Written Evidence Submitted by 1Day Sooner (EMD0047)

1Day Sooner[1] welcomes the Science and Technology Committee's Call for Evidence and the opportunity to submit our thoughts and evidence on:

"the extent of UK preparedness for an emerging disease outbreak with pandemic potential, and how this can be enhanced, including an assessment of recent policy announcements such as the refresh of the UK Biological Security Strategy."

1Day Sooner is a non-profit organisation that aims to reduce the global burden of infectious disease and avert future pandemics by working to accelerate the development and implementation of vaccines, treatments, and mechanical interventions. We do so as advocates for people who want to be in high-impact medical studies, including human challenge studies.[2]

Introduction

In human challenge trials, fully informed, consenting volunteers are actively "challenged" with a pathogen under controlled conditions. These types of studies can help researchers gain a better understanding of how a virus spreads, how the immune system responds to it, and how effective candidate vaccines and treatments may be. Having this information as soon as possible would be pivotal in successfully fighting pandemics.

The United Kingdom has historically been a leader in human challenge studies. The Common Cold Research Unit, which conducted challenge studies with thousands of volunteers between the 1940s and 1980s in Harvard Hospital in Wiltshire,[3] published over a thousand papers and generated a number of critical into respiratory viruses (including first discovering coronaviruses in 1960).

A few months into the onset of the COVID-19 pandemic, many calls were made to use human challenge trials to accelerate vaccine development, from both the scientific community and the general public.[4] Although human challenge studies were ultimately conducted in the UK, they began more than a year after the WHO's declaration of the SARS-CoV-2 pandemic.[5]

The United Kingdom should take well-justified pride in being the only country in the world to conduct COVID-19 challenge studies, which were scientifically valuable and may still provide significant benefits for second-generation vaccine development. But coronavirus challenge studies would have been more useful had they been conducted earlier in or ideally before the pandemic. In May 2020, the WHO issued a set of guidelines for the ethical considerations and criteria for conducting human challenge trials for COVID-19.[6] However, it wasn't until 10 months later, that the first participants began to be inoculated in March 2021.[7]

We must work to prepare for and optimise human challenge trials in the UK, so we can harness the full potential and knowledge we can gain from these studies in future pandemics. By doing this, we will strengthen our pandemic preparedness and response initiatives, and accelerate the development and equitable distribution of life saving vaccines and treatments.

The UK's leadership in vaccinology extends beyond COVID-19 and encompasses research on neglected diseases and biosecurity threats. For instance, researchers at the University of Oxford had been working on vaccines for SARS-CoV-1 and MERS prior to the emergence of COVID-19,[8] laying the groundwork for their rapid response to the novel

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[1] More about our organisation can be read on our website

[2] Also known as "Human Challenge Trials (HCTs)", "Controlled Human Infection Models (CHIMs)", "Human infection studies"

[3] https://wellcomecollection.org/works/bhtpkxjx

[4] For calls from the scientific community, see **Appendix A**. For calls from the general public, see **Appendix B**

[5] https://www.gov.uk/government/news/worlds-first-coronavirus-human-challenge-study-receives-ethics-approval-in-the-uk

[6] World Health Organization. (2020). Key criteria for the ethical acceptability of COVID-19 human challenge studies. https://www.who.int/publications/i/item/WHO-2019-nCoV-Ethics_criteria-2020.1

[7] https://www.gov.uk/government/news/worlds-first-coronavirus-human-challenge-study-receives-ethics-approval-in-the-uk

coronavirus. Oxford's contributions to malaria research are also noteworthy, as they have been instrumental in the development of novel interventions to combat this devastating disease. Similarly, GlaxoSmithKline's (GSK) efforts in creating a malaria vaccine (developed with more than a dozen challenge studies) have demonstrated the UK's commitment to addressing global health challenges.[9] As the nation continues to lead the way in human challenge trials and vaccinology, it is setting a powerful example for the international community to follow in addressing global health challenges.

Therefore, In this response, we will:

- Discuss why human challenge trials should be part of the pandemic preparedness toolkit
- Describe how human challenge trials can help prepare for future pandemics; and finally
- Outline steps to optimise their utility after pandemics begin.

Why Human Challenge Trials should be a part of the pandemic preparedness toolkit

Vaccine development typically requires years to demonstrate the necessary efficacy and safety data for approval, requiring the collection and comparison of thousands of individual cases who receive either a vaccine or placebo.[10] A human challenge trial, however, could accelerate vaccine development by identifying the correlates of protection needed for efficacy approval. We must therefore optimise human challenge trials, and ensure this valuable tool is part of our pandemic preparedness plan.

Human Challenge Trials vs Typical Vaccine Trial Development

In a typical vaccine trial, researchers randomly assign volunteers to receive either the treatment or a placebo, then wait for them to encounter the pathogen naturally in order to see if the vaccine works. They then compare the two groups to see how they differ in their health outcomes. However, this process can take a long time to gather the necessary data to show their effectiveness, especially if society is taking cautionary methods to avoid infecting others. Human challenge trials offer a way to speed up this process.

Compared to traditional vaccine trials, human challenge trials require fewer participants and can provide the necessary efficacy data for vaccine approval sooner. These studies have been used for a variety of pathogens and have provided data on efficacy of new vaccines, correlates of immune protection and the immune response to pathogen exposure.[11] Gaining such information could be crucial in accelerating the vaccine development process.

Human challenge trials offer several valuable use cases.[12] They are used to:

- Accelerate the process of narrowing down vaccines and therapeutics during development
- Define correlates of risk or protection that would then justify regulatory approval
- Understand the durability of naturally acquired or vaccine-induced immunity
- Distinguish between protection against infection and protection against transmission, especially in asymptomatic infected participants
- Increase our knowledge and understanding of the initial stages of viral pathogenesis and the immune response from day 0 of infection
- Determine and compare the reinfection rates of different variants

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[8] Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC, (2020) Coronavirus vaccine development: From SARS and MERS to COVID-19, Journal of biomedical science. *U.S. National Library of Medicine*. Available at: https://pubmed.ncbi.nlm.nih.gov/33341119/

[9] CP., B.W.R.C. (2007) Two decades of commitment to malaria vaccine development: GlaxoSmithKline biologicals, The American journal of tropical medicine and hygiene. *U.S. National Library of Medicine*. Available at: https://pubmed.ncbi.nlm.nih.gov/18165505/

[10] Plotkin, S., Robinson, J. M., Cunningham, G., Iqbal, R., & Larsen, S. (2017). The complexity and cost of vaccine manufacturing - An overview. *Vaccine*, *35*(33), 4064–4071. https://doi.org/10.1016/j.vaccine.2017.06.003

[11] Adams-Phipps, J., Toomey, D., Więcek, W., Schmit, V., Wilkinson, J., Scholl, K., Jamrozik, E., Osowicki, J., Roestenberg, M., & Manheim, D. (2023). A Systematic Review of Human Challenge Trials, Designs, and Safety. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *76*(4), 609–619. https://doi.org/10.1093/cid/ciac820

[12] Choy, R. K. M., Bourgeois, A. L., Ockenhouse, C. F., Walker, R. I., Sheets, R. L., & Flores, J. (2022). Controlled Human Infection Models To Accelerate Vaccine Development. *Clinical microbiology reviews*, *35*(3), e0000821. https://doi.org/10.1128/cmr.00008-21

- Test the effectiveness of vaccines against newly emerging variants, including new variants that have been identified but are not prevalent enough in the population to be studied easily by traditional clinical trials

Having such data could be pivotal in the development of vaccines and our future response to pandemics.

Human Challenge Trials during the COVID-19 pandemic

The rapid spread and mortality rate of SARS-CoV-2 only heightened the need for an acceleration of the vaccine development process. By the time a COVID-19 vaccine was authorised, around 70 million cases had been documented across the globe,[13] and according to the International Monetary Fund (IMF), the world's economic output is predicted to have decreased by $12.5 trillion by 2024.[14]

The substantial calls for human challenge trials led to debate amongst bioethicists and on social media. In the UK, however, the proposal of such trials received significant support from the public. A survey conducted in October 2020 of over 2,400 people, found that 69% agreed with a study taking place[15] and a review 1Day Sooner conducted studying media coverage on COVID-19 challenge studies from the top British media sites over 13 months during the pandemic, found 76.5% of articles to be positive, 20% neutral, and only 3.5% negative.[16] This presents an opportunity to build public support and trust for future challenge studies in pandemic scenarios in the UK, through educational and media resources.

Ultimately, the world's first COVID-19 human challenge trial ran from spring to autumn in 2021, during which 36 healthy volunteers were exposed to a low dose of wild type severe acute respiratory syndrome coronavirus (SARS-CoV-2).[17] The results[18] were published on the 31st March 2022, and revealed the average incubation period for COVID-19 was 42 hours, a notably shorter duration than existing estimates, which put the average incubation period at 5-6 days. If such information were available in the early stages of a pandemic, would better inform policymakers when deciding to implement infection calming measures (e.g. lockdowns, stay-at-home requirements).

The results of Imperial's SARS-CoV-2 infection study provided valuable information about viral pathogenesis, which can be crucial for developing effective treatments and vaccines for viral infections. Employing the human challenge model to study COVID-19 provided unique perspectives we would not have been able to gain using other types of studies. Researchers were able to examine the initial stages after exposure to the virus, which cannot be observed in other forms of studies as participants are not typically identified until after symptoms emerge.

Unfortunately, the relatively late date at which COVID challenge studies were conducted has limited their utility for developing vaccines and other countermeasures. Earlier studies may have assisted in vaccine dose-finding and dose scheduling and provided clearer immunological data to guide later candidates. Had common cold betacoronavirus challenge trials been conducted pre-pandemic, they may have provided insight into the likelihood that initial COVID vaccines would be effective and on aerosol transmission of the virus.

The need for human challenge trials

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[13] CEPI (2022). *Delivering Pandemic Vaccines in 100 Days - What will it take?. CEPI.* Available at: https://cepi.net/wp-content/uploads/2022/11/CEPI-100-Days-Report-Digital-Version_29-11-22.pdf?swcfpc=1

[14] Business Standard (2022). *World Economy to Lose $12.5 Trn in Output by 2024 Due to Covid: IMF Chief. business-standard.com*. Available at: https://www.business-standard.com/article/international/world-economy-to-lose-12-5-trn-in-output-by-2024-due-to-covid-imf-chief-122012100063_1.html

[15] Barker C, Collet K, Gbesemete D, Piggin M, Watson D, Pristerà P, Lawerence W, Smith E, Bahrami-Hessari M, Johnson H, Baker K, Qavi A, McGrath C, Chiu C, Read RC, Ward H. Public attitudes to a human challenge study with SARS-CoV-2: a mixed-methods study. *Wellcome Open Res*. 2022 Feb 10;7:49. doi: 10.12688/wellcomeopenres.17516.1. PMID: 35321005; PMCID: PMC8921687.

[16] Eberts, J. and Hansell, D. (2022) *Covid-19 challenge trial media coverage in the UK was strongly positive*, *1Day Sooner*. Available at: https://www.1daysooner.org/1day-sooner-blog/uk-covid-19-challenge-trial-media-coverage-highly-positive (Accessed: 19 March 2023).

[17] O'Hare, R. (2022) Covid-19 human challenge study reveals detailed insights into infection. Imperial News. Imperial College London. Available at: https://www.imperial.ac.uk/news/233514/covid-19-human-challenge-study-reveals-detailed/

[18] Killingley, B., Mann, A.J., Kalinova, M. et al. (2022) Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. *Nat Med* 28, 1031–104. https://doi.org/10.1038/s41591-022-01780-9

The useful insights obtained from human challenge trials pertaining to pathogens of pandemic potential (PPPs) can substantially support and accelerate the development of vaccines and therapeutics, and can guide policy-making decisions.

Evidence suggests we will see a rise in the occurrence of pandemics in the coming decades.[19] It is, therefore, crucial we prime ourselves for the next outbreak by using challenge studies to prepare prototype countermeasures against PPPs and committing to a plan to employ and optimise the use of challenge trials (when ethically appropriate) after a pandemic occurs.

How human challenge trials can help prepare for future pandemics

We applaud the government's support of the 100 Day Mission[20] and its ambitious aim to develop an armoury of diagnostics, therapeutics, and vaccines within the first 100 days of a future pandemic threat detection. We are also pleased to hear about the progress being made in developing prototype vaccines candidates against viral families with pandemic potential.

As argued by CEPI and the G7, the first 100 days of a pandemic are crucial to changing its course.[21] Human challenge trials can provide a valuable role in supporting this mission to minimise the impact of future pandemics by accelerating the vaccine development process.

Use challenge studies to test prototype countermeasures against viral families with pandemic potential

The 100 Day Mission requires human testing of prototype countermeasures before a pandemic occurs to establish their safety and (for vaccines) immunogenicity so that they can be rapidly deployed. Conducting challenge studies is important for this goal because it will usually be the only way to determine human efficacy of a prototype countermeasure in advance of a pandemic. Moreover, challenge studies can help determine whether the immune response generated is likely to correlate with protection because of the controlled nature of the challenge experiment and intensive data collection it facilitates.

How to optimise human challenge trials to accelerate our pandemic response

Responding promptly and efficiently to emerging pandemics requires clear guidelines in place on when it would be appropriate to run human challenge trials and how - including clear ethical framework for the approval process, preparation to collect and produce challenge strains rapidly and safely during a pandemic, model protocols agreed to in advance, dedicated facilities in which to conduct challenge studies, and a clear regulatory path for how pre- and post-pandemic clinical trial evidence (including challenge studies) will be used to authorise the vaccines and therapeutics that are developed.

Before a pandemic occurs, authorities and institutions could create standardised guidelines for challenge trials, which would be open to public scrutiny. These guidelines might address expected responses to variables such as pathogen fatality rates, as well as other considerations, including the provision of medical support for trial volunteers. Additionally, by executing multiple stages concurrently and shortening the testing timeline, a significant amount of time can be saved. Conducting trials that simultaneously involve vaccinated individuals, previously infected persons, and uninfected volunteers enables a prompt evaluation of vaccine performance and the potential for reinfection. For an effective response, it is essential to rapidly produce pathogen strains for use in human challenge trials. This process requires close coordination among trial designers, regulators, and funding sources. Modifying and parallelising the Good Manufacturing Practice (GMP) production and Quality Assurance (QA) processes can further accelerate these efforts. To validate the efficiency of accelerated GMP manufacturing processes, it is advisable to test these methods in advance on diseases such as influenza, which can serve as a valuable model for future pandemics.

Develop the necessary guidelines for when and how to effectively use human challenge trials in the event of a pandemic

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[19] Carlson, C. J. Albery, G.J., Merow, C., Trisos, C. H., Zipfel, C. M., Esker, E. A., Olival, K. J., Ross, N., Bansal, S. (2022) 'Climate change increases cross-species viral transmission risk', *Nature*. doi: 10.1038/S41586-022-04788-W.

[20] The G7 (2021, June 12) *100 Days Mission (to respond to future pandemic threats), gov.uk*. Available at: https://www.gov.uk/government/publications/100-days-mission-to-respond-to-future-pandemic-threats

[21] CEPI (2021, April) *'The Urgency of Now' Investment Case, CEPI*. Available at: https://cepi.net/wp-content/uploads/2021/03/CEPI_3.5_billion_investment_case_10032021.pdf

In the absence of these preparations, there is a possibility of unnecessary delays in conducting these trials, which could lead to the underutilisation of their benefits. In the case of the COVID-19 pandemic, despite challenge discussions beginning in March 2020, viral production did not begin until late summer,[22] and Imperial's COVID-19 challenge study was not subject to ethical approval until after viral production was complete. Ethics approval then took multiple months after submission.

To fully harness the valuable information human challenge trials can offer, it is crucial that we establish the required infrastructure and framework to implement human challenge trials quickly and effectively in future pandemics.

- **Create the necessary ethical framework to prepare for pandemics**

Ethical uncertainty can lead to delays that can severely limit the utility of human challenge studies in a pandemic. In order to help clarify these ethics, 1Day Sooner commissioned the UK Pandemic Ethics Accelerator[23] to write a report entitled, "*The ethics of controlled human infection model studies for mitigating pandemic risks*".[24] The full report and summary of its recommendations can be found in **Annex A**. The list of stakeholders who contributed to the report can be found in **Annex B**.

The report proposes a possible model for determining when human challenge trials should be conducted in a pandemic setting and provides an example of how to determine when population benefit is proportional to participant risk. The authors argue that if the participant's expected harm is low, and the population's expected benefits are high, it is ethically required that we conduct human challenge trials.

Table 1: Comparing expected population benefit to expected participant risk

	High participant expected harm	Moderate participant expected harm	Low participant expected harm
Very high expected benefit			
High expected benefit			
Moderate expected benefit			

Dark green: ethically required; Light green: permissible; Orange: maybe permissible; Red: impermissible

The report concludes with three main recommendations:[25]

1. Establish a clear public mechanism for determining when a CHIM study with a PPP is in the public interest
2. Establish procedures to streamline ethics review of CHIM studies with PPPs
3. Develop and maintain the infrastructure and expertise required to conduct high quality CHIM studies efficiently

We believe the government should further the UK's ability to respond quickly and effectively to emerging pandemics by committing to synthesise the recommendations of this UK Pandemic Ethics Accelerator's report.

- **Set a clear regulatory path for how to authorise prototype vaccines during a pandemic**

In an outbreak, every day counts. Setting a clear regulatory path in advance for how to authorise vaccines during a pandemic, will encourage more stakeholders to use this accelerated vaccine development process and save valuable time when a pandemic does emerge. This could be achieved by publishing guidance documents for developers of prototype vaccines, which clearly set out the MHRA's expectations for what these products must achieve in order to receive authorization (including the use of challenge trials). Additionally, collaboration between international regulatory bodies and organisations to align regulatory requirements and share information can help expedite the global distribution of approved prototype vaccines.

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[22] BSL-3 facilities in which to isolate and produce the virus were scarce, as were testing facilities.

[23] UK Pandemic Ethics Accelerator by the Oxford Uehiro Centre for Practical Ethics, funded by the UKRI. Bringing UK ethics research expertise to bear on the multiple, ongoing ethical challenges arising during pandemics. They provide rapid evidence, guidance and critical analysis to decision-makers across science, medicine, government and public health. For more information see: https://ukpandemicethics.org/about/

[24] Williams, B., Morrison, J., Wilkinson, D., Savulescu, J. (2023) *The ethics of controlled human infection model studies for mitigating pandemic risks*, 1Day Sooner. Available at: https://www.1daysooner.org/uk-pandemic-ethics-accelerator

[25] A summary of the report's recommendations and a breakdown of their sub-recommendations can be found here.

Conclusion

Human challenge trials are a vital component of pandemic preparedness, expediting vaccine development and offering critical insights into immunity and emerging variants. The COVID-19 pandemic emphasised the need for such trials, as such it is crucial to optimise their use and incorporate them into future response strategies.

The government's support for the 100 Day Mission and efforts to develop prototype vaccines are commendable. To maximise the benefits of human challenge trials, it is crucial to establish clear guidelines, ethical frameworks, infrastructure, and regulatory pathways. By implementing these measures, the UK can be better prepared to respond quickly and effectively to future pandemics, ultimately minimising their impact on global health and economies.

Our nation has long maintained an exceptional reputation in medical research, boasting a well-funded research infrastructure, a talented workforce, and world leading research institutions and laboratories. This strong foundation creates an ideal environment for the country to employ human challenge trials, further solidifying its position as a global leader in vaccine development and pandemic preparedness.

We, once again, appreciate the opportunity to respond to the Committee's Call for Evidence on Emerging diseases and learnings from COVID-19. By preparing for and optimising human challenge trials for future pandemics, we believe the UK government can enhance their pandemic preparedness and response initiatives, and continue to champion the development of pandemic ending vaccines and therapeutics.

Appendices

Appendix A

Calls from the Scientific Community to conduct Human Challenge Trials

Deming, M. E., Michael, N. L., Robb, M., Cohen, M. S., & Neuzil, K. M. (2020). Accelerating Development of SARS-CoV-2 Vaccines - The Role for Controlled Human Infection Models. *The New England journal of medicine*, *383*(10), e63. https://doi.org/10.1056/NEJMp2020076

Eyal, N., Lipsitch, M. and Smith, P. G. (2020) 'Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure', *The Journal of infectious diseases*, 221(11), pp. 1752–1756. Available at: https://academic.oup.com/jid/article/221/11/1752/5814216

Plotkin, S. A., & Caplan, A. (2020). Extraordinary diseases require extraordinary solutions. *Vaccine*, *38*(24), 3987–3988. https://doi.org/10.1016/j.vaccine.2020.04.039

Appendix B

Calls from the General Public to conduct Human Challenge Trials

Barker, C., Collet, K., Gbesemete, D., Piggin, M., Watson, D., Pristerà, P., Lawerence, W., Smith, E., Bahrami-Hessari, M., Johnson, H., Baker, K., Qavi, A., McGrath, C., Chiu, C., Read, R. C., Ward, H. (2022). Public attitudes to a human challenge study with SARS-CoV-2: a mixed-methods study. *Wellcome Open Res*. 2022 Feb 10;7:49. doi: 10.12688/wellcomeopenres.17516.1. PMID: 35321005; PMCID: PMC8921687.

Eberts, J. and Hansell, D. (2022) *Covid-19 challenge trial media coverage in the UK was strongly positive*, *1Day Sooner*. Available at: https://www.1daysooner.org/1day-sooner-blog/uk-covid-19-challenge-trial-media-coverage-highly-positive (Accessed: 19 March 2023).

Annexures

Annex A

"The ethics of controlled human infection model studies for mitigating pandemic risks" - by Bridget Willams, Josh Morrison, Dominic Wilkinson, and Julian Savulescu

This report was commissioned by 1Day Sooner and developed in conjunction with the Oxford Uehiro Centre for Practical Ethics as part of the UK Pandemic Ethics Accelerator. Both documents have been published and are available from: https://www.1daysooner.org/uk-pandemic-ethics-accelerator and https://ukpandemicethics.org/library/

The full report is available at: https://ukpandemicethics.org/wp-content/uploads/2023/03/The-ethics-of-controlled-human-infection-model-studies-for-mitigating-pandemic-risks-Report.pdf

A summary of the reports recommendations is available at: https://ukpandemicethics.org/wp-content/uploads/2023/03/The-ethics-of-controlled-human-infection-model-studies-for-mitigating-pandemic-risks-Summary-of-Recommendations.pdf

Annex B

List of UK stakeholders consulted on the report

- **Andrew Pollard**, Director of Oxford Vaccine Group; Professor of Paediatric infection and immunity, University of Oxford
- **Adrian Hill**, Professor of Vaccinology; Director Jenner Institute; Co-Director Oxford Martin Programme on Vaccines, University of Oxford
- **Cristina Cassetti**, Program Officer, US National Institutes of Health
- **Emma Smith**, HIC-VAC Network Manager, Imperial College London
- **Garth Rapeport**, Visiting Professor, National Heart and Lung Institute, Imperial College London
- **Helen McShane**, Professor of Vaccinology; Director of Oxford NIHR Biomedical Research Centre, University of Oxford
- **In-Kyu Yoon**, Acting Director of Programmes, CEPI
- **Jakob Cramer**, Head of Clinical Development, CEPI
- **Jonas Sandbrink**, Researcher, Future of Humanity Institute
- **Jonathan Montgomery**, Professor of Health Care Law, University College London
- **Matthew Memoli**, Director Laboratory of Infectious Diseases Clinical Studies Unit, US National Institutes of Health
- **Peter Openshaw**, Professor of Experimental Medicine, University College London
- **A UK government political staffer involved with decision-making around CHIM studies in the UK**

(March 2023)