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.

containing the spread of the virus, was not addressed in the study. While interventions to control the spread of SARS-CoV-2 are in place, countries will need to work toward returning to normalcy; thus, knowledge of the effect of each intervention is urgently required. Air travel data were used to model the effect of travel restrictions on delaying overall epidemic progression, and were found to have a marked effect at the international scale, but only a 3–5 day delay within China.[4] A study[5] focused on the effects of extending or relaxing physical distancing control measures in Wuhan has suggested that if the measures are gradually relaxed in March, a second wave of cases might occur in the northern hemisphere mid-summer. Country-specific models of the effects of travel restrictions and social distancing, as well as the alternative strategies after the relaxation of these interventions, such as the use of face masks, temperature checks, and contact tracing, are now needed.

Case fatality rate (CFR) is one of the important unknowns of COVID-19. Leung and colleagues estimated the confirmed CFR (cCFR) outside Hubei was 0·98% (95% CI 0·82–1·16), which was consistent with the report from the Chinese Center for Disease Control and Prevention.[6] Since the epidemics in the studied locations did not overwhelm the health-care capacities, the data on the number of confirmed cases are believed to be reliable. Leung and colleagues also found the cCFR was correlated with provincial per capita gross domestic product and the availability of hospital beds per 10 000. In Wuhan, the CFR was up to 5·08% by March 28, 2020.[7] The remarkable difference in the CFRa between these locations and Wuhan might be attributed to the difference in the degrees of health-care capacity. Therefore, consideration should be given to the variations in health-care capacity when implementing interventions. While the epidemic is growing exponentially, the health-care system will face severe burdens. Governments should act and prepare immediately to ensure that the health-care system has adequate labour, resources, and facilities to minimise the mortality risk of COVID-19.

We declare no competing interests.

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Global coalition to accelerate COVID-19 clinical research in resource-limited settings

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There is no available vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and no drug with proven clinical efficacy, although there are several candidates that might be effective in prevention or treatment. Encouragingly, the response from the research community to the pandemic of coronavirus disease 2019 (COVID-19) has been vigorous. A review of clinical trial registries, as of March 24, 2020, identified 536 relevant registered clinical trials.[1] Of the 332 COVID-19 related clinical trials, 188 are open for recruitment and 146 trials are preparing to recruit.[1,2] The distribution of these clinical trials is centred in the countries most affected by COVID-19 in the past 2 months, particularly China and South Korea, with high-income countries in Europe and North America planning most of the forthcoming trials. Very few trials are planned in Africa, south and southeast Asia, and central and South America.

The number of confirmed COVID-19 cases reported in resource-poor settings is still relatively small,[3] but

the availability of testing is also low and numbers of COVID-19 cases are expected to rise substantially in the coming weeks. The capacity of weak health-care systems to manage a surge of severe pneumonia is limited, and the low availability of appropriate personal protective equipment (PPE) for front-line health-care staff means that these key staff are likely to be disproportionately affected by COVID-19. Disruption or complete breakdown of those health-care systems would result in high direct and indirect mortality since care of all illness would be affected.

COVID-19 trials should be adequately powered to generate evidence. They need to be large and well designed. Priority should be given to interventions that reflect the specific needs of countries and are readily implementable. For resource-poor settings, that means interventions need to be affordable and available, and adaptable to the health-care systems and the populations they serve. The adverse impacts of COVID-19 on health and welfare are likely to be considerable in low-income or middle-income countries (LMICs). Clinical trials, and evaluations of affordable and implementable interventions of all types—behavioural, organisational, medical, and supportive—are a priority.[4]

On March 18, 2020, the Director-General of WHO announced the launch of the SOLIDARITY trial, an international study of potential treatments for COVID-19 to be conducted in Asia, South Africa, Europe, and the Americas.[5] WHO has an important convening role in setting COVID-19 research priorities, facilitating trials, and coordinating efforts. The WHO COVID-19 research and development blueprint[6] and the R&D Blueprint Scientific Advisory Group will provide guidance and ensure the necessary coordination and sharing of information. WHO will also have a central role in reviewing the evidence generated by trials and in producing guidelines. Yet despite these international efforts, there remain substantial organisational and bureaucratic obstacles to a rapid research response. Strong political support, effective collaboration, adequate expertise and resources, and informed guidance will be needed to overcome these barriers.

Managing COVID-19 will place considerable pressures on health-care systems. COVID-19 results in severe pneumonia and death in approximately 4–5% of patients admitted to hospital in well supported health-care

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settings.[3,7] Evidence is needed on pre-exposure prevention, post-exposure prevention, and patient management. Several countries are already recommending chemoprevention or treatments for which there is no convincing evidence of benefit and banning export of these medicines, thereby compromising the trials needed to establish the evidence. It is possible that none of the current therapeutic interventions being trialled or recommended will prove beneficial. Large, well conducted clinical trials are needed urgently to support guidelines on prevention and clinical management. These trials must not detract from already overstretched health services and, with travel bans in many places, they must be designed to accommodate remote initiation and monitoring. There is also much that might be improved in supportive care and organisation in LMIC settings that could reduce direct and indirect COVID-19 morbidity and mortality. Research is needed now to guide the increasingly difficult choices that resource-limited health-care systems will face. Yet additional challenges that relate to ethics review, regulation, manufacturing, clinical trial support and logistics, open science and data sharing, and equitable and affordable access will need to be overcome for these studies to be successful.

The 2013–16 outbreaks of Ebola virus disease in west Africa showed the ethical challenges of doing research in the context of a Public Health Emergency of International Concern. Lessons learned—eg, shortcomings in community engagement, access to basic care, and front-line worker welfare—will need to be applied to the COVID-19 pandemic. Ethics committees

and review boards in many countries are unprepared for applications that require rapid review.[8,9]

Regulatory clearance, including importation of products, is required for many drug and vaccine trials and, as for ethical review, this can be very slow. Accelerated clearance pathways for COVID-19 studies such as those recently set up by WHO, the European Medicines Agency, the UK Medicines and Healthcare products Regulatory Agency, and the US Food and Drug Administration are needed in all countries where trials will be held.

For the **COVID-19 Therapeutics Accelerator** see https://www.gatesfoundation.org/MediaCenter/Press-Releases/2020/03/COVID-19-Therapeutics-Accelerator

For the **Coalition for Epidemic Preparedness Innovations** see https://cepi.net/covid-19/

For the **SARS-CoV-2 Diagnostic Pipeline** see https://www.finddx.org/covid-19/pipeline/

In terms of manufacturing, preparation of clinical trial medicines and vaccines might require new doses or formulations and placebos. Many LMIC settings will not have ready access to suitable Good Manufacturing Practice (GMP) manufacturers, and those that do have access may need support in ensuring quality assurance and obtaining regulatory approvals. This also applies to validated diagnostics.

There is tension between the maximum recommended and minimum essential requirements to conduct a good trial. In LMIC settings, the infrastructure required to support clinical trials—eg, preparation of trial products, materials, protocols, case report forms, databases, statistical support, monitoring, and reporting—is seldom readily available. Facilities for laboratory measurement and microbiology identification are often insufficient in these settings[10] and might soon become unavailable because of the COVID-19 pandemic. Essential clinical trial materials are unavailable in many areas, with PPE to protect staff and swabs to obtain nasal and pharyngeal samples for virus identification both in short supply. Some countries forbid export of laboratory samples.

Much of the public and private research is being funded by governments and charities. These funding agreements must mandate open collaboration and data sharing while protecting the rights of participants and patients.[11] Open science and data sharing principles need to be applied at all stages of COVID-19 research to accelerate progress. This includes research undertaken by the private sector. The FAIR guiding principles (Findability, Accessibility, Interoperability, and Reusability) for data should be implemented, and mechanisms put in place to enable equitable use and reuse of data.[12] Evidence will need to be shared with WHO for review and development of policies in line with WHO's normative role.

If interventions are shown to be effective, there should be specific commitments to ensure that they are made available as soon as possible. There should be commitments to, and provisions for, equitable and affordable access.

To address these challenges and accelerate the research needed in resource-limited settings, we propose an international research coalition that brings together existing multinational, multidisciplinary expertise and clinical trial capacity. The coalition will synergise with existing initiatives, such as the COVID-19 Therapeutics Accelerator, the Coalition for Epidemic Preparedness Innovations (CEPI), and the SARS-CoV-2 Diagnostic Pipeline. Our objective is to use our existing research capabilities to support, promote, and accelerate multicentre trials of the safety, efficacy, and effectiveness of interventions against COVID-19 in resource-limited settings. For therapeutics, research in such settings should focus primarily on evaluation of affordable repurposed medicines—ie, those already developed and approved for other indications—and implementable supportive measures. If applicable, testing of new diagnostic tools, vaccines, and other potentially beneficial strategies will be added to the trials.

Our objective is not to control the research agenda but to facilitate it. With partners, we have four goals. First, we aim to facilitate rapid and joint protocol reviews by ethics committees and national regulatory agencies, as was done for the Ebola vaccine trials. Second, we aim to facilitate approvals for the importation of study medications and materials through agreed coordinated fast-track mechanisms. Third, we aim to ensure standardised and simple collection of key data, sufficient for robust analysis of efficacy and safety of the tested interventions. Fourth, we aim to provide a governance framework to share outcomes before publication.

We propose to facilitate COVID-19 research in LMIC settings by identifying and supporting established local investigators, local manufacturers, and clinical trial sites. We will make existing clinical trial support capacity and trial platforms available. This approach will ensure optimal data gathering, management, security, and analytical capacity, and will support adaptive designs if necessary and feasible. The platform will ensure independent data governance and a controlled and rapid data sharing mechanism. Finally, we will facilitate

the establishment and operation of data and safety monitoring boards.

We are scientists, physicians, funders, and policy makers who have come together in an international coalition, the COVID-19 Clinical Research Coalition, to support WHO's efforts to counter the COVID-19 pandemic. We commit our combined experience, expertise, and trial capability to accelerate COVID-19 research in resource-limited settings. We welcome collaboration with organisations ready to contribute existing capacity to join us at the website of the COVID-19 Clinical Research Coalition.

MEB and PH are principal investigators or co-investigators in multiple vaccine development programmes, including for SARS, Middle East respiratory syndrome, and COVID-19 and have grants from the US National Institutes of Health (NIH), for research towards the development of COVID-19 vaccine. PC reports grants from Merck and ViiV Healthcare. SC has a patent PCT/IB2011/055209 with royalties paid to Nearmedic Plus for a tuberculosis drug candidate. JF is Director of the Wellcome Trust. AG receives non-financial support from University of Nairobi. DR reports grants from the Bill & Melinda Gates Foundation, the Wellcome Trust, the Governments of Australia, Ireland, Germany, Monaco, Netherlands, Switzerland, Korea, the UK, and the USA, GHIT Japan, EDCTP, UNITAID, and WHO. MT reports personal fees for board membership from Fondation Botnar (not-for-profit), personal fees for member of scientific advisory board from Novartis Institute for Tropical Diseases, personal fees for board membership from Gebert-Rüf Foundation (not-for-profit), personal fees for board chair from R Geigy Foundation (not-for-profit), personal fees for board membership from University Hospital Basel, Switzerland (public hospital), and personal fees for member of University Senate from the University of Neuchatel (public institution). We declare no other competing interests.

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For the **COVID-19 Clinical Research Coalition** see www.covid19crc.org

See **Online** for appendix

An alarming rise in incidence of infective endocarditis in England since 2009: why?

Infective endocarditis is a life-threatening condition with a 50% requirement for early cardiac surgery and 30% mortality at 1 year.[1] We have used publicly available annual admission data for hospitals in England[2] to examine the incidence of infective endocarditis admissions (primary ICD-10 diagnostic code I33) between 1998 and 2019. These data show stable incidence between 1998–99 (26·6 cases per million) and 2009–10 (26·9 cases per million), but an 86% increase to 50·0 cases per million in 2018–19 (figure).

One hypothesised cause of infective endocarditis is oral pathogens entering the bloodstream during invasive dental procedures. Consequently, use of antibiotics before invasive dental procedures in patients who are at risk is a long-held preventive measure; however, antibiotic prophylaxis remains controversial. Since 2007, international guidelines have recommended that antibiotic prophylaxis should be restricted to patients at the highest risk of adverse outcomes—ie, those with a history of infective endocarditis, prosthetic or repaired heart valves, or complex congenital heart disease. These guidelines reflect a scarcity of evidence for antibiotic prophylaxis effectiveness, concerns for risk of adverse drug reactions, and the possibility that antibiotic prophylaxis contributes to an ever increasing global