

## Flooded by the torrent: the COVID-19 drug pipeline

The world is rushing to test potential COVID-19 treatments. But do we really need so many trials? Asher Mullard reports.



The coronavirus disease 2019 (COVID-19) drug pipeline is not growing at quite the same speed as the pandemic. But its rate of expansion is nevertheless cause for pause. In the months since COVID-19 has spread, researchers have launched more than 180 clinical trials of everything from repurposed antivirals and immunomodulators to unproven cell therapies and vitamin C. A further 150 trials are preparing to recruit patients.

For pandemic preparedness experts, this begs crucial questions. “Do we need 300 trials? Is that a good use of resources?” asks Daniel Bausch, director of the UK Public Health Rapid Support Team and infectious disease expert at the London School of Hygiene & Tropical Medicine. “I would probably say we don’t.”

There are good reasons to build up a full pipeline of COVID-19 drugs. Up to 90% of new entrants into clinical trials never make it to approval, and so investigators want to have as many shots on goal as possible. Scientific understanding of COVID-19 is also changing so quickly that it makes sense to keep options open. But other motives, including public relations and financial gain, might also be in play. “During a crisis, some people will go out of their way to sacrifice their lives, and others will hoard medicines and be complete jerks. On institutional levels, we have the same span of good actors and bad actors”, says Bausch.

And in the absence of comprehensive trial coordination mechanisms, signs of disarray are emerging. “The scale of these trials is too small, and the variation in terms of how they are being run is too large”, says John-Arne Røttingen, chief executive of the Research Council of Norway and proponent of a more

collaborative approach. “These trials aren’t really designed to answer the questions that need to be answered.” Clinical trial literature, moreover, is riddled with drugs that looked promising in small trials only to prove ineffective in bigger, more rigorous studies.

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Merdad Parsey, chief medical officer at Gilead, agrees. “We are seeing that the level of evidence on some of the therapeutics that are out there is not great. Given how broadly some of these agents are being used, this may impact our ability to actually detect signals with other molecules”, he explains.

The research community faces a tricky dilemma, with little time for reflection. “On the one hand, we want to be coordinated. On the other hand, we don’t want to spend too much time getting coordinated because the pace of this thing is so rapid”, explains Parsey. “Everyone’s doing their best”, he adds.

“The most important things to get right are primary outcomes, inclusion and exclusion criteria, and standard of care”, says Bin Cao, a pulmonary and critical care specialist at the China-Japan Friendship Hospital in Beijing. Cao helped to coordinate some of the first trials of COVID-19 drugs in China. Getting the standard of care right for these trials was particularly important, he adds, when systems were overwhelmed and so little was known about the disease.

WHO has now taken steps to provide greater coordination through its Solidarity trial, a study of four therapeutic approaches for hospitalised patients with confirmed

COVID-19. These consist of Gilead’s RNA polymerase inhibitor remdesivir, the antimalarials hydroxychloroquine and chloroquine, the HIV protease inhibitors lopinavir and ritonavir, and lopinavir and ritonavir in combination with the immunomodulatory agent interferon beta-1a. First results could be available within 12–16 weeks, insiders say.

Not only will the umbrella trial test multiple drugs at scale, but it also seeks to align the research community behind key clinical trial design features that can make the most of incoming data. By enrolling patients from around the world, the Solidarity trial might be able to answer questions more quickly than standalone trials can. Already, 70 countries have committed to joining up. Countries with the least developed health-care infrastructures can follow a backbone protocol, whereas those with better capabilities will launch “daughter” trials that will collect additional data.

“I like the Solidarity trial”, says Zhi Hong, chief executive officer of the biotech Bii BioSciences and former head of infectious disease research and development at GlaxoSmithKline. Although the trial is not double-blinded, that is acceptable



in a pandemic, he says. “You really want to make this as easy and simple as possible”, says Hong, who is not involved in the trial. By enrolling as many and as diverse a population as possible, the data will be more likely to reflect real-world efficacy, he adds.

Expectations for these agents, however, need to be tempered. “I don’t want to set expectations too high”, says Røttingen, who chairs the executive group and the international steering committee of the Solidarity trial. “I’m not saying these will be a cure for COVID-19”, he adds. “But even if we can reduce the proportion of patients that need ventilators by, say, 20%, that could have a huge impact on our national health-care systems.”

Marie-Paule Kieny, director of research at INSERM, which is taking part in Solidarity, and former assistant director-general at WHO, is also hedging her bets. “Will we have a magic bullet? Most likely not”, she says. A 200-patient trial of the lopinavir plus ritonavir combination has already failed, Cao and colleagues reported in the *New England Journal of Medicine* in March, although subgroup analyses of the data suggest the drugs might still have efficacy.

Researchers have been finding preliminary antiviral efficacy signals with repurposed agents including hydroxychloroquine for decades, says Bausch. But these rarely translate into clinical success. “I have no optimism for hydroxychloroquine”, adds Bausch.

“I am not opposed to the study of hydroxychloroquine. But I am opposed to what I’m seeing around the world, with this drug being worked into clinical algorithms already.”

This leaves plenty of room—and need—for other agents. Beyond the

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traditional antivirals, a few candidates are already attracting attention. Virally targeted antibodies might be able to help the immune system to ward off infection, for example. There is also hope that anti-inflammatory agents might be able to keep overactive immune responses in check.

The Solidarity trial has been set up such that some of these other agents can be added in as new arms, as the trial progresses. But there is a trade-off here—and elsewhere throughout the COVID-19 drug development landscape—between speed and breadth. “If we add more arms, it will take longer to actually collect solid data on the therapeutic options that are in the existing arms”, cautions Røttingen.

The different classes of agents might also be most useful in different stages of diseases. Antiviral agents, for example, might be most beneficial when used as early as possible in the course of disease, prophylactically even if possible. Anti-inflammatory agents might, by contrast, be harmful if used early on, if they dampen the immune response too much.

Many more trials, consequently, are going to be needed. WHO might yet start another Solidarity trial in an earlier disease setting. Other large trials to build up the evidence base include the UK’s multiarm RECOVERY trial in hospitalised patients, which has already recruited 4300 patients and is adding 400 more a day, and an international

40 000-patient prevention trial with chloroquine and hydroxychloroquine.

Industry sponsored trials will also be needed, both to prioritise which agents to test at scale and potentially to secure regulatory approvals. Gilead is aiming to recruit more than 3000 patients into its phase 3 trial of remdesivir, in addition to its collaborative efforts with WHO, the US National Institutes of Health, and others.

Having multiple parties and funders pursue their own favoured agents also provides a safeguard against groupthink, adds Kieny. “We shouldn’t have a single approach, and it is absolutely fair to do more trials”, she says. “But it would be good if other investigators look at what we have done with Solidarity, committing to a consortium to increase the likelihood of finding an answer to the most pressing scientific questions.”

Bausch similarly urges for more coordination around clinical data collection. “If everyone has their own case-report forms to record the different clinical signs and symptoms of disease, they might record these in different ways”, explains Bausch. “This makes it very difficult to later merge the databases and make sense of things across different trials.”

While finding effective drugs is no easy feat on its own, it is also only at best a single step on a long journey towards taming the COVID-19 beast. Manufacturing, regulatory approval, and supply and access decisions are also going to need collective solutions, as will vaccine and diagnostic development.

It remains to be seen how this will all play out. “There is a saying that everyone wants to see more coordination, but no one wants to be coordinated. I think that is an issue we are now seeing”, says Røttingen.

Parsey nevertheless remains optimistic. “We are all working through different options and trying to help each other out”, says Parsey. “It’s really heartening.”

Asher Mullard

