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Global clinical trial mobilization for COVID-19: higher, faster, stronger

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The clinical trial landscape for Coronavirus 2019 (COVID-19) is radically different from that of previous epidemics. Compared with H1N1, Ebola, and Zika, COVID-19 had an order of magnitude more clinical trials within the first 3 months following the declaration of a Public Health Emergency of International Concern (PHEIC). These trials have started much faster, are more geographically diverse, and are less likely to be funded by industry. However, the almost simultaneous design and initiation of hundreds of trials with 0.3 million participants across 78 countries creates the potential for congestion and inefficiencies and enhances risks for investors. Thus, an international coordination mechanism for clinical trials could be valuable in this and other situations.

Introduction
The COVID-19 situation is unquestionably an unprecedented public health emergency. In addition to the toll it has taken on human life, the economic harm occurring simultaneously is enormous. The initial estimates of the Organisation for Economic Co-operation and Development (OECD) place it at a 20–25% reduction in gross domestic product (GDP) [1], which implies a daily reduction in GDP in OECD countries in the range of US$33 billion–41 billion. It is likely that a return to ‘normal’ will only be possible if effective vaccines or treatments become widely available.

Clinical trial activity is one important indicator of the extent to which biomedical innovation has been mobilized to work towards new or repurposed treatments. Clinical trial landscape studies can help to inform and assess the current state of affairs within specific clinical areas [2–4]. We wanted to see how the response of the biomedical innovation pipeline to the COVID-19 situation compared with other recent epidemics with respect to clinical trials [5].

Four epidemics, four public health emergencies
In line with several other studies investigating the landscape of clinical trials [6–8] (including those for COVID-19 [9]), our data source was ClinicalTrials.gov. We included epidemics designated a PHEIC by the WHO, which distinguishes our current study from previous investigations. This led us to select the H1N1 influenza outbreak (designated a PHEIC on 26 April 2000 [10]), Ebola (8 August 2014 [11], with a subsequent PHEIC declared in 2019), Zika (1 February 2016 [12]), and COVID-19 (30 January 2020 [13]). We excluded the 2014 polio PHEIC because existing polio vaccines were available. We searched for all interventional trials for these diseases, including Phase I to Phase IV trials. Our evaluation focused upon four aspects of the clinical trial response within each of the four disease areas: magnitude (i.e., the count of clinical trials as well as the collective sum of patients enrolled in those trials); speed (i.e., how many trials were launched within 3 months following the WHO declaration of PHEIC because only the first 3 months of COVID-19 had been observed at the time of study, including range of interventions being tested (e.g., drug
of patients enrolled, with 536 488 (which was the result largely of a single vaccine trial with 500 000 patients), followed by COVID-19 with 352 311, H1N1 with 75 783, and Zika with 35 201.

### Speed

When restricted to the first 3 months following the PHEIC announcement, COVID-19 accounted for 435 of the 455 trials launched within that time frame, followed by Ebola with 13, H1N1 with 7, with no trial yet launched for Zika. In terms of the share of the 342 033 patients enrolled in trials, COVID-19 accounted for 336 329, H1N1 accounted for 4849, and Ebola accounted for 855. A major Ebola vaccine trial enrolling 500 000 patients was launched on 14 November 2019, ~5 years after the first Ebola PHEIC declaration. No Zika trials were launched between 1 February 2016 and 1 May 2016. COVID-19 was also unique in the variety of the type of interventions being trialed within the first 90 days, with COVID-19 covering all possible categories in contrast to H1N1 and Ebola, which were more limited to testing drugs and biologicals (Fig. 2).

### Funding composition

H1N1 had the largest proportion of industry-sponsored trials at 54% (94/175), followed by Zika at 41% (12/29), Ebola at 39% (32/83), and COVID-19 at 14% (64/471). Similarly, H1N1 had the largest share of patients enrolled in industry-sponsored clinical trials at 60% (42 275/75 783), COVID-19 with 6% (21 509/352 311), followed by Zika with 4% (1526/35 201), and Ebola with 2% (12 201/536 488). However, these proportions were dynamic and changed over time, with most trials sponsored by non-industry sources in the initial months following the outbreak and industry sources taking a somewhat larger role in the later months following the outbreak (Fig. 3).

### Implications of the COVID-19 trial landscape

The COVID-19 clinical trial response has been unprecedented in terms of its magnitude, speed, and composition. Even though this study only captures the first 3 months since the PHEIC announcement for COVID-19, more trials have initiated and patients enrolled

| Disease area | Trial count | Number of patients enrolled |
|--------------|-------------|----------------------------|
| H1N1         | 175         | 75 783                     |
| Ebola        | 83          | 536 488                    |
| Zika         | 29          | 35 201                     |
| COVID-19     | 471         | 352 311                    |
| Total        | 758         | 999 783                    |

### Geographic diversity

The number of countries with a registered clinical trial facility (Table 1) indicates the most widespread geographic diversity, with H1N1 leading at 783, followed by Ebola at 647 and COVID-19 at 645. Other disease categories such as H1N1 and COVID-19 were represented in just three countries, while Zika was represented in 21 countries.

### Four very different clinical trial landscapes

Overall, our searches within the four disease areas collectively located 758 relevant clinical trials enrolling 999 783 patients in 78 different countries (Table 1). Of the 758 trials, 202 (27%) were industry sponsored and 556 (73%) were sponsored by non-industry sources. Of the 999 783 patients enrolled, 80 511 (8%) were enrolled in industry-sponsored trials and 919 272 (93%) in non-industry sponsored trials.

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**Table 1**

Magnitude, speed, geographical diversity, and funding composition of global clinical trial mobilization for four recent PHEIC

| Magnitude (number of trials initiated and patients enrolled) | Number of patients enrolled |
|------------------------------------------------------------|----------------------------|
| Disease area                                               |                            |
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| Ebola                                                      | 536 488                    |
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Clinical trials for Coronavirus 2019 (COVID-19) have started much faster following outbreaks compared with trials for other diseases. There was a delay of ~6 months following the start of the H1N1 and Ebola outbreaks until clinical trials got underway; for Zika, the delay was about 15 months. For COVID-19, clinical trials started within a month, with unprecedented alacrity as the potential scale of the epidemic quickly became apparent.
already been launched than have ever been initiated for H1N1, Zika, and Ebola combined. This is likely chiefly because of the anticipated public health impact of COVID-19, compared with the other epidemics. In this context, it is useful to keep in mind that the 2009 H1N1 pandemic is estimated to have caused an excess mortality of approximately 285,000, with 80% being in individuals under 65 years old [14]. However, the speed and magnitude have come at a cost. With >300,000 people in trials even before vaccine trials had begun, there were challenges to ensure that the most useful trials are able to find enough patients. Two trials in China testing remdesivir in patients with COVID-19 were terminated early because of insufficient numbers of patients. The issues here are compounded by geographical and interventional diversity; with investigators in so many different countries proposing their own studies, it is likely that there will be an inefficient allocation of patients across trials. There is also a risk of trials overlapping; for example, there are 23 COVID-19 trials using hydroxychloroquine or chloroquine.

Given the number and geographical diversity of trials, and their simultaneity, a coordinating mechanism for trials would be valuable, as has been argued elsewhere [15–17]. Although regional coordinating bodies are taking form, such as those in Europe [17], the fact that clinical trials are also being conducted in several low- and lower middle-income countries is important for ensuring that proposed therapies are well targeted to global health needs [18]. Without limiting autonomy, it would be useful to have a centralized advisory service for assistance in planning clinical trials in a pandemic context so that there is an appropriate allocation of patients and expertise across different therapies and vaccines. The WHO is ideally situated to provide such assistance.

The large number of trials for COVID-19 also creates exceptional risks for investors. For example, many vaccine candidates are competing aggressively to arrive first, given that the earliest vaccines will capture the lion’s share of sales. From the perspective of society, such competition is highly desirable; but from the perspective of investors, increased competition means that an individual product is less likely to be first. The hundreds of therapies that are being tested further increase the risks for any individual product that some other product will have arrived before it. This combination of high value to society but high risk to investors suggests that subsidies to support clinical trials are justified or even necessary.

With respect to the composition of the response, our results also show that, across each disease area, industry-led trials are initiated relatively late in the process. These results are likely in part because of the time it takes to develop a targeted therapy or vaccine; rapid publicly funded trials tend to assess the repurposing of existing drugs, such as hydroxychloroquine. We can expect the role of industry to grow with the acceleration of vaccine and antibody trials, which appear to have the greatest promise for effectively addressing COVID-19.

Our analysis has several important limitations: first, our data included only trials
registered in ClinicalTrials.gov and, therefore, might omit some relevant trials. In the absence of a centralized and coordinated global clinical trial registry, the number of omissions cannot be quantified accurately. Second, with respect to COVID-19, we are considering only the trials announced within a very short period, and this reflects how quickly trials can start, rather than how quickly they yield useful results, which is probably of greater interest. Third, we categorized trials according to their listed sponsor, without consideration of collaborators. Fourth, not all four pandemics have had equivalent geographical spread or presence in hubs of pharmaceutical innovation (e.g., Europe or the USA) compared with COVID-19; although our analysis has not controlled for this, we believe this illustrates an important point, namely, the value of building greater global pharmaceutical innovation capacity to be less dependent upon where an infectious disease is centralized at a given time. Finally, some trials do not list geographical locations, and it is possible that we are undercounting countries.

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