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.

Learning and confirming in publicly funded antiviral trials

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Reporting the phase 2 results from the UK AGILE CST-2 study of molnupiravir for SARS-CoV-2 in *The Lancet Infectious Diseases*, Saye H Khoo and colleagues[1] present output from a platform trial with public funding that has taken an approach inspired by commercial drug developers. The COVID-19 pandemic exposed our lack of potent oral antivirals and, given the previous two decades of outbreaks of RNA viruses, including SARS-CoV, MERS-CoV, and Ebola virus, one could argue that we should have been better prepared.

However, developing drugs for acute infections is fraught with difficulties. One single pivotal phase 3 trial without positive results can lead to a company going out of business and the commercial case for developing agents used as a short course against a virus with pandemic potential is limited. Thus, public funding is required.

Drug development follows cycles of learning and confirming.[2] For antivirals, this process means an initial preclinical cycle, in which it is learned whether a compound has in-vitro activity and then this activity is confirmed in animal models. This first cycle would have ruled out any possible efficacy of hydroxychloroquine for patients with COVID-19,[3] for example.

During clinical drug development, we learn about drug safety and dose–response in phases 1 and 2, which are then followed by pivotal, confirmatory phase 3 trials. To ensure that results are robust to regulatory scrutiny, double-blinding and placebo control are usually used. To maximise the probability of success, trials target the phase of disease during which interventions are most likely to be efficacious. In the case of SARS-CoV-2, this approach means treating patients within the first few days of symptom onset, as was known from preprints of viral dynamic models from March, 2020.[4] Continuous learning via secondary endpoints, such as pharmacokinetics, viral load, sequencing and viability measures, and markers of immune function, is particularly important in phase 2 trials.

Unlike Khoo and colleagues, the leaders of national and international SARS-CoV-2 platform trials sought to shortcut this tried and tested approach. Taking antiviral monotherapies with little or questionable in-vitro activity straight to confirmatory phase 3 trials, often in late-stage COVID-19 when viral replication has slowed, very predictably, does not work.[5] A paucity of systematic collection of secondary data in SARS-CoV-2 drug trials further undermines the ability to understand why interventions have failed. A notable exception has been the DISCOVERY trial, published in *The Lancet Infectious Diseases*, which showed why remdesivir does not have clinical benefit in late COVID-19: it does not reduce viral load.[6]

The rapid setup and roll-out of high-quality clinical learning studies is perfectly possible in an emergency setting: Khoo and colleagues opened recruitment to AGILE CST-2 in November, 2020. The double-blind, 2×2 factorial FLARE trial[7] investigating favipiravir with or without lopinavir–ritonavir for the treatment of patients with COVID-19 opened recruitment in September, 2020, without UK Research and Innovation funding or Urgent Public Health badging. But, in both cases, these high-quality trials requiring 180 patients (AGILE CST-2) or 240 patients (FLARE) took more than 1 year to recruit.

Accordingly, were resources used for rapidly deployed phase 3 platform trials well directed? Had the FLARE trial design been adopted for a platform oral antiviral study, for example, with only 960 participants, eight drugs and their 2×2 combinations could have been ruled appropriate or inappropriate for a phase 3 trial.

With large portions of the population having been vaccinated, infected with SARS-CoV-2, or both, rates of so-called hard or severe clinical endpoints, such as hospitalisation and death, have plummeted. Low event rates mean larger sample sizes will be required to detect an effect, threatening the future viability of both antiviral and vaccine phase 3 trials.

The development of COVID-19 vaccines, conducted largely by commercial developers, followed a compressed traditional path, in that no vaccine was taken into a phase 3 trial without first showing it could produce an antibody response in phase 2. A low event rate for traditional phase 3 endpoints is now leading to discussion about so-called correlates of protection:[8] what level of antibody response can be considered sufficient for licensing a vaccine without large-scale efficacy trials? Perhaps now is the time to start considering a similar approach for antivirals. The modest effect on viral load by favipiravir in early COVID-19[7] predicted favipiravir's phase 3 failure,[9] and retrospective

studies highlight the relationship between viral load and clinical outcome.[10]

In the study by Khoo and colleagues,[1] molnupiravir shortened the time to negative PCR compared with placebo (8 days [95% CI 8–9] *vs* 11 days [10–11]), although the predefined threshold for recommending molnupiravir for further testing was not reached. As half the participants in the study were unvaccinated and the median age of the study cohort was 43 years (IQR 28–55), whether results will be similar in a largely vaccinated, older population remains to be seen. It is also unknown whether a correlate of protection based only on viral load is possible and whether secondary virological endpoints, such as the evolution of the viral genome sequence or infectivity with time on treatment, correlate with clinical outcome.

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1 Khoo SH, FitzGerald R, Saunders G, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Infect Dis* 2022; published online Oct 19. https://doi.org/10.1016/S1473-3099(22)00644-2.
2 Sheiner LB. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther* 1997; **61:** 275–91.
3 Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature* 2020; **585:** 584–87.
4 Gonçalves A, Bertrand J, Ke R, et al. Timing of antiviral treatment initiation is critical to reduce SARS-CoV-2 viral load. *CPT Pharmacometrics Syst Pharmacol* 2020; **9:** 509–14.
5 Gastine S, Pang J, Boshier FAT, et al. Systematic review and patient-level meta-analysis of SARS-CoV-2 viral dynamics to model response to antiviral therapies. *Clin Pharmacol Ther* 2021; **110:** 321–33.
6 Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis* 2022; **22:** 209–21.
7 Lowe DM, Brown L-AK, Chowdhury K, et al. Favipiravir, lopinavir-ritonavir or combination therapy (FLARE): a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19. *medRxiv* 2022; published online Feb 15. https://doi.org/10.1101/2022.02.11.22270775 (preprint).
8 Goldblatt D, Alter G, Crotty S, Plotkin SA. Correlates of protection against SARS-CoV-2 infection and COVID-19 disease. *Immunol Rev* 2022; **310:** 6–26.
9 Golan Y, Campos JAS, Woolson R, et al. Favipiravir in patients with early mild-to-moderate COVID-19: a randomized controlled trial. *Clin Infect Dis* 2022; published online Sept 6. https://doi.org/10.1093/cid/ciac712.
10 Rico-Caballero V, Fernández M, Hurtado JC, et al. Impact of SARS-CoV-2 viral load and duration of symptoms before hospital admission on the mortality of hospitalized COVID-19 patients. *Infection* 2022; **50:** 1321–28.

The 2022 monkeypox outbreak: the need for clinical curiosity

In the UK, the 2022 monkeypox outbreak was heralded by an imported case on May 7, 2022, with a typical history and presentation for imported monkeypox, including a widespread vesiculopustular rash and relevant travel history.[1] Shortly afterwards, and perhaps due to public notification and increased awareness following this case, a cluster of cases was identified among gay, bisexual, and other men who have sex with men with no travel history and no epidemiological link to the index case.[1] Since then, more than 60 000 laboratory confirmed cases have been identified in 105 countries and territories.[2]

What is striking about this outbreak, as highlighted in the study by Kristina Angelo and colleagues in *The Lancet Infectious Diseases*,[3] is how the outbreak has confounded what was previously known (or thought to be known) about the epidemiology, transmission, and clinical features of monkeypox. The wide geographical reach Angelo and colleagues' study provides a truly global picture of the current outbreak and increases our understanding of how this outbreak is behaving differently from what was previously assumed of the disease. Historically, monkeypox has been considered for patients presenting with compatible lesions usually in the same stage of development, a febrile prodrome, and history of travel to an endemic country or contact with a diagnosed case. However, in this cross-sectional study, travel was not a risk factor, and a sizeable minority of cases (>40%) had lesions at multiple stages of development: previously this would have been considered relatively unusual for monkeypox and might have prevented

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