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.

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editorial

Adrian Wildfire

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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ical (attack rates and shedding) or host symptomologies or most likely a combination of all three, is not yet clear. Without definitive markers of efficacy studies need to be very large. Up to 10,000 subjects per arm may need to be enrolled to achieve statistical relevance for anti-SARS-CoV-2 vaccines and several hundred for COVID drugs (depending on the delta of effect and thresholds for efficacy) [5]. The FDA and some academics have expressed concerns that many COVID-19 studies are currently underpowered for statistical relevance and that early drug efficacy data trials may be flawed, particularly regarding Type 1 errors [6,7]. Additionally, whilst COVID-19 trials are receiving priority funding and accelerated regulatory approval timelines, over 1000 clinical trials for other conditions have been placed on hold or halted all together [8]. We need to find a solution to simply jumping to Phase III every time we want to define true efficacy.

Given the pressures placed on the scientific community to provide successful solutions to the current crisis with appropriately powered proofs, new methods for modelling disease should be sought that are not reliant on an over-recruitment of subjects to counter low or variable prevalence ratios or that rely on extrapolated trend data from underpowered studies. Using Phase I clinical trials as a reference point, it is possible to envisage studies where consenting adults are deliberately infected with the pathogen of interest and then closely monitored before, during and after dosing with an investigational medicinal product (IMP) to observe and directly measure therapeutic effects. Where the incidence of disease is thus controlled i.e. the likelihood of infection is above 75% (COVID-19 incidence in the UK is currently circa 0.9%) the number of volunteers required to power the study could be exponentially reduced.

Human Challenge Trials (HCT) also referred to Controlled Human Infection Modelling (CHIM) offer an environment where infection and disease can be emulated in cohorts that are prescreened for serosusceptibility. The inclusion of 'pathogen naïve' subjects ensures high attack rates when inoculated and also a higher rate of symptomatic illness than might be seen in volunteers with unknown priming or imprinting through prior exposure. In influenza challenge studies rates of symptomatic and paucisymptomatic illness are comparable to community studies [9] and the incidence of serious adverse events (SAEs) are observed to be negligible. The high levels of safety achieved to date may be related to the extensive characterisation, inclusive of dose titration of the IMP i.e. the challenge agent (CA), prior to use in clinical studies allied to an elevated degree of clinical and scientific oversight typical for such trials. Despite some claims to the contrary, challenge modelling may be considered to be a relatively simple concept; made complex only by virtue of inherent elements of control. Controlling for infectivity, pathogenicity, immune status, subject health, age and other co-factors e.g. allergies or inherited diseases, creates a 'calm pool' or a norm into which the researcher can repeatedly cast their stone to measure the ripples generated out from the baseline. Naturally occurring outliers may be largely screened out allowing for data with less 'noise' to be generated. Creating such a controlled environment for COVID-19 research may be one way of sifting the many drug candidates currently in development to identify those of most immediate value.

Globally there are very few research centres geared up for performing COVID-19 challenge trials. Pandemic virus strains 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, tuberculosis 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 Retroscreen Virology, 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-

teers using such agents will allow for additional data to be collected regarding real-world effects of G614 on viral and host dynamics as well the performance of a range of COVID-19 drugs and vaccines.

Looking forward, overt governmental support and the approval of challenge modelling by many non-governmental organisations, including regulatory agencies [14] will be important in engaging the public with positive perceptions regarding the modelling of pandemic diseases in healthy populations. With the world watching over the shoulder of the actors in this play it is important that all relevant scientific and regulatory advice is heeded in the development of a COVID-19 challenge model and that this important step-change in clinical evaluation does, and is seen to, lead us towards accelerated solutions in not just this current crisis but in the fight against future pandemic threats to public health.

Conflict of interest

This article is based upon work supported and performed by hVIVO, part of the Open Orphan Plc. group. The author declares no competing interests.

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Adrian Wildfire, Scientific Director is a Fellow, Master, DMS and accredited specialist in the fields of Virology, Medical Microbiology and Parasitology. He is a subject matter expert in controlled human infection modelling (CHIM) of drugs and vaccines primarily for diseases of the upper and lower respiratory tract.

Adrian Wildfire
hVIVO, Queen Mary BioEnterprises Innovation Centre, 42 New Road, London E1 2AX UK