neutralising antibody titres were measured for all doses 28 days after the second injection. Because similar responses were seen with doses of 3 μg (seroconversion rate 98·0% [95% CI 92·8–99·8]) and 6 μg (99·0% [94·5–100·0]) in phase 2, and these doses elicited better responses than did the 1·5 μg dose, the authors proposed the use of a 3 μg dose in the phase 3 trial. This report is a companion to an earlier report of the safety and immunogenicity of CoronaVac in adults aged 18–59 years.[5]

Several limitations were acknowledged in this report, which are consistent with rapid-fire trials executed during the pandemic. The durability of immune response and latent adverse effects were not evaluated during the 2 month period. All participants were of Han Chinese ethnicity, and greater ethnic diversity in populations will be examined in the phase 3 trials. The 4 week interval from prime to boost might not be optimal, and no measures of T-cell or cytokine responses were included. However, these reported limitations represent a veneer of deeper issues capable of shaking confidence in vaccine utility in an ageing population.

Correlates of immune protection have not been established for SARS-CoV-2 vaccines to date, posing a foundational constraint to any vaccine development, although many vaccines have been granted emergency use approvals around the globe. Comparisons of various vaccine platforms have been hampered because, until recently, there were no standard pooled convalescent sera from infected individuals to use as a reference standard.[6] Interpretation of immune responses is limited in that no consensus standard methods for measuring neutralising antibody titres are in place, thereby confounding comparisons between age groups and comparisons with different vaccine strategies.

Immune senescence is complex and there are no validated methods to identify early stages or measures of severity.[7] A correlation between anti-receptor-binding domain IgG and neutralising antibodies has been reported for adults aged 18–59 years,[5] but this relationship might not hold true for older individuals with various stages of immune senescence. A similar relationship between T-cell responses and IFN-γ observed in adults might not exist in immune-senescent individuals. We encourage measurement of comparable immune features in future studies of individuals aged 18–59 years or 60 years and older. A diminished T-cell response in an older population is anticipated, but a possible reduction in neutralising antibody titre in people older than 70 years has not been fully studied. We encourage a granular evaluation of age groups to permit identification of age-related limitations in vaccine utility. IgM or the transition to IgG were not reported in Wu and colleagues' study,[4] so the integrity of B-cell function is not known. In general, it might be safe to proceed, but adjustments in dose and the interval between prime and boost in the population aged 60 years and older might be necessary, based on the measures from this study.

100 million people will soon have recovered from SARS-CoV-2 infection. Most recovered individuals have had antibody and T-cell responses against multiple SARS-CoV-2 proteins, but vaccination of these individuals might be necessary to prevent reinfection. Compared with other vaccines targeting only the spike protein, inactivated vaccines could provide an added benefit to these individuals by boosting their T-cell responses against many of the SARS-CoV-2 proteins.

Advancements in the development of an inactivated vaccine provide additional opportunities, but the pace of development must be balanced with quantitative measures of safety and efficacy. Inclusion of additional viral antigens in the inactivated vaccine could provide efficacy over time and as variants emerge. However, shifting viral antigens could also predispose an inactivated vaccine to causing antibody-dependent enhancement of disease.[8] It is important to create a vaccine portfolio composed of different strategies for a more robust defence against the SARS-CoV-2 pandemic.

We declare no competing interests.

*Patrick L Iversen, *Sina Bavari*
sinabavari@comcast.net

Oregon State University, Corvallis, OR, USA (PLI); Edge BioInnovation and Healion Bio, Frederick, MD, USA (SB)

1 Flanagan KL, Best E, Crawford NW, et al. Progress and pitfalls in the quest for effective SARS-CoV-2 (COVID-19) vaccines. *Front Immunol* 2020; **11:** 579250.

2 WHO. Draft landscape of COVID-19 candidate vaccines. Jan 15, 2021. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed Jan 15, 2021).

3 US Centers for Disease Control and Prevention. COVID-19—older adults. Dec 13, 2020. http://cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html (accessed Jan 4, 2021).

4 Wu Z, Hu Y, Xu M, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; published online Feb 3. https://doi.org/10.1016/S1473-3099(20)30987-7.

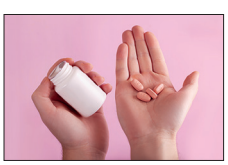
5 Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2020; published online Nov 17. https://doi.org/10.1016/S1473-3099(20)30843-4.

6 NIBSC. Coronavirus (COVID-19)-related research reagents available from the NIBSC. https://www.nibsc.org/science_and_research/idd/cfar/covid-19_reagents.aspx (accessed Jan 4, 2021).

7 Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV. Remodeling of the immune response with aging: immunosenescence and its potential impact on COVID-19 immune response. *Front Immunol* 2020; **11:** 1748.

8 Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol* 2020; **20:** 615–32.

Raltegravir in patients with tuberculosis



iStock - YakubovAlim

Published **Online** March 2, 2021 https://doi.org/10.1016/S1473-3099(20)30937-3

See **Articles** page 813

Treatment of patients with tuberculosis and HIV infection is complex, with pill burden and treatment adherence presenting major challenges. Rifampicin is a potent inducer of hepatic cytochrome P450 and uridine diphosphate glucuronosyl transferase 1A1 enzymes and the drug efflux pump P-glycoprotein, with potential for major drug–drug interactions with many antiviral drugs. Before publication of the ANRS 12 300 Reflate TB 2 study by Nathalie De Castro and colleagues[1] in *The Lancet Infectious Diseases*, the only other randomised phase 3 controlled trials of rifampicin and antiretroviral regimens included the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz.[2,3] Benefits of efavirenz include that no dose adjustments are required with rifampicin and it is available in single pill once a day combinations. However, in most guidelines efavirenz is no longer the recommended first-line HIV treatment due to its neuropsychiatric side-effects, increased risk of suicide, and concerns regarding increasing prevalence of transmitted primary NNRTI resistance, as observed in antiretroviral therapy (ART) programmes in low-income and middle-income countries (LMICs).[4]

The open-label, randomised, phase 3 ANRS 12 300 Reflate TB 2 study assessed the non-inferiority of integrase strand-transfer inhibitor (INSTI) raltegravir 400 mg twice daily to efavirenz in ART-naive patients within 2–8 weeks of commencing treatment for tuberculosis.[1] On the basis of the tolerability and efficacy of raltegravir 400 mg twice daily with tuberculosis treatment in the previous phase 2 Reflate TB study[5] and on data from the associated pharmacokinetic substudy,[6] it was anticipated that the raltegravir group would meet the prespecified non-inferiority margin of –12% with respect to the primary endpoint of virological suppression (HIV RNA <50 copies per mL) at week 48. In the intention-to-treat population, 140 (61%) of 230 participants in the raltegravir group and 150 (66%) of 227 patients in the efavirenz achieved virological suppression (between-group difference –5·2% [95% CI –14·0 to 3·6]). Thus, since the lower bound of the 95% CI was –14%, raltegravir did not show non-inferiority compared with efavirenz.

Although the proportion of participants who had achieved virological suppression at week 48 was lower than that used to derive the sample size and might have affected the ability to demonstrate non-inferiority, a preliminary analysis of this study showed that measured adherence, baseline HIV RNA concentrations, and sex, but not treatment group, were associated with virological outcome.[7]

Pharmacokinetic properties of raltegravir might have driven the findings of this study, since low trough concentrations have been associated with poorer virological outcomes. In a pharmacokinetic study of raltegravir 400 mg twice daily given with rifampicin, high intraindividual and interindividual variability was observed and the concentration of raltegravir 12 h after administration was reduced by 31%.[6] However, no differences in virological suppression at week 24 (when the treatment of tuberculosis with rifampicin was completed) were identified between treatment groups. Furthermore, of the patients who met criteria for resistance testing in ANRS 12 300 Reflate TB 2, 26 patients in the raltegravir group and 24 patients