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editorial

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Modelling the World – can deliberately infecting healthy volunteers really tell us much about what happens outside the clinic during an epidemic or pandemic?

With the global prevalence of novel, emergent and largely zoonotic pathogens achieving new historical heights, it is imperative that researchers in the field of infectious disease find ways of modelling interventions that match or exceed traditional drug development pathways to accelerate appropriate pipeline candidates to authorisation in a manner and speed relevant to their potential impact on society.

The COVID-19 pandemic has mandated unprecedented new advisories from regulators and global health organisations alike. For the first time, an emphasis has been placed on demonstrating safety over efficacy in the early clinical development phase of any candidate SARS-CoV-2 drug or vaccine [1]. The Committee for Medicinal Products for Human Use (CHMP) has also advised against small, local studies during this time of crisis. In a statement released in March 2020, the CHMP gave: ‘A call to pool EU research resources into large-scale, multi-centre, multi-arm clinical trials against COVID-19’ [2]. The outcome of such public counsel is that many promising therapies are now moving directly into large, phase III, combination studies for safety and efficacy with limited or indeterminate phase II data and this leap-frog over conventional, step-wise, or phased progression to licensure has become the new normal for developing drugs and vaccines for COVID-19. Contributory to accelerating pressures on the global, multi-site system of clinical testing, the prevalence of COVID-19 is proving highly variable. With seasonal fluctuations in transmission similar to other epidemic upper-respiratory diseases becoming evident [3], identifying large pools of subjects with a high chance of contacting SARS-CoV-2 is increasingly limited by incidence of the virus and varying levels of host immunity.

As of October 2020, some 120 vaccines are currently in preclinical or clinical development [4]; this unprecedented number of novel candidates will each require compelling safety as well as efficacy data from large numbers of healthy volunteers before value judgements may be made regarding the potential for any one product to protect diverse populations from infection and disease. Whether markers of efficacy will comprise primarily immunological (humoral i.e. antibody or cellular measures), virolog-
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Drugs are almost invariably allocated highly restrictive classifications by the WHO [10] and other regulatory bodies (e.g. the CDC) upon emergence owing to the elevated contagion risk – this restricts their use to specialist containment facilities. For propagative work (e.g. virus culture, isolation or neutralisation assays) SARS-CoV-2 has been designated BSL3 (the same as influenza A/California/04/2009, tuberculosus or West Nile Virus). The majority of Containment Facilities e.g. ‘Poliopolis’, Antwerp University, ‘Hotel Influenza’, Saint Louis University or the Imperial Challenge Unit, Hammersmith Hospital, have been designated BSL2. Although recent discussions with the EMA and MHRA have opened the door for reclassification of specific BSL2 units to BSL2+ under certain contingencies e.g. negative air-pressure and role-based access control, this has so far only been applied to a limited number vaccine manufacturers and a single challenge agent seed stock producer in the Netherlands (Artemis). The US vaccine manufacturer Codagenix have a codon-deoptimised, live, attenuated SARS-CoV-2 vaccine (CodaVax-COVID) in development and currently preparing for Phase I trials at hVIVO. The CodaVax-COVID manufacturing facility (the Serum Institute of India) operates almost uniquely under both GMP and BSL-3. To facilitate the UK Government’s COVID-19 vaccination programmes, hVIVO (as a specialist Human Challenge CRO and part of the Open Orphan Group) has partnered with the Royal Free Hospital to access a BSL3 containment ward, previously used for COVID-19 patients, and has repurposed it to form the world’s first COVID-19-specific challenge unit. hVIVO has a long history of successfully delivering human challenge studies. The Company, formerly called Retro-CR, was originally established in 1989 as a spin out from Queen Mary University, London. Prior to this, hVIVO’s founders worked at the Common Cold Research Unit at Harvard Hospital near Salisbury, England. Employing a broad range of challenge agents, including influenza A (H1 and H3), RSV(A), rhinovirus (hRV16) and betacoronavirus (229E), objective measures have been generated by multiple hVIVO challenge trials, allowing for estimations of efficacy for a wide range of novel drugs and vaccines as well as facilitating research into some basic elements of disease including transmission [11]. A subgroup within hVIVO is developing two strains of SARS-CoV-2 challenge virus to current (c)GMP standards for use in COVID-19 modelling. Retaining inherent, wild type (WT) characteristics of the SARS-2 virus is important to ensuring data generated from disease modelling is prognostic to COVID-19 field studies. Apparently contradictory endpoints for virus manufacture: retaining WT qualities whilst balancing virulence and pathogenicity against subject safety, may be largely controlled for by varying the infective viral titre inoculated; up or down-selection of subjects based on pre-existing immunity during the characterisation study and selecting for challenge viruses with preferential qualities. For example, current circulating strains of SARS-2 carry a single genomic mutation (a G-to-A base change at position 23,403 in the Wuhan reference strain) that has been shown to increase transmissibility and reduce pathogenicity in laboratory testing [12]. The resultant single amino-acid change in the spike protein has enabled D614G-containing viruses to become the dominant strain wherever it has been introduced globally [12,13]. To reflect this predominance, seed stock virus chosen by hVIVO for CA manufacture will include this mutation. It is hoped that subsequent studies in healthy volun-
Conflict of interest
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