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.

benefits might be maximised through large-scale evidence generation regarding dosing intervals, there is merit in examining the optimal timing of boosting in special populations.

Third, we should remember that vaccination is only one of the tools we have to protect against infection. Globally, where vaccine rollout has to occur in phases, individuals at risk should be prioritised for vaccination and receive both doses of a regimen, a lesson well highlighted in this Article. And until incidence declines substantially, ongoing non-pharmaceutical interventions such as masking will remain imperative.

Fourth, given the differences in immunogenicity between subgroups observed in Lustig and colleagues' study, long-term follow-up studies to evaluate immunological waning and memory cellular responses should be undertaken in different contexts, as results are also likely to vary with different vaccines.

Last, predictive forecast models have been influential in policy making during this pandemic; however, they are, of course, limited by their foundational assumptions. Models might be "always wrong but sometimes useful",[12] but little thought is given to what defines 'sometimes', or under what circumstances might empirical evidence of vaccine effectiveness lead to erroneous assumptions.[12] The relevance of reduced immunogenicity in vulnerable groups, even if this effect is masked by studies of population effects of vaccination, could be borne in mind when building predictive models and for future scenario modelling.

What matters is what we ought to do given what we know and have observed. The findings from Lustig and colleagues matter because they remind us not to ignore what we know about individuals when considering the meaning of what we observe in populations. When building models, making policies, planning evaluations, or interpreting data, maintaining these levels of perspective will help us to achieve the effectiveness we seek and the benefits that we are after.

NB-Z has received investigator-initiated research grants from Merck and the Serum Institute of India. AS has received investigator-initiated grants from Pfizer and the Serum Institute of India.

*Naor Bar-Zeev, Anita Shet
nbarzee1@jhu.edu

International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21231, USA (NB-Z, AS).

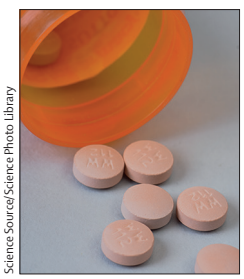
1 Shilo S, Rossman H, Segal E. Signals of hope: gauging the impact of a rapid national vaccination campaign. *Nat Rev Immunol* 2021; **21:** 198–99.
2 Lustig Y, Sapir E, Regev-Yochay G, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. *Lancet Respir Med* 2021; published online July 2. https://doi.org/10.1016/S2213-2600(21)00220-4.
3 Palich R, Veyri M, Marot S, et al. Weak immunogenicity after a single dose of SARS-CoV-2 mRNA vaccine in treated cancer patients. *Ann Oncol* 2021; published online April 29. https://doi.org/10.1016/j.annonc.2021.04.020.
4 Müller L, Andrée M, Moskorz W, et al. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. *Clin Infect Dis* 2021; published online April 27. https://doi: 10.1093/cid/ciab381.
5 Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol* 2021; **22:** 765–78.
6 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; **384:** 1412–23.
7 Pawlowski C, Lenehan P, Puranik A, et al. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. *medRxiv* 2021; published Feb 27. https://doi.org/10.1101/2021.02.15.21251623 (preprint).
8 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; **397:** 1646–57.
9 Mason T, Whitston M, Hodgson J, et al. Effects of BNT162b2 mRNA vaccine on Covid-19 infection and hospitalisation among older people: matched case control study for England. *medRxiv* 2021; published online April 22. https://doi.org/10.1101/2021.04.19.21255461 (preprint).
10 Khoury DS, Cromer D, Reynaldi A, et al. What level of neutralising antibody protects from COVID-19? *medRxiv* 2021; published online March 11. https://doi.org/10.1101/2021.03.09.21252641 (preprint).
11 Thompson MG. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers—eight US locations, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 495–500.
12 Box GEP, Draper NR. Empirical model-building and response surfaces. Wiley: New York, 1987.

PRINCIPLE: a community-based COVID-19 platform trial

Published **Online** July 28, 2021 https://doi.org/10.1016/S2213-2600(21)00360-X

See **Articles** page 1010

As COVID-19 evolved in early 2020, several crucial issues for public health became apparent, including the need to reduce pressure on secondary care through effective treatment in the community for those at highest risk of hospital admission. PRINCIPLE, which began in April, 2020, was designed to test multiple therapeutic candidates efficiently using a master protocol within a platform trial.[1,2] In *The Lancet Respiratory Medicine*, Christopher Butler and colleagues[3] report the findings of one of the possible treatments for COVID-19; a relatively cheap and safe antibiotic doxycycline, for which community prescribing increased early in the pandemic.[4] This trial aimed to assess the efficacy of doxycycline to treat suspected


Science Source/Science Photo Library

COVID-19 in the community among people at high risk of adverse outcomes. As antibiotic prescribing promotes antimicrobial resistance, it was imperative to quickly establish if increased doxycycline exposure in the population was offset by realisable benefits.

Designing and implementing randomised trials in pandemics is challenging, due to delays in initiation, and difficulties in finding locations with prevalent virus. A platform design offers the possibility of finding safe and effective interventions quickly. Given the inevitable uncertainties in the design (in population, intervention, control, and outcomes), flexibility is needed, which PRINCIPLE achieved admirably.

With regards to population, recruitment to community-based COVID-19 studies is notoriously hard; in PRINCIPLE, an adaptive recruitment strategy generated 25% of participants from more than 200 general practices, with the remainder from online self-referral, to whom study medication was delivered by courier. An additional challenge in this trial was pandemic service disruption; from November, 2020, further adaptions included enrolling high-risk individuals with positive test results independent of contact with their general practitioner.[5] In December, 2020, recruitment to the doxycycline group was stopped, having met the criteria for statistical futility.

The intervention was not adapted, and there was high compliance with doxycycline (82·2% of participants self-reported taking doxycycline for at least 6 days). There is some controversy around control groups in platform trials,[6] as controls and participants in intervention groups might not have been contemporaneously randomised. Here, the control was usual care only; PRINCIPLE opened on April 2, 2020, but randomisation to the doxycycline group only began on July 24, 2020. However, the authors adjusted for any potential temporal drift directly using Bayesian regression modelling, and by doing a sensitivity analysis in only those who were contemporaneously randomly assigned (ie, all participants who were randomly assigned to usual care plus doxycycline or usual care only during the time period when the usual care plus doxycycline group was open to randomisation), and findings were robust. The primary outcome was changed—a major step—from COVID-19-related hospitalisations or deaths to time to self-reported recovery, as the early observed numbers of hospitalisations and deaths indicated that 1500 participants per group would be required for adequate power to show even a large difference. This change was made then for good reason, and before any interim analyses were done. Somewhat strangely, the underpowered original primary outcome was retained as a coprimary outcome, but by using a gate-keeping approach no power was wasted. The study also used response adaptive randomisation, and allocated more participants to treatments that seemed to be working as the trial progressed. This approach is controversial;[7] however, in this trial where doxycycline was shown to be ineffective (median time to first self-reported recovery 9·6 days [95% Bayesian Credible Interval (BCI) 8·3–11·0] in the usual care plus doxycycline group *vs* 10·1 days [8·7–11·7] in the usual care only group, hazard ratio 1·04 [95% BCI 0·93–1·17]), adaptive randomisation has marginal influence on randomisation allocation ratios.

The UK Department of Health and Social Care general practice treatment advice changed in January, 2021, on the basis of these results, and doxycycline is now only recommended in patients with evidence for bacterial co-infection, which appears to be relatively uncommon in COVID-19.[8] The effect of this change on general practitioner prescribing behaviour will be interesting to examine.

A key question that remains is how secure is the conclusion that doxycycline is ineffective? As microbiological confirmation of SARS-CoV-2 infection was not obtained for many participants in PRINCIPLE, some individuals might have been misclassified as having COVID-19, which could reduce power. The assumed treatment effects were large; however, the 95% BCI on the revised primary outcome ruled out a benefit of more than 17% improvement. The dose of doxycycline might have been inadequate. Furthermore, treatment was started up to 14 days after symptom onset, which might have obscured evidence for effective early treatment. During PRINCIPLE, as a recommended COVID-19 treatment, doxycycline was widely prescribed in the general population, which might have led to dilution of any treatment effect.

The scarcity of microbiological confirmation of infection and imperfect testing in those tested is the reality of most community treatment of infection. Any suggestion of a possible benefit from doxycycline in patients with positive tests should be seen in this context. In-vitro evidence suggesting possible

effectiveness of doxycycline against SARS-CoV-2 also suggested that the treatment regime tested in PRINCIPLE was appropriate.[9] Results of experimental treatment evaluations often show potential that is not realised in real-world settings. These findings from PRINCIPLE, which provide no evidence of benefit of doxycycline in the community management of COVID-19 patients at high risk of adverse outcomes, should likewise be seen in this context. This pragmatic trial[10]—with few exclusion criteria, inclusion of patients with suspected COVID-19 who did not necessarily have a positive PCR result, and no placebo or blinding—estimated real-world effectiveness, not idealised efficacy. PRINCIPLE included sensitivity and subgroup analyses in participants with positive PCR confirmation of infection and by duration of illness before randomisation, neither of which showed any meaningful effect. Whether doxycycline might work, and at what dose and duration, could still be investigated in early-phase efficacy studies in future waves of the SARS-CoV-2 pandemic.

The findings reported by Butler and colleagues strongly suggest that doxycycline is not effective in reducing symptom duration or COVID-19-related hospitalisations or deaths in patients with COVID-19 who are at high risk of adverse outcomes. PRINCIPLE has shown it is possible to produce robust evidence from a randomised trial for interventions in community settings during a pandemic, by using a pragmatic platform effectiveness design that was flexibly and skilfully implemented. The PRINCIPLE design should be studied carefully, for future deployment when needed.

JN declares he is Chair of the Medical Research Council and National Institute for Health Research (NIHR) Efficacy and Mechanisms Evaluation funding panel; NIHR funded the PRINCIPLE study. JN had no involvement in any aspect of the PRINCIPLE study. JM declares no competing interests.

*John Macleod, John Norrie
john.macleod@bristol.ac.uk

Centre for Academic Primary Care, University of Bristol, Bristol UK (JM); Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, UK (JN)

1 Park JJH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019; **20:** 572.
2 LaVange L, Adam SJ, Currier JS, et al. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV): designing master protocols for evaluation of candidate COVID-19 therapeutics. *Ann Intern Med* 2021; published online June 29. https://doi.org/10.7326/M21-1269.
3 Butler CC, Yu L-M, Dorward J, et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet Respir Med* 2021; published online July 27. https://doi.org/10.1016/S2213-2600(21)00310-6.
4 Zhu N, Aylin P, Rawson T, Gilchrist M, Majeed A, Holmes A. Investigating the impact of COVID-19 on primary care antibiotic prescribing in north west London across two epidemic waves. *Clin Microbiol Infect* 2021; **27:** 762–68.
5 Beckman J, Smith A. PRINCIPLE—accelerated recruitment for clinical trials through rapid access to large, linked datasets and integrated patient engagement. April 1, 2021. https://www.hdruk.ac.uk/case-studies/accelerated-recruitment-for-clinical-trials-through-rapid-access-to-large-linked-datasets-and-integrated-patient-engagement/ (accessed July 15, 2021).
6 Dodd LE, Freidlin B, Korn EL. Platform trials—beware the noncomparable control group. *N Engl J Med* 2021; **384:** 1572–73.
7 Begg CB. Ethical concerns about adaptive randomization. *Clin Trials* 2015; **12:** 101.
8 Robinson J. Azithromycin and doxycycline should not be used in the management of COVID-19, DHSC advises. Feb 1, 2021. https://pharmaceutical-journal.com/article/news/azithromycin-and-doxycycline-should-not-be-used-in-the-management-of-covid-19-dhsc-advises (accessed July 15, 2021).
9 Gendrot M, Andreani J, Jardot P, et al. In vitro antiviral activity of doxycycline against SARS-CoV-2. *Molecules* 2020; **25:** 5064.
10 Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016; **375:** 454–63.

Moving from collective to distributed epidemiological cancer research

Published **Online**
August 18, 2021
https://doi.org/10.1016/S2213-2600(21)00205-8

See **Articles** page 1030

Some lung and laryngeal cancers are preventable with lifestyle changes, several methods for early detection of these cancers have been studied,[1] and various drugs have been developed to treat respiratory tract cancers—some of which have been shown to be effective in prolonging survival.[2] Despite these advances in screening and treatment, it is beneficial to understand the global epidemiology of respiratory tract cancers in order to best utilise the latest early detection and treatment strategies available.

To ensure effective prevention and management of respiratory tract cancers, it is useful to obtain global data on prevalence and risk factors, which is the focus of the study by the GBD 2019 Respiratory Tract Cancer Collaborators[3] in *The Lancet Respiratory Medicine*. The data presented in this analysis, from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, allow governments, researchers, pharmaceutical companies, and the general public to understand the associated risk factors for these cancers relevant to their country or region, allowing implementation of suitable