

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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active. 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",<sup>12</sup> but little thought is given to what defines 'sometimes', or under what circumstances might empirical evidence of vaccine effectiveness lead to erroneous assumptions.<sup>12</sup> 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.

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### PRINCIPLE: a community-based COVID-19 platform trial

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.<sup>1,2</sup> In *The Lancet Respiratory Medicine*, Christopher Butler and colleagues<sup>3</sup> 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.<sup>4</sup> This trial aimed to assess the efficacy of doxycycline to treat suspected



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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.<sup>5</sup> 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 selfreported 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;<sup>7</sup> 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.<sup>8</sup> 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<sup>10</sup>—with few exclusion criteria, inclusion of patients with suspected COVID-19 who did not necessarily have a positive PCR result, and no placebo or blindingestimated 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-19related 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.

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# Moving from collective to distributed epidemiological cancer research

Some lung and laryngeal cancers are preventable with lifestyle changes, several methods for early re detection of these cancers have been studied,<sup>1</sup> da and various drugs have been developed to treat of respiratory tract cancers—some of which have Co been shown to be effective in prolonging survival.<sup>2</sup> da Despite these advances in screening and treatment, of it is beneficial to understand the global epidemiology 20 of respiratory tract cancers in order to best utilise the latest early detection and treatment strategies as 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<sup>3</sup> 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



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