Executive Summary

Controlled human infection model (CHIM) studies involve intentionally exposing human subjects to known pathogens under controlled conditions. Within a few months of the onset of the COVID-19 pandemic, there were calls from ethicists and epidemiologists to conduct CHIM studies using SARS-CoV-2 to accelerate vaccine development. There was substantial support for SARS-CoV-2 CHIM studies amongst the public in the United Kingdom (UK) and media coverage was largely positive. Such studies were ultimately conducted, but they began more than a year after the WHO’s declaration of the COVID-19 pandemic.

This has highlighted the need for clarity around the ethics of conducting CHIM studies for novel pathogens and pathogens with pandemic potential (PPPs). A central value of CHIM studies is their ability to rapidly generate and evaluate foundational information about a pathogen and to inform development of potential medical countermeasures. As the risk of pandemics is likely to increase with changes in climate and land-use patterns, the possible role of CHIM studies in pandemic risk mitigation should be explored.

This report provides guidance on when it may be appropriate to conduct CHIM studies and the requirements for their ethical conduct. This includes guidance on conducting CHIM studies prior to an outbreak and at the beginning of an outbreak with a known PPP or novel pathogen that may have pandemic potential. The report has been developed for the context of the UK. It aims to inform UK policymakers, researchers, regulators, and members of research ethics committees.

This primary goal of this report is to reduce uncertainty around ethical decisions concerning pandemic challenge studies. It aims to help establish a determinate decision-procedure for when to conduct and not conduct CHIMs before and during pandemics. This seeks to guide action and set expectations on which policymakers and stakeholders can rely when preparing for a pandemic and conducting emergency response.

This report is informed by three linked activities: literature review, stakeholder consultation and ethical analysis. Stakeholder consultation consisted of a series of interviews with vaccinologists, infectious diseases doctors and researchers, clinical trialists, and other people involved in research decision-making in the UK. Ethical analysis was conducted iteratively by the writing team, with input also sought from a wider group of ethical and technical experts with relevant expertise.

Drawing on existing ethical analysis of CHIM studies, we have developed a framework to guide decision-making about CHIM studies with PPPs. This framework consists of two key questions:

1. Is the proposed study in the public interest?
2. Does the proposed study satisfy other ethical requirements?

There are three sub-questions to determine if the study is in the public interest:

- Is there a valid scientific rationale?
- Do expected benefits justify expected harms
- Is this the best method to achieve benefits?

There is then a procedural requirement that an external review must agree with the assessment that the study is in the public interest.

There are five sub-questions to determine if the study satisfies other ethical requirements:

- Is there a fair and comprehensive system of compensation?
- Is there a process to ensure voluntary and sufficiently informed consent?
- Is the recruitment process fair and protect the interests of vulnerable groups
- Are the interests of the local community around the study site protected?
- Is there a comprehensive plan for communication with stakeholders?

When expected population benefit justifies expected participant risk is likely to be a contentious question. We suggest that an approach to answering this question should be developed ahead of time. This approach should be informed by ethicists, scientists, policymakers and the general public of the UK. We provide an example of one possible approach to answering this question, which stratifies the expected harms to participants as low-, medium- or high-risk. In our example approach, the requirements for benefit rise non-linearly for higher-risk research to ensure that the greater degree of personal risk that participants take on is respected. However, this is provided as a model to stimulate discussion for what an optimal approach would look like.
The report concludes with three major recommendations, for each of which there are several sub-recommendations.

The major recommendations are:

1. Establish a clear 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

A summary of the sub-recommendation is provided on the following page.
SUMMARY OF RECOMMENDATIONS

RECOMMENDATION 1 - ESTABLISH A CLEAR MECHANISM FOR DETERMINING WHEN A CHIM STUDY WITH A PPP IS IN THE PUBLIC INTEREST

1.1 Establish a process to determine when expected benefits ethically justify expected harms
1.2 Develop models to quantify benefits and risks of CHIM studies with PPPs
1.3 Identify example scenarios where CHIM research would be appropriate (and not appropriate) in an outbreak setting
1.4 Develop processes to understand and monitor public sentiment to CHIM research
1.5 Develop educational materials for policymakers and the public, including resources for the media
1.6 Establish a group who would be charged with making the determination of when a CHIM study during a public health emergency would be justified

RECOMMENDATION 2 - ESTABLISH PROCEDURES TO STREAMLINE ETHICS REVIEW OF CHIM STUDIES WITH PPPS

2.1 Maintain a standing Specialist REC for CHIM research in an outbreak
2.2 Adapt the HRA REC checklist to develop a special checklist for CHIM research with PPPs
2.3 Create template protocols for CHIM studies with PPPs
2.4 Develop informed consent procedures for CHIM research
2.5 Review the approach to compensation for high-risk research in the UK
2.6 Create a template communications plan for CHIM research in an outbreak

RECOMMENDATION 3 - DEVELOP AND MAINTAIN THE INFRASTRUCTURE AND EXPERTISE REQUIRED TO CONDUCT HIGH QUALITY CHIM STUDIES EFFICIENTLY

3.1 Produce a report on the expertise and facilities available to conduct CHIM research in the UK and globally
3.2 Conduct a roundtable discussion to discuss the role of CHIM research in development of medical countermeasures against PPPs
3.3 Review the procedures for manufacturing challenge agent and identify options for accelerating this process in an outbreak
3.4 Investigate the potential for conducting person-person transmission studies
3.5 Develop a roadmap to ensuring CHIM research capacity for pandemic preparedness

CHIM = CONTROLLED HUMAN INFECTION MODEL    PPP = PATHOGEN WITH PANDEMIC POTENTIAL    REC = RESEARCH ETHICS COMMITTEE
1. Introduction

Controlled human infection model (CHIM) studies involve exposing human participants to known pathogens under controlled conditions. These studies have been performed using a wide variety of pathogens and have provided data on efficacy of new vaccines, correlates of immune protection and the immune response to pathogen exposure (Adams-Phipps et al., 2022). They enable evaluation of medical countermeasures against diseases during periods where there is little or no incidence, and in settings where non-human animal models are a poor proxy for human immune responses.

A few months into the COVID-19 pandemic, there were calls to conduct CHIM studies using SARS-CoV-2, for the purposes of accelerating vaccine development and roll-out and gain information to guide policy choices (Eyal, Lipsitch and Smith, 2020). Although this resulted in substantial debate in the academic bioethics literature and social media, the proposal for a SARS-CoV-2 CHIM study had significant support from the public in the United Kingdom (UK). A survey of over 2,400 adults conducted in October 2020 found that 69% agreed with a study taking place (Barker et al., 2022). A review of the digital media articles covering COVID-19 CHIM studies, published in the top British media sites over 13 months of the pandemic, found 76.5% to be positive, 20% neutral, and only 3.5% negative (Eberts and Hansell, 2022). Articles focused substantially more on the scientific benefits of CHIM studies and the perspectives of volunteers than concerns about ethics or scientific utility. The World Health Organization produced guidelines for the ethical conduct of SARS-CoV-2 CHIM studies in May 2020 (World Health Organization, 2021).

A SARS-CoV-2 CHIM study was ultimately conducted in the UK beginning in April 2021 (Rapeport et al., 2021; Killingley et al., 2022). The participants in this study had not previously been exposed to SARS-CoV-2. A second study was commenced in May 2021 in participants who had previously been infected with, or vaccinated against, SARS-CoV-2 (University of Oxford, 2021).

Although this work has produced useful knowledge on viral infectivity and immune response, results only became available after vaccine roll-out had started in many countries limiting its value to medical product developers and policymakers. Although several factors contributed to this delay, including technical and regulatory complexity, it’s likely that ethical uncertainty and controversy were among them. This has highlighted the need for clarity around the ethics of conducting CHIM studies for novel pathogens and pathogens with pandemic potential.

Providing clarity around the ethics of conducting such CHIM studies is particularly important as evidence suggests that pandemics will become increasingly common in the coming decades (Carlson et al., 2022). As such, it is important to identify under what circumstances it is appropriate to conduct CHIM studies within an outbreak that has the potential to become a pandemic to ensure that this scientific model is deployed appropriately.

2. Purpose of the report

This report provides guidance on when it is appropriate to conduct CHIM studies with PPPs and the requirements for ethical conduct. This includes guidance on conducting CHIM studies with known PPPs prior to an outbreak and at the beginning of an outbreak with a known PPP or novel pathogen that may have pandemic potential.

The report has been developed for the context of the UK. It is aimed to inform UK policymakers, researchers, regulators and members of ethics review committees. Specifically, the report aims to:

- Provide ethical guidance that evaluates and makes recommendations concerning:
  - Pathogens with pandemic potential for use in challenge models pre-pandemic; and
  - Relevant features that would determine when to deploy challenge models in a pandemic (or upon detection of an outbreak of a novel pathogen)
- Create confidence and specificity as to likelihood of ethical approval on which policymakers can rely when planning a pandemic response.
- Generate recommendations based on this analysis for governments as to policies to announce pre-pandemic.

Although this report focuses on CHIM research in the UK, much of the analysis will be applicable to other settings. However, CHIM research in other settings may face complications that are not addressed in this report. For example, the existence of the UK’s National Health Service means that the question of how to ensure that a participant experiences a delayed or long-term adverse health event as a result of the study will be less complicated than it would be in a setting without universal health care.

This report complements existing ethical guidance on CHIM studies by providing a series of clear questions that need to be answered when evaluating CHIM studies and provides guidance on who should answer these questions. It also provides detailed discussion of each question and the factors to consider when answering it.
Importantly, we identify that the question of whether the expected benefits of a study justify the level of risk to voluntary participants. We describe a possible approach to answering this question, but suggest that an agreed upon answer should be determined with input from analytic ethicists, virologists, clinical trials specialists, epidemiologists, and the members of the public.

3. Methodology

This report is informed by three linked activities: literature review, stakeholder consultation and ethical analysis. A critical interpretative literature review was conducted to identify relevant ethical considerations for CHIM studies with PPPs. The search strategy is provided in Appendix A.

Stakeholder consultation consisted of a series of interviews with vaccinologists, infectious diseases doctors and researchers, clinical trialists, a policymaker and a previous chair of the UK's Health Research Authority. A list of interviewees and a list of the questions covered in interviews are provided in Appendix B. Where participants preferred to participate pseudonymously we have noted their role in broad terms to protect anonymity. Research ethics approval was received from the Oxford University Social Sciences and Humanities Interdivisional Research Ethics Committee (Reference: R81200/RE001).

Ethical analysis was conducted iteratively by the writing team, with input sought from a wider group of ethical and technical experts with expertise in the ethics of CHIM studies.

4. Background

4.1 Pathogens with Pandemic Potential

A key motivator of this study is that there are a wide range of viruses already known to science that could cause another COVID-like pandemic or worse, and conditions for these to transfer into humans are increasing.

The classical definition of a pandemic is “an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people” (Porta, 2008). However, the term is generally reserved for epidemics of severe disease that pose significant risks to individuals. The US Department of Health and Human Services, defines pathogens with pandemic potential as those that are highly transmissible and highly virulent (Office of the Assistant Secretary for Preparedness, 2017). Although not referred to as ‘pathogens with pandemic potential’, the UK Vaccine Network has a list of priority pathogens of epidemic potential, which are prioritised for funding in emerging disease vaccine research (Noad et al., 2019). They are as follows:

- Middle East Respiratory Syndrome (MERS)
- Lassa fever
- Crimean Congo Haemorrhagic fever
- Nipah
- Zika
- Ebola
- Rift Valley Fever
- Chikungunya
- Dengue
- Hantavirus
- Plague
- Marburg
- Q Fever
- Disease X

Similar lists have been developed by the WHO (World Health Organization, no date) and the Coalition for Epidemic Preparedness (CEPI) (CEPI, no date). The US The National Institute of Allergy and Infectious Disease has developed a list of pathogens of high pandemic and epidemic potential (National Institutes of Allergy and Infectious Diseases, 2018). These lists are provided in Appendix C.

Disease X refers to a novel disease that is as yet unknown. There is evidence that climate change and increased human interactions with wild animal populations will increase the risk of zoonotic spillover of disease, increasing the risk of novel pathogens arising with pandemic potential (Carlson et al., 2022). Preparing for a novel PPP has been a focus of pandemic prevention research in recent years, with the emergence of COVID-19 demonstrating the importance of planning for the unknown. Adalja et al. suggest that efforts to mitigate the risk of Disease X could be improved by considering which characteristics increase a pathogen's pandemic potential (Adalja et al., 2019). They suggest the following characteristics are associated with high pandemic risk:

- Respiratory transmission
- Pre-symptomatic or early-in-illness transmission
- Immunologically naive population
- RNA virus

They suggest that a pathogen spread by the respiratory route is much more likely to cause a pandemic than pathogens spread by other routes (faecal-oral, blood-borne, contact with other body fluids, and vector-borne). However, they note that due to the wide geographic range of the anopheles and aedes mosquitoes, pathogens spread through this vector have higher pandemic potential. They suggest that viruses are the most likely pathogen-type to lead to pandemics due to their rapid replication and the lack of broad-spectrum antivirals, and list the following as
viral groups that merit close attention; orthomyxoviruses, paramyxoviruses, pneumoviruses, coronaviruses, picornaviruses (Adalja et al., 2019).

The study of prototype pathogens from viral groups and development of vaccines for these prototype pathogens has been proposed by several groups (Graham and Corbett, 2020; National Institute of Allergy and Infectious Diseases, 2021; CEPI, no date; Saville et al., 2022). Pre-existing research on the MERS and SARS viruses has been credited with improving the speed with which at least one of the SARS-CoV-2 vaccine was developed (Corbett et al., 2020).

This report considers the ethics of CHIM research with known PPPs, current pandemic pathogens (e.g. SARS-CoV-2), novel pathogens that may have pandemic potential, attenuated PPPs, and prototype pathogens from viral families where some other viruses in the family are PPPs.

4.2 Controlled human infection model studies

CHIM studies have contributed to scientific understanding of pathogen kinetics, epidemiology and immune response, and have contributed to the development of modern vaccinology (Jamrozik and Selgelid, 2021). Although non-human animal models are often used to understand infectious diseases and evaluate countermeasures, there are imperfect proxies for the human immune system (Louz et al., 2013). CHIM studies can also be helpful when it is difficult to conduct large field trials. For example, in 2017 a vaccine against cholera was approved on the basis of the results of CHIM studies (Mosley et al., 2017).

CHIM studies have been conducted with a range of pathogenic agents, including bacteria, viruses, parasites and bacterial toxins (Jamrozik and Selgelid, 2021; Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022). Malaria, respiratory syncytial virus (RSV) and influenza have been the most common pathogens studied with a CHIM (Adams-Phipps et al., 2022).

CHIM research has been important in the development of therapeutic agents and vaccines for these and other infectious diseases, including influenza (Memoli et al., 2016), malaria (Cooper et al., 2019), dengue (National Institutes of Health, 2018) and shigella (Raqib and Venkatesan, 2021). One vaccine, against cholera, has received regulatory approval on the basis of CHIM studies (Shirley and McArthur, 2011).

There have been very few serious adverse events in CHIM studies conducted in modern times. A systematic review assessing the rate of adverse events in CHIM studies from 1980 found that 0.2% of participants experienced a serious adverse event (events that result in death, hospitalization, permanent injury, disability or are life-threatening) (Adams-Phipps et al., 2022). In the subset of studies that reported on the severity of adverse events, 5.6-15.8% of participants reported a severe adverse event (not requiring hospitalization). However, these studies were conducted with pathogens that had a very low risk of serious harm, or where a reliable rescue therapy was available.

4.3 Ethical issues in CHIM studies

Although modern CHIM studies have been conducted with the approval of human research ethics review boards, the history of CHIM studies involves several incidents of highly controversial and unethical research (Jamrozik and Selgelid, 2021). Edward Jenner’s inoculation of James Phipps with cowpox in the late 18th century would likely be considered highly unethical today. The 20th century saw several incidents of CHIM studies performed in vulnerable populations and without consent. These included experiments involving US researchers deliberately infecting Guatemalans, with low levels of education and low income, with sexually transmitted diseases in the late 1940’s and the infection of children with intellectual disability with hepatitis virus at Willowbrook State school in the US from the 1950’s to 1970’s (Krugman, 1986; Frieden and Collins, 2010). During the Second World War, Germany and Japan deliberately infected prisoners with a wide range of pathogens including cholera, malaria and tuberculosis, often causing extreme suffering and death (Eckart and Vondra, 2000; Tsuchiya, 2008).

These studies are highly unethical. But there is general agreement in the academic literature that this isn’t due to deliberate infection per se, but other aspects of the study, including the lack of informed consent, the questionable scientific validity, the exploitation of vulnerable populations, and the cruel treatment of the victims (Miller and Grady, 2001; Shah et al., 2017; Jamrozik and Selgelid, 2021).

These incidents contributed to the development of research ethics as a field and the development of guidelines for ethical research. The Nuremberg Code was created in 1947 during the Nuremberg Trials. Amongst other principles, the code highlights the need for voluntary consent for research subjects, minimization of risk and for risks to be proportional to expected benefits of research (Shuster, 1997). The Declaration of Helsinki was developed by the World Medical Association in 1964 and provides a statement of ethical principles, primarily aimed at physicians involved in medical research, stressing the importance of protecting the rights of individual research subjects and the ultimate responsibility of physicians for the safety of research participants (World Medical Association, 2013). These documents have influenced other reports including the Belmont Report (The National Commission for the Protection of Human Subjects of Biomedical Research, 1979), which led to the development
of Institutional Review Boards in the US, as well as the International Ethical Guidelines for Biomedical Research Involving Human Subjects produced by the Council for International Organizations of Medical Sciences (CIOMS) (Council for International Organizations of Medical Sciences, 2016) and the UK Research and Innovation Principles for Ethical Research (Economics and Social Research Council, 2021).

4.3.1 Frameworks for ensuring ethical challenge studies

In 2001, Miller and Grady published a systematic analysis of ethical issues CHIM studies (Miller and Grady, 2001). They suggested that CHIM studies ought not to be thought of as fundamentally different to other research with respect to ethics. Many types of research expose subjects to harms and risks for the purpose of gaining generalizable knowledge, rather than for their own benefit. From their analysis, Miller and Grady developed a set of guidelines for conducting CHIM studies. This was later built upon by Bambery et al. in 2016 (Bambery et al., 2016), and a report by the US National Institutes of Health on the ethics of conducting Zika challenge trials in 2017 (Shah et al., 2017).

In 2018 the Academy of Medical Sciences, the Wellcome Trust, the Medical Research Council and the Human Infection Challenge Vaccine Network (HIC-Vac) convened a meeting to discuss CHIM studies in the UK and review a 2005 report on the scientific, safety, ethical, legal and societal issues raised by CHIM studies (Academy of Medical Sciences, 2018). The report outlines factors that should be considered in ethical evaluation and calls for development of an ethical framework for evaluating CHIM studies.

In 2021 the WHO produced a report on the ethics of CHIM studies (World Health Organization, 2021). This covered CHIM studies broadly but included specific guidelines for conducting COVID-19 CHIM studies. These guidelines were used by the Specialist REC that reviewed the SARS-CoV-2 CHIM studies.

The key considerations listed in each of these frameworks is shown in Table 1.
Although it is generally accepted that CHIM studies can be ethically acceptable, some of the requirements for their ethical conduct have been contentious. There is widespread agreement that CHIM studies require voluntary informed consent of subjects, risk minimization and that they should avoid burdening vulnerable communities. Two questions that have been more contentious are what level of risk to participants is acceptable and whether participants ought to receive payment for the medical risk of CHIM studies.

The CIOMS guidance does not put an explicit limit on risk, instead suggesting that the risks of research must be justified by the expected benefits (Council for International Organizations of Medical Sciences, 2016). However, commentary accompanying the guidance suggests that studies involving very high mortality risk (such as infection with anthrax or Ebola virus) would not be acceptable. This is similar to the position of Bambery et al. who suggest that CHIM studies that pose a risk of incurable or fatal infection ought not to be acceptable (Bambery et al., 2016). This approach of limiting risk in CHIM studies has been criticized for being too vague, with some ethicists arguing that there shouldn't be any strict limit on risk, but rather the risks should be justified by the benefits (Shaw, 2014; Binik, 2020; Eyal, 2020). Another approach is to compare the risks of CHIM studies to other risks that people voluntarily accept for altruistic purposes, including volunteering as a firefighter or donating an organ (London, 2006; Miller and Joffe, 2009; Shah et al., 2017; Jayaram, Sparks and Callies, 2022).

Some have argued that payment for participation in CHIM research is coercive, may result in vulnerable populations being used in research, and may lead to participants being mistreated by researchers (Jamrozik and Selgelid, 2020). However, others have argued that payment is a useful way to incentivize participation in research, and that failure to provide sufficient payment is unfair to participants (Anomaly and Savulescu, 2019; Grimwade et al., 2020). One review of the ethics of payment in SARS-CoV-2 challenge studies suggested that it is appropriate to pay participants for reimbursement, compensation and as an incentive for participation, but that this should be accompanied by efforts to minimize undue influence, ensure public trust and fairness in recruitment (Fernandez Lynch and Largent, 2020). The existing literature, and particularly the ethical frameworks summarized in Table 1, provide useful guidance on the ethical evaluation of challenge studies. However, there is value in developing explicit guidance.

### Table 1: Existing ethical frameworks for CHIM research and the factors they identify as important for ethical evaluation

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<td>● Scientific rationale</td>
<td>● Reasonable, minimized risks, justified by social value</td>
<td>● Rationale</td>
<td>● Scientific justification</td>
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<tr>
<td>● Risks</td>
<td>● Absence of alternative</td>
<td>● Protection of vulnerable populations</td>
<td>● Risks and discomforts</td>
<td>● Assessment of risks and potential benefits</td>
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<td>● Discomforts</td>
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<td>● Vulnerable subjects</td>
<td>● Benefits and harms</td>
<td>● Compensation</td>
<td>● Financial compensation and compensation for harm</td>
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<td>● Informed consent</td>
<td>● Selection of study participants</td>
<td>● Compensation for injury</td>
<td>● Right to withdraw</td>
<td>● Site selection</td>
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<td>● Financial compensation</td>
<td>● Independent review</td>
<td>● Community engagement</td>
<td>● Independent review and publicly available rationale</td>
<td>● Participant selection</td>
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<td>● Right to withdraw from research</td>
<td>● Publicly available rationale</td>
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<td>● Knowledge and data sharing</td>
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<td>● Protection of public</td>
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on the circumstances when CHIM studies using PPPs, or during an outbreak of a novel pathogen, are acceptable.

4.4 CHIM studies with pathogens with pandemic potential

Most of the diseases that have been studied using a CHIM are endemic diseases that are usually associated with low risk of severe illness and/or have a therapy that can reduce the risk of severe illness, i.e., a “rescue therapy” (Adams-Phipps et al., 2022). Given this low risk of severe illness, these would not generally fit the general definition of a PPP. Although the existence of a rescue therapy wouldn’t necessarily prevent the epidemic being considered a pandemic as there may be insufficient stockpiles of the therapy or insufficient health system capacity.

Although the Zika outbreak was not considered a pandemic, it seems possible that Zika virus could result in a pandemic and can be considered a PPP. To decide whether to continue with a proposed Zika virus CHIM study in 2016, the potential funders, NIAID and the Walter Reed Institute, arranged for a review of the ethics of the decision (Shah et al., 2017; Palacios and Shah, 2019). The report concluded that it would not be ethically appropriate to conduct a CHIM study for two main reasons; firstly the duration of viral transmissibility was uncertain, and as a result, the report writers thought that it would be difficult to avoid risks to third parties who had not agreed to participate in the trial, and secondly, the incidence of the disease was high at that time, which created opportunities for conducting field trials, which was thought to reduce the need for the study (Shah et al., 2017). Several years later, after the outbreak had diminished several vaccine candidates have become available but there is now not possible to conduct field trials due to the low incidence of the disease. A WHO-NIAID meeting of experts suggested that CHIM studies would be appropriate to conduct given the lack of alternatives, and the increased knowledge around transmission that would allow risks to bystanders to be reduced (Vannice et al., 2019).

The experience highlighted some of the particular considerations for conducting CHIM studies of PPPs. The authors of the Zika report suggest that there are two considerations that may limit the appropriateness of conducting CHIM studies for emerging diseases during an outbreak; the potentially high and uncertain risks of novel diseases and the crowded field of research opportunities, which may impact the social value of a CHIM study (Shah et al., 2017).

The COVID-19 pandemic demonstrated these two elements. Firstly, there was significant concern about the level of risk that infection with SARS-CoV-2 would entail, especially in the absence of a rescue therapy (Dawson, Earl and Livezey, 2020; Kahn et al., 2020; Spinola et al., 2020).

Evidence from relatively early in the pandemic suggested that the mortality risk for young people was low (0.03%), and much lower than the risk for older people (Verity et al., 2020). However, even though the risk was low, it was higher than the mortality risk for other diseases that had been studied with a CHIM (Adams-Phipps et al., 2022).

Uncertainty was another prominent feature in discussion of COVID-19. Many argued that the risks of the disease, particularly the longer-term consequences were too uncertain for participants to make an informed decision about their participation (Dawson, Earl and Livezey, 2020; Kahn et al., 2020; Spinola et al., 2020). In response, proponents of a COVID-19 CHIM study argued that participants could incorporate this uncertainty into their decision-making, and to that assume that they couldn’t, would be paternalistic (Chappell and Singer, 2020; Eyal, Lipsitch and Smith, 2020; Steel, Buchak and Eyal, 2020).

In the consideration of a Zika trial, risks to third parties, who hadn’t consented to participation, were a major source of concern. This was largely due to the uncertainty in the duration and potential modes of transmissibility of infection, and the potential to cause significant birth defects. In COVID-19, it was clear that participants in a CHIM study would need to be effectively isolated during the course of their infection. There was concern about transmission into the local community, but the additional risk a CHIM study would pose would be low given that SARS-CoV-2 was circulating widely in the locations proposed as study sites (Lee and Eyal, 2021), although the risk would be higher if there was use of a variant that was no longer circulating in the community.

The need for a CHIM study was also challenged by the large number of populations experiencing epidemics, which provided many locations to conduct field trials. One of the key rationales for a COVID-19 CHIM study was to accelerate vaccine development (Deming et al., 2020; Eyal, Lipsitch and Smith, 2020; Baay and Neels, 2021; Eyal and Lipsitch, 2021). Ultimately field trials were conducted and vaccine roll-out had begun before a COVID-19 CHIM was started. However, some of these trials experienced disruption when transmission reduced in the locations of the trial, requiring additional sites to be established (Blakely and Philp, 2020).

COVID-19 also highlighted some other issues in CHIM studies that are particular to the setting of an outbreak of a PPP. There was concern that the CHIM study would divert scarce resources from an overwhelmed healthcare system (Kahn et al., 2020). It also highlighted that a pandemic is an emergency situation where the speed of conducting research matters enormously. At the peak of the pandemic over 10,000 people were dying daily (Our World in Data, no date), so there is a strong reason to accelerate research and the evaluation of medical countermeasures.
Additionally, there may be a role for CHIM studies involving PPPs ahead of an outbreak. Studies may allow potential vaccine candidates to be tested ahead of a novel outbreak. However, in this case, the risk of the study causing a local outbreak that would not occur otherwise is greater when there is no existing circulation of the virus in the community. In addition, deliberate infection of humans gives the pathogen the opportunity to adapt to the human host, which may result in increased transmissibility and increased pandemic risk.

In summary, there are important considerations that arise when a CHIM is being considered for a PPP, rather than another pathogen.

The considerations that might lead to greater caution in conducting such studies are:

- The uncertainty in risks and benefits, including to third parties
- The likely higher risk posed to participants
- The availability of locations of high incidence to conduct field trials
- The scarcity of health system resources
- The potentially greater risk of precipitating an outbreak

The considerations that might lead to greater support in conducting such studies are:

- The scale of the study's possible benefit
- The increased urgency for research and development of medical countermeasures

5. Overview of the decision-making framework

Drawing on existing ethical analysis of CHIM studies, we have developed a framework to guide decision-making about CHIM studies with PPPs.

5.1 What should be asked when evaluating a study?

This framework consists of two key questions:

1. Is the proposed study in the public interest?
2. Does the proposed study satisfy other ethical requirements?

There are three sub-questions to determine if the study is in the public interest:

- Is there a valid scientific rationale?
- Do expected benefits justify expected harms?
- Is this the best method to achieve benefits?

There is then a procedural requirement that an external review must agree with the assessment that the study is in the public interest.

There are five sub-questions to determine if the study satisfies other ethical requirements:

- Is there a fair and comprehensive system of compensation?
- Is there a process to ensure voluntary and sufficiently informed consent?
- Is the recruitment process fair and protect the interests of vulnerable groups?
- Are the interests of the local community around the study site protected?
- Is there a comprehensive plan for communication with stakeholders?

This is summarized in Figure 1 and described in detail in Sections 6 and 7.
Figure 1: Decision-making framework for evaluating CHIM studies: A negative answer to any of the questions means that a study is ethically suboptimal calling for revision or cancellation

**Is the study in the public interest?**

- Is there a valid scientific rationale?
- Do expected benefits justify expected harms?
- Is this the best method to achieve benefits?

Does an external review agree?

**Does the study satisfy other ethical requirements?**

- Is there a fair and comprehensive system of compensation?
- Is there a process to ensure voluntary and sufficiently informed consent?
- Is the recruitment process fair and does it protect vulnerable groups?
- Are the interests of the local community around the study site protected?
- Is there a comprehensive plan for communication with stakeholders?

5.2 Who should make decisions?

Who answers these questions is also an ethical question. Usually, RECs are charged with making the decision of whether a proposed research study involving human subjects is ethical. While this is appropriate in most circumstances, in public health emergencies (such as the outbreak of a novel pathogen with pandemic potential) the decision of whether to conduct a CHIM study might affect a large portion of society through its effects on government decision-making and/or medical countermeasure development. The actions of policymakers may also greatly influence the assessment of the study's effects, as these will depend on the policy options that are being considered and the effect the CHIM study may or may not have on the decision of which policies to pursue.

Therefore, we think that in a public health emergency the first question in our framework, ‘Is the study in the public interest?’ should be answered by a pre-determined group that includes representatives from relevant government agencies including the HRA, funders, ethicists, and scientists. If this group decided that a study was in the public interest, then the relevant REC would evaluate part two of the framework ‘Does the study meet other ethical requirements?’. If these requirements weren’t met, efforts would need to be made to rapidly modify the study.

6. Is the study in the public interest?

The first question in our framework asks whether the study is in the public interest. This encompasses an assessment of whether the study is likely to be an effective use of resources aiming to improve health, and whether the expected benefits of the study justify the expected harms to voluntary participants. It therefore involves an empirical assessment of the rationale and expected effects of the study, a comparison with other research that could be pursued, and an ethical assessment of whether the benefits are proportionate to the risk that participants are taking on.

6.1 Is there a scientific rationale for the study?

A requirement for any study to be ethically appropriate is for it to have a sound scientific rationale. There are several valid scientific questions that can be investigated with a CHIM study. These can be classed into two broad categories: gaining a detailed understanding of pathogenesis and immune response of the pathogen and facilitating the development of medical countermeasures.

6.1.1 Understanding pathogenesis and immune response

CHIM studies are well placed to provide a detailed understanding of pathogen infection and growth and the human immunobiological response. Compared to other studies, CHIM studies have the advantage of allowing the exact exposure dose and timing of infection to be known.
In observational and field studies the timing of infection can be estimated but is not known with precision. Thus, CHIM studies provide particularly useful estimates of the kinetics of viral growth, including the time until virus can be detected and the pattern and duration of viral load, including load of viable virus throughout illness. CHIM studies also enable comparison of symptomatology and viral load and the time from infection until symptom onset. Having an accurate estimation of the incubation period can be a helpful tool in epidemiological forecasting and in health policy considerations. CHIM studies may also help to identify which routes of exposure lead to infection.

CHIM studies involve the collection of participant specimens (e.g., serum) that yield detailed information on antibody production, immune cell proliferation and differentiation, and elaboration of chemical mediators of immune response. Together, such data can be used to establish and characterize the correlates of immune protection from infection and disease progression. These can be useful in evaluation of population immunity and in estimating vaccine efficacy without requiring infection. CHIM studies may also help to identify why some individuals are susceptible to infection and why others are not, through study of those participants who do not show evidence of infection following exposure.

6.1.2 Developing medical countermeasures and devices

CHIM studies may be useful in developing and testing medical countermeasures, including vaccines and therapeutic treatments, and devices, including rapid diagnostic tests.

CHIM studies can provide an estimate of the efficacy of a vaccine quickly and are particularly well-suited to comparing vaccine efficacy as they can be replicated easily (Roestenberg, Kamerling and de Visser, 2018). If there are multiple vaccine candidates this may enable selection of the best candidates to progress for further development and evaluation. In an outbreak situation this may dramatically speed up the process of choosing the most appropriate vaccine and dosing regimen, so that an effective vaccine can be licensed. It is possible that in some severe and urgent situations CHIM studies would provide sufficient evidence of efficacy to begin administering vaccine to populations who are at highest risk.

CHIM studies may also be useful for optimizing certain aspects of vaccination that otherwise may require extensive field trials. CHIM studies may be useful for testing different vaccine strategies, including the use of vaccine adjuvants, dose spacing, heterologous vaccination and booster vaccines, including variant-specific boosters. Correlates of immune protection obtained in a CHIM study may enable assessment of the efficacy of vaccines when it is inappropriate to conduct challenge studies, for example in populations who can’t consent, such as children (Eyal and Gerhard, 2022).

CHIM studies can also be used to evaluate diagnostic tests. An important finding of the SARS-CoV-2 challenge study was that it provided evidence that lateral flow tests were strongly associated with viable virus (Killingley et al., 2022). Comparison of the timing of infection detection by different tests throughout illness may be helpful in designing population-level testing policies.

In a non-pandemic period CHIM studies may be particularly useful when there is insufficient circulating virus to perform a Phase III study. This has been considered for the evaluation of influenza vaccines and a Zika virus vaccine (Memoli et al., 2016; Palacios and Shah, 2019).

CHIM studies are generally less well-suited to studying therapeutic agents that aim to mitigate the most severe disease outcomes. In cases where there is ongoing circulating virus, these types of therapeutic agents can usually be best evaluated in clinical settings. However, CHIM studies have been useful for evaluating some therapeutic agents and comparing the timing of treatment over the course of illness. CHIM studies can be used to monitor the change in viral production in response to treatments, which may be an initial useful step in evaluating therapeutics. They can also be used to evaluate the ability of agents to prevent infection and transmission. Oseltamivir was evaluated as treatment for influenza using a CHIM (Hayden et al., 1999).

It is also possible that CHIM studies, particularly those conducted in a non-pandemic period, may assist in the development of novel therapeutic agents. In particular, investigating the differences in immune responses of participants may provide promising areas of investigation for novel antiviral agents.

6.1.3 Scientific limitations of CHIM studies

It’s important to note the limitations of CHIM studies. As noted earlier, CHIM studies are not well-suited to investigate severe disease, as opposed to mild infection. This limits their use in evaluating medical countermeasures that aim to prevent severe disease rather than infection. For example, they may underestimate the effect of a vaccine that reduces severity of disease, but not infection.

There are also several limitations of CHIM studies that stem from measures taken to reduce the risk the studies pose to participants. Firstly, CHIM studies often involve an infection using a low dose to minimize risks of severe disease, and for this reason cannot fully recapitulate the process of natural infection. Even if the route of infection mimics
the natural route, the manner in which people become infected, including the dose of virus they are exposed to, will have some influence on their immune response and viral load kinetics. Being unable to completely mimic natural infection will reduce the generalizability of results, both in terms of understanding the dynamics of viral growth and estimating efficacy of vaccines and therapeutics.

Secondly, CHIM studies are typically conducted in the subset of the population with the lowest risk of progressing to severe disease. As such it is unclear how well their results generalize to the rest of the population. In some instances, vaccines (for example, influenza vaccines) have performed differently for different demographic groups. This may be particularly the case when evaluating vaccines for their prevention of disease, rather than infection, as the lower-risk subset of the population is less likely to develop disease.

Another limitation of CHIM studies occurs when an attenuated pathogen is used, rather than the wild-type circulating pathogen. An attenuated pathogen causes less severe disease and will be used when the risks to participants from challenge with the wild-type pathogen are deemed unacceptably high. An example is the use of Bacille Calmette–Guérin vaccine (BCG) as a replacement for challenge with mycobacterium tuberculosis in CHIM studies investigating tuberculosis (Harris et al., 2014). Although this reduces the risk to participants it also reduces the generalizability of the results to the wild-type pathogen.

6.2 Do expected benefits justify expected harms?

The expected benefits and harms from the study should be evaluated and compared. This should include consideration of expected harms and benefits to participants and to the population which the study aims to benefit. However, it is worth noting that it will generally be easier to quantify the harms to participants than the benefits to the population. There should then be an assessment made of whether the expected harms to participants are ethically justified by the benefits to the population.

6.2.1 What is the expected harm for participants?

Harm from infection

An expected harm that is unique to CHIM studies is the harm from the deliberately induced infection. This will include the symptoms of disease, the risk of long-term sequelae of infection, severe acute illness and in some cases, the risk of death.

As noted earlier, a significant concern for CHIM studies with a novel pathogen, or any pathogen with which there is limited experience in humans, is that there is little data to inform the assessment of the medical risks to participants. This is particularly true for longer-term risks. Some data from observational studies will be necessary to enable characterization of risk, including the areas of uncertainty, and identify the subset of the population that is at lowest risk and might be appropriate to participate in a CHIM study. However, it is likely that in the event of a pandemic this data will be gathered from observational studies relatively quickly, as occurred in COVID-19. The degree of confidence we have in our estimates of the expected harms of infection is ethically relevant and will inform decision-making about whether to progress studies.

When assessing the infection risks to participants it is necessary to consider not only the risks that occur from infection, but also take into account the background population risk that the prospective participants would face and the effect of study participation on risks once infected. If a participant is likely to be infected in the community then participation in a CHIM study will contribute only a small addition to their overall risk from the pathogen. Participation in a CHIM study will likely reduce risk of serious harm relative to infection in the community. This is because the participant will be challenged with a low dose of virus and will be monitored closely, which will enable prompt medical treatment. Participants, particularly those who do not receive a vaccine, will likely receive broad-spectrum antiviral agents before or at the onset of symptoms.

Harm from study procedures

Almost all research involves some small harm or burden to the research subjects. This is often relatively minor, comprising the pain and discomfort of venipuncture and other types of testing, the inconvenience of attending appointments or the loss of freedom due to residing in a research facility for the duration of the study and any required quarantine period after the study.

There are also rare complications that can occur due to research activities, including the very small risk of nerve damage with venipuncture, or the risk of serious mental illness if the research requires a period of quarantine or isolation. These risks are not unique to CHIM studies and will occur to greater and lesser degrees in all medical research studies. However, all research should aim to minimize these risks by limiting the number of invasive procedures to only those necessary to answer the research questions and take active steps to ensure that any study requirements impose as little burden as possible.
**Risk minimization**

There are several steps that can be taken to minimize the risk of significant disease. Some of these steps limit the generalizability of the study results and so a balance will need to be struck between lowering risk to participants and gaining the most useful information from the study. Minimizing risk at the expense of study usefulness will not always be the appropriate choice.

**Low-risk study participants**

Selecting the subset of the population that is at lowest risk of severe disease from infection is an effective way to reduce the risks of a study. This was a key feature of reducing the risks of the SARS-CoV-2 CHIM. The study used a population-based scoring system that incorporated several features known to influence risk and determined a risk score to serve as a cut-off. The cut-off was equivalent to the risk faced by a 30-year-old with no risk factors, which was calculated to be 1 in 250,000 risk of death or 1 in 4902 risk of hospitalization (Killingley et al., 2022).

Some commentators suggested that the use of a low-risk population would limit the utility of the study results, as it is unclear whether the results apply to other populations, especially older population who are at highest risk of severe disease (Kahn et al., 2020). While it’s likely that there is a limit to the generalizability of studies to different populations, in the case of SARS-CoV-2 vaccines, vaccine efficacy has been lower in the elderly, but has been fairly similar across age groups (Folegatti et al., 2020; National Institutes of Health, 2020; Pfizer, 2020).

The relative risk to different age groups from SARS-CoV-2 infection was dramatic. Future pathogens may not have such an age-gradient. There may not be a low-risk population in future diseases. If there wasn’t such a discrepancy in risk for a pathogen that is causing significant societal disruption, then it would be more difficult to conduct useful CHIM studies. It is possible that future pathogens will also pose lower risk of disease to a subset of the population but this is not guaranteed, and the lack of a low-risk population would limit the feasibility of conducting CHIM studies.

**Low-dose challenge**

Another method of reducing the risk of infection is to carefully titrate the challenge agent in the dosing studies to identify the lowest dose of challenge agent that will induce a mild symptomatic infection, this being the accepted standard for creating a human disease model. This is done because lower inoculum doses are generally associated with a less severe illness.

**Attenuated pathogens**

If the risks of using a particular pathogen are thought to be unacceptably high, then the use of an attenuated pathogen should be considered. Attenuation reduces the virulence of a pathogen and can substantially reduce the risks to participants. However, as noted above, this comes at the cost of reducing the generalizability of the study results. One of our interviewees involved in the UK SARS-CoV-2 CHIM noted that the group had considered using an attenuated pathogen, but it was decided that the risk to participants was sufficiently low that the further reduction in risk would not outweigh the more useful information that would come from using the wild-type pathogen.

If using an attenuated pathogen, it may be useful to conduct some studies using the wild-type pathogen in order to determine the degree of concordance and generalizability between the study models. Depending on the features of the pathogen it may be appropriate to do this using a small number of human volunteers or an animal model. It may be possible to combine CHIM studies using attenuated and wild-type pathogens in creative ways, such as using an attenuated model to screen vaccine candidates and follow this with a wild-type challenge only for candidates that show promise.

**Availability of antivirals and appropriate facilities**

It is necessary to ensure that the facilities where challenge studies are conducted are well-equipped to provide medical care to patients should they develop severe disease. CHIM studies will be easier to justify when there exists a ‘rescue therapy’ that can be given to a participant after the onset of symptoms. However, few treatments reduce risks to zero, so if risks can be kept to acceptable levels through other means, then the absence of a rescue therapy need not be a barrier to a CHIM study going ahead.

**Collective expected harm to participants**

When assessing the overall impact of a study it is necessary to multiply these expected risks to the individual by the number of participants in the study. These impacts, taken collectively, are likely to be relatively small compared to the benefits and harms of the study to the population, but ought to be considered in the assessment of the study’s overall harm and benefit.

**6.2.2 What is the expected benefit for participants?**

Consideration should also be given to the benefits for study participants, including the potential immunity derived from intentional exposure to the virus. Depending on their risk of community-acquired infection, participation in the study may provide an expected health benefits.
benefit, as they will receive more careful monitoring and better access to healthcare during the study compared to if they had acquired the infection in the community. Participation in the study may provide indirect benefits, if the research is expected to shorten the pandemic, which is likely causing significant negative effects on participants’ lives. Finally, if they are highly likely to become infected with the novel pathogen naturally during the course of a pandemic, receiving the vaccine prior to a controlled lab-based exposure may result in a better medical outcome than being exposed naturally without any immunity.

6.2.3 What is the expected benefit for the population?

To determine whether the expected harms to participants are justified, it is necessary to determine the expected benefits of the study to the population and compare these to the expected costs, including financial costs and expected harms. This should also be compared with the expected benefits and costs of alternative methods for achieving the aims of the study.

The expected benefit of a study refers to the potential benefits of the study, weighted by their probability of occurrence. This requires an assessment of a) the expected health impacts of the outbreak, and b) the degree to which the study would reduce those health impacts.

These assessments would be specific to the pathogen and the context in which it is being considered. Several features of the pathogen and the situation will influence the expected benefit of the study.

Assessing the expected impacts of the outbreak

Pathogen features

- Virulence

The virulence of a pathogen, that is, its ability to cause damage to its host, plays an important role in determining the benefits of conducting CHIM studies. The more danger a pathogen poses to an individual, the greater harm it poses to a population, and the greater the benefit in developing medical countermeasures and in improving the policies enacted to prevent transmission.

- Transmissibility

Along with virulence, the transmissibility of a pathogen, contributes to its expected effect on the population. If a pathogen is highly transmissible then it’s likely that a large proportion of the population will be at risk of exposure, making efforts to slow transmission and prevent severe disease even more important. In general, pathogens with airborne transmission will be much harder to control than pathogens transmitted through direct contact with bodily fluids, as will pathogens where transmission occurs prior to symptom onset.

The pattern of transmissibility amongst the population may also play a role in determining the size of an outbreak. If a pathogen is highly transmissible by children or young adults then this will likely contribute to a larger outbreak, as people in these age groups have high rates of social contact, and it is difficult to get children to adhere to infection prevention methods like mask-wearing, social distancing, or hand hygiene.

- Natural immune response

If infection induces robust and long-lasting immunity, then this may suggest that a pandemic may resolve more rapidly than if reinfection was expected to be common. It may also suggest that we could expect vaccine development to be more successful. However, some pathogens may be relatively resistant to host immune responses or elicit protection that is of relatively short duration.

Situational features

- Nature of outbreak

The size of an outbreak will also be driven by environmental factors, including the density and living situations of the population and their patterns of contact, building design, and often the local climate, which will influence viral stability in the environment. If an outbreak initially occurs in a sparsely populated area, then control mechanisms may be more effective than if it had originated in a densely populated area. The size and speed of an outbreak will influence the benefit to be gained from understanding its viral growth properties, interaction with the human immune system and speeding up the development of medical countermeasures.

- Efficacy of existing medical countermeasures

For some novel pathogens, vaccines developed for related pathogens may offer partial protection. For example, the smallpox vaccine offers partial protection against the monkeypox virus. Similarly, some therapeutic agents, such as broad-spectrum antivirals, may be effective against a novel agent. The availability and efficacy of these measures will influence the expected benefit of additional research aimed towards developing new medical countermeasures.

This also points to the fact that CHIM studies performed before an outbreak occurs can be useful in reducing the risk of that outbreak. CHIM studies may aid the development of vaccines against PPPs, or prototype pathogens from viral families with pandemic potential.
• **Effects of non-pharmaceutical interventions**

If governments have implemented non-pharmaceutical interventions the effects of these should also be included as impacts of the pandemic. The degree to which these interventions are causing social and economic disruption will influence how important it is to gain knowledge of the pathogen that might allow them to be modified, or to hasten the develop of medical countermeasures that may allow them to be relaxed.

**Assessing the study’s expected effect on identified impacts**

• **Value of knowledge**

CHIM studies can provide useful information that can inform policy choices. For example, understanding the kinetics of viral growth can allow a more accurate determination of appropriate periods of isolation after infection. As occurred for COVID-19, CHIM studies can validate diagnostic tests to develop strategies to reduce rates of community transmission. To determine the potential benefit of information gained in CHIM studies, it would be important to identify which policies may change depending on the study data and estimate the expected effect on community transmission.

It would also be important to consider the other benefits that might arise from reformed policies. For example, if a strategy can be developed that allows some services or social interaction to return then the economic and mental health benefits of this ought to be considered. Although it may be difficult to make these calculations, the COVID-19 pandemic has led to substantial data on the broad range of impacts of policy choices, which could be used to assess the benefits of relaxing certain restrictions, beyond epidemic control.

CHIM studies performed outside the context of an outbreak can detailed information on viral growth and pathogenesis, as well as humoral and cellular immune responses, that could inform the development of medical countermeasures or plans for non-pharmaceutical interventions in a future outbreak.

• **Vaccine development**

Historically, CHIM efforts have been utilised in down-selection of promising vaccine candidates for known pathogens by providing direct evidence of human immune responses. The role that CHIM studies can play in vaccine development for a novel, and potentially pandemic pathogen will be influenced by the expected timeline of vaccine development, the ease of developing a highly effective vaccine, the added benefits that knowledge of correlates of protection can provide for vaccine development, and the likelihood that there will be multiple vaccine candidates with varying levels of efficacy.

Outside the context of an outbreak, CHIM studies may play an important role in vaccine development, as there are few opportunities to evaluate a vaccine when there is no active outbreak of disease. However, conducting a CHIM study with a pathogen that is both highly transmissible and highly virulent would be highly risky. Therefore, use of less virulent members of a pathogen family (prototype pathogens) is likely to be more appropriate in these circumstances.

• **Timelines**

A period of several months would be required to develop a challenge agent to Good Manufacturing Practice (GMP) standards and generate sufficient stock to conduct a CHIM study. As such, if a vaccine is developed within a period of months, as occurred in SARS-CoV-2, then this delay may limit the role of CHIM studies in their evaluation.

It should be noted that there may be ways to reduce the time required for GMP stock production by technical advances in the viral manufacturing processes and by discussion and clarification of key quality control and safety requirements with regulatory authorities. Furthermore, even if vaccines were to be developed quickly, there still are a number of important translational issues that could be addressed by CHIM studies without requiring extensive field trials, e.g., assessment of the duration of protection, vaccine re-formulation with alternative adjuvants, and testing of modified vaccines to counter new mutant forms.

Several of our interviewees noted that SARS-CoV-2 was unusually well-suited to vaccine development. Not only had there been substantial study of similar viruses (SARS-CoV-1 and MERS), but the spike protein served as a particularly good target for action for vaccines. It is unclear, and perhaps unlikely, that de novo vaccine development will be as successful – in terms of both speed and efficacy - for future pathogens unless there is substantial effort to develop vaccines for prototype pathogens. This highlights the potential value of developing vaccines against prototype pathogens.

Further, the delay in producing sufficient GMP standard meeting stock could suggest a priority area for research and development ahead of the next pandemic.

**Contribution to vaccination strategy and regulatory approval**

In future outbreak scenarios it may be the case that vaccine development will take a sufficiently long period of time that CHIM studies could contribute to the development of an initial vaccine, whether through
providing an initial assessment of efficacy to guide the choice of which vaccines to prioritise for Phase 3 testing, or through contributing evidence of efficacy for regulatory assessment. CHIM studies could also ascertain correlates of immune protection that could be used to evaluate vaccine efficacy.

CHIM studies may also be used to improve strategies for vaccine roll-out, including through assessing the effect of using vaccine adjuvants or determining the optimal dosing. This may be particularly important in settings where there is vaccine scarcity, as identifying the minimal effective dose may enable doses to be distributed to more people more quickly, potentially alleviating some of the problems of global vaccine inequity that has occurred in the roll-out of vaccines against SARS-CoV-2.

Outside of an outbreak, CHIM studies may play a role in evaluating new vaccines for pathogens that are not in constant circulation, for pathogens that have yet to have satisfactory vaccines and for which there may be increased need in the future (e.g., RSV), for the evaluation of universal influenza vaccines, or the investigation and testing of vaccines against prototype pathogens. CHIM studies may be particularly useful for evaluating vaccines that aim to prevent transmission rather than disease. It was mentioned that CHIM studies may be necessary for the evaluation of transmission-blocking vaccines for SARS-CoV-2. CHIM studies designed to document interruption of transmission may require a different paradigm, involving controlled exposure of vaccinated participants to individuals infected by challenge material, which may involve some additional ethical, safety and design considerations.

Evidence from CHIM studies was used as the basis of regulation of the cholera vaccine (Mosley et al., 2017). However, in this instance it was not feasible to conduct field trials to evaluate vaccine efficacy. Whether evidence for CHIM studies would be sufficient for regulation of medical countermeasures would depend on situation factors including the feasibility of conducting a field trial and the outbreak situation.

**Protection against transmission vs virulence**

Another complication to the use of CHIM studies data in vaccine development in an outbreak situation is that CHIM studies use mild symptomatic infection as a study endpoint, rather than disease. Although interruption of transmission is more important to limiting the size of an outbreak, reducing the severity of disease is also an important public health goal, as it prevents loss of life and reduces the strain on healthcare systems. Several of our interviewees suggested that developing a vaccine that reduces severity of disease was generally simpler than developing a vaccine that reduces transmission, which contributed to this being the priority for vaccine developers at the onset of the COVID-19 pandemic.

Two of our interviewees noted that efforts were underway to develop vaccines that block SARS-CoV-2 transmission, and that CHIM studies would be highly useful, even necessary, to evaluate these vaccines. The ability to monitor levels of viable virus in the nasopharynx from inoculation would be very useful to assess transmissibility. Such close monitoring of viral levels would not be possible in field trials, particularly as such trials generally identify patients by participants seeking medical attention once symptomatic. Evaluation of transmissibility would be even more difficult in situations where the onset of the infectious period precedes symptoms, as occurs in COVID-19.

**Therapeutics development**

CHIM studies may assist in the development or evaluation of novel therapeutic agents, especially those aimed at preventing mild-moderate disease. In particular, CHIM studies assessing changes in viral titre in response to therapeutic agents would be helpful in determining when lager studies to assess efficacy are warranted.

**Specific considerations for CHIM studies outside the context of a disease outbreak**

For studies conducted outside the context of an outbreak (i.e. studies on prototype pathogens performed in a non-pandemic period) there is an additional challenge in considering their benefits; the degree of benefit depends on the likelihood of a relevant outbreak occurring. There is a chance that the results of these studies won’t ever inform public health responses. Predicting the future is an undeniably difficult exercise that will have significant uncertainty, and we should be cautious in using the outputs of models that aim to predict future events. However, it may be possible to generate a rough estimate of the expected benefit of these studies that combines estimates of the probability of an outbreak occurring and the expected impact of reducing the severity of a disease outbreak.

Another consideration is that some of the value of conducting a CHIM study in ‘peace time’ may come from ensuring that there are facilities and staff that are able to conduct a CHIM quickly in the event of an outbreak of a PPP. Several of our interviewees emphasised the importance of readiness to conduct CHIM studies quickly and suggested that this requires regular conduct of CHIM studies. It is plausible that the majority of the benefit of some CHIM studies conducted during peace time would come from enabling the rapid conduct of a different study at the beginning of a significant pandemic.
**Summing up the expected benefits**

An estimate of the expected benefits of the study should incorporate an estimate of the benefit of reducing the duration and severity of the epidemic, taking into account the expected reduction in morbidity and mortality directly attributable to the epidemic, the indirect health effects of allowing resumption of normal healthcare services, and the economic impact.

### 6.2.4 What is the expected harm for the population?

#### Risk of local transmission

Pathogens with pandemic potential raise additional risks of transmission from participants to the local community. If there is active community transmission in the area surrounding the CHIM study facility and the laboratory where the challenge agent would be manufactures, then the study is unlikely to pose a significant addition of risk. However, the risk may be more important if a different strain of the pathogen to what was circulating locally were to be used in the study.

When considering CHIM studies with PPPs outside an outbreak, the risk of local transmission will become a more important consideration. If there isn’t circulation of the pathogen in the community then a CHIM study poses a more significant counterfactual risk than if the pathogen were already circulating. The risk of precipitating a local outbreak needs to be taken seriously. The use of high containment facilities and strict infection prevention protocols can significantly reduce the risk but not eliminate it. CHIM studies should only be performed in clinical and laboratory environments with the appropriate biosafety infrastructure and staff training.

An additional concern is that intentional inoculation of volunteers with a dangerous pathogen might, in itself, make the pathogen more dangerous, as it creates the opportunity for the pathogen to adapt to humans. Such an “escape pathogen” brings the risk of becoming a greater threat to the population. This unintended potential consequence of CHIM studies needs to be considered and would need to be included when considering the biosafety requirements of CHIM studies. It may provide a reason to conduct CHIM studies with low-virulence prototype pathogens rather than pathogens that have the potential to cause consequential disease (including if they only cause severe disease in a subsection of the population). This concern applies particularly when considering CHIM studies with known PPPs outside an outbreak but is less important in settings where there is high infection rate in the community, such as at the onset of an outbreak of a novel pathogen.

A common requirement for ethical research is the right of a participant to withdraw from a study. In the case of CHIM studies this is complicated by the fact that the participant may pose an infection risk to third parties, who have not consented to participate in the research. We think the most reasonable approach is to allow a participant to withdraw from the study – and therefore no longer participate in study procedures including testing – but to require the participant to remain in isolation whilst infectious. One of our interviewees emphasized that study participation comes with responsibility to provide data that accounts for the value of the study and to comply with local restrictions. It was noted that in the case of SARS-CoV-2, participants were required to isolate whilst infectious to remain in compliance with public health orders for the general community.

#### Use of local resources

A concern that was raised when COVID-19 CHIM studies were being considered was that the study would take up healthcare resources that were needed in the community. Healthcare systems in many countries, including the UK, were put under immense pressure during the pandemic and diversion of some resources adds to that strain, possibly resulting in slightly poorer care.

One of our interviewees who was involved in the UK COVID-19 CHIM study noted that the time of healthcare personnel required for the study was greater than expected. This suggests this concern for the use of local resources should be included in estimates of the study’s expected effects.

#### Risk of impairing public trust

Finally, a concern that was voiced by many during discussions of COVID-19 CHIM studies is the effect it could have on public perception of science and vaccines, especially if a serious adverse event occurred in one of the trials. Although most people complied with public health interventions and were quick to take up vaccines once they were available, distrust in public health officials and scientists was a dominant feature of media during the pandemic.

As outlined by Eyal, there are two main potential consequences of impairing public trust: 1) that people may be less likely to comply with public health interventions, including advice to receive a vaccine, and 2) that people may be less likely to participate in research studies in the future, particularly CHIM research (Eyal, 2022). Eyal notes that there is little empirical evidence to gauge the extent to which CHIM studies may influence public behaviour. Survey results during the COVID-19 pandemic suggested substantial public support for CHIM research in the UK (Barker et al., 2022).
It has been suggested that the death of a participant in a trial for a novel gene therapy set back gene therapy research by decades (Eyal, 2022). However, there are reasons to believe that the researchers in that study neglected key ethical duties, such as promptly reporting adverse events, providing fully informed consent, and neglecting signs that the patient may have been at higher risk of an adverse event. Most importantly, the study design failed to minimize expected harm (Savulescu, 2001).

It is also possible that by accelerating the delivery of a viable vaccine in an emergency response, CHIMs could increase public trust in science and public health rather than impair it. If CHIM studies provide knowledge that can shorten the use of non-pharmaceutical interventions this may also help to improve public opinion of scientific advice to political decision making.

Although it’s unclear if and how, CHIM studies would influence public trust in public health advice and science, if an untoward event did occur the consequences could be significant and could be a key determinant of the effects of the research. As such, it may be appropriate to have a higher bar for the degree of benefit that a study should be expected to produce. This will be discussed further in Section 6. This also suggests that research should be conducted to better characterize how CHIM studies could influence public trust in research and public health authorities.

**Dual-use risks of CHIM studies**

As with all scientific research, it is necessary to consider the potential for the results of CHIM studies to be used to cause harm. In particular if CHIM studies are conducted when there is no outbreak, they have the potential to generate information on the genetic and other features that make a pathogen more transmissible or more virulent. This information could be used by malicious agents seeking to develop a biological weapon, the risk of which is increasing due to increasingly accessible biotechnology. Careful thought will need to be given to the potential misuse of information gained in a CHIM study. If it is possible that results could be dangerously misused, then this may be sufficient reason not to conduct the study, or to restrict the information gathered during the study. This is not an issue unique to CHIM research, and is a consideration for many types of research in the life sciences.

**Summing up expected population harms**

Developing an estimate of expected harms requires an estimation of the expected harm to participants, taking into account the severity of potential adverse events and their likelihood of occurring. This should be multiplied by the number of participants required for the trial. This should be combined with an estimate of the expected harms to the community, again incorporating the severity of the potential harm and its likelihood of occurring.

For CHIM studies conducted outside an outbreak, estimating the expected benefits and harms will be especially challenging. The benefits are dependent on the likelihood of a pandemic of the studied pathogen occurring, which is difficult to estimate. The risks include the potential of precipitating an outbreak (including the capacity to control it), pathogen adaptation to humans, and the potential for misuse of information gained in the study.

**6.2.5 Population benefit proportional to participant risk**

An important component of ensuring respect for persons is ensuring that the degree of risk taken on by participants weighs appropriately in decision-making. We suggest that this can be achieved by requiring a greater degree of expected population benefit for research that carries greater expected harm to participants. This greater requirement for benefit would respect the magnitude of the greater personal investment of participants in higher risk research by not asking them to take on great personal risk for small gains to others.

Low-risk research may simply require any degree of expected population benefit that is considered cost-effective as per standard approaches in health economics. If the expected population benefit is very high and the risk to participants is low, then it seems relatively clear that the study is permissible. As was suggested in the Academy of Medical Science’s 2018 workshop on CHIM research, it may even be considered ethically required that the study occur if the ratio of expected benefits to risks is high (Academy of Medical Sciences, 2018). Higher risk research should require a substantially greater expected population benefit. We might also require a greater degree of confidence in the estimate of benefit when studies involve greater personal risk to participants. However, if the risks to the participant are higher and/or the net expected benefit is lower, then the permissibility of the research becomes less clear.

It is necessary to assess whether it is acceptable to allow volunteers to take on these risks for the purposes of the research. This is a difficult and divisive ethical question. It is common for ethicists to suggest that there should be some absolute limitation on risk in research studies, and that it would not be ethical to conduct a study with a high risk of mortality of significant long-term injury. However, as Binik has argued, it is difficult to clearly define an absolute limit on risk that is not arbitrary (Binik, 2020). In particular, advice to not conduct research that could result in death...
or serious harm is unhelpful as most activities, including participation in research, will involve a small risk of death or serious harm.

Furthermore, several authors have argued that it would be inconsistent to allow people to take risks for other altruistic purposes but not allow the same for participation in CHIM research. In particular, during discussion of a COVID-19 CHIM study, an analogy was made to living organ donation, with the argument that consistency would require us to permit risks that are allowed in other altruistic medical acts, namely living organ donation (Jayaram, Sparks and Callies, 2022). The risk of death has been estimated to be 0.03% (Lentine, Lam and Segev, 2019) for living kidney donation and 0.2% for living liver donation (Trotter et al., 2006; Cheah et al., 2013). Another argument that could be made is that we ought to allow informed people to voluntarily take on risks for research that they would be allowed to take on in other areas. For example, the mortality risk of attempting to climb Mount Everest is around 1% (62). If we do not prevent people from participating in this dangerous activity, then we ought not to prevent people from participating in CHIM research with a similar level of risk. We might consider this a potentially acceptable high level of risk.

We agree with others who have suggested that the acceptable level of risk for CHIM studies should depend on the expected benefits of the study, and that it may be acceptable to allow adequately informed volunteers to accept what might be considered a high degree of risk if the expected population benefit is sufficiently high (Hope et al., 2004; Palacios and Shah, 2019). In Section 6 we provide one possible method for determining whether the expected population benefit is high enough to justify the risk to participants. However, as we note in that section, determining when risks are justified should be subject to further ethical analysis and debate and be informed by input from the public, researchers and policymakers.

6.3 Are there better methods to achieve similar benefits?

Consideration should be given to the alternative methods of achieving the aims of the study, and a comparison made between the expected benefits and harms of these studies and the benefits and harms of a CHIM study. It is likely that multiple research approaches will be used, and the triangulation of data from different types of research will provide a greater understanding of pathogenesis and more accurate estimates of the effectiveness of medical countermeasures.

6.3.1 Nonhuman animal models

Nonhuman animal models are commonly used to study infection and growth of a pathogen and to test the efficacy of medical countermeasures, including for pathogens with pandemic potential (Louz et al., 2013). These studies provide useful data but cannot completely replicate the human immune response and often require “adapting” the pathogen so that it can replicate in the non-human host, further complicating the interpretation of data. Therefore, it is difficult to draw clear inferences from these studies to humans. Furthermore, there are ethical concerns about the use of nonhuman animals in research (Levy, 2012). Although there have been improvements in the treatment of laboratory animals in recent years, raising an animal solely for use as a research subject, who cannot consent to the research continues to raise ethical concerns for many.

One of our interviewees noted that a benefit of using CHIM studies where appropriate is the reduced reliance on nonhuman animal research and reduction of the harms this research brings to animals, particularly in situations where the usefulness of animal studies is limited.

CHIM studies may also be used to validate animal models, which may be useful in support of regulatory filings that include animal data. This may reduce the number of unhelpful animal studies that are conducted and allow for the use of animal, rather than human, models where appropriate, potentially reducing the need for some human studies.

6.3.2 Epidemiological studies

When a virus is circulating in a community, careful epidemiological studies can provide estimates of viral load kinetics and immune responses. Estimates of the incubation period can be made through close analysis of cases and estimates of the time of their likely exposure. However, a limitation of these studies is that they rely on recall of information and cannot estimate the initial exposure dose and only provide an estimate of the time of exposure, whereas the exact dose and time of exposure is known precisely in CHIM studies. Other methods for estimating incubation period similarly rely on estimates and cannot offer the precision of CHIM studies.

The conventional alternative to the use of CHIM studies is to evaluate the efficacy of vaccines is standard Phase III field trials. These typically involve a randomized controlled trial involving tens of thousands of people. An advantage of these trials over CHIM studies is that they involve larger numbers of participants of varying ages and ethnicities, so can usually give a more precise measure of efficacy across different populations. They also provide additional safety data. As Phase I and II trials, which evaluate the vaccine for safety in humans, generally involve only hundreds of people some rare side effects will be missed. Disadvantages of Phase III trials are that they are laborious, costly and time-consuming, and require many more people to be exposed to the pathogen of interest without any vaccine protection (participants in the placebo arm).
The time required to conduct these studies was one of the primary drivers of efforts to promote CHIM studies during the COVID-19 pandemic, as bringing the distribution of vaccines forward by even small amount of time would be expected to save many thousands of lives. The fact that the studies also require many more people to be exposed to the virus without vaccine protection was also an important driver.

### 6.3.3 Person-person transmission challenge

As noted earlier, the length of time required to generate challenge material to GMP standard is a barrier to conducting timely CHIM studies. During the discussion of COVID-19 CHIM studies, the possibility of conducting studies that involved deliberate infection through person-person transmission, rather than artificial inoculation, was raised (Eyal and Lipsitch, 2021). Rather than study participants being inoculated directly with challenge material, they would be exposed to a person with active SARS-CoV-2 infection. This would remove the time delay posed by challenge material manufacture. This study model was demonstrated in 2011, when a person-person challenge model was conducting to characterize influenza transmission (Killingley et al., 2012).

Some of the researchers we spoke to suggested that there was reluctance to use this approach due to the lack of control this method introduced, relative to artificial inoculation. It was noted that participants who are intended to pass on the disease of interest may also have other active infections, or potential variants of the pathogen, and the dose could not be well controlled. It was also noted that the lack of experience conducting this type of study would pose a barrier to its use.

### 6.3.4 Alternative pandemic mitigation strategies

The scientific models mentioned above are plausible alternatives to answering the specific research questions that could be answered with a CHIM. However, it’s also important to compare the benefits of answering these questions to other actions that could be taken to reduce the expected harms of future pandemics.

In the context of an outbreak on a similar scale to COVID-19, it seems plausible that conducting a CHIM study could be a priority action, especially if it might accelerate vaccine development. Outside the context of an outbreak it may also be the case that CHIM studies, and improving the capacity to conduct CHIM studies merits investment. But it is important to conduct more rigorous analysis on the relative costs and benefits of improving capacity to conduct CHIM studies and of other pandemic mitigation measures.

#### 6.4 Expert review

An expert review would serve as an additional check to ensure that the rationale and methodology are scientifically sound, that the procedures minimize risk and maximize benefit, and that there aren’t other methods (including using different study populations) that could better achieve the study’s aims. However, in an emergency situation it may not be appropriate to delay study preparations for a review. The timeliness and extent of review required should be balanced against the need to expedite the study.

#### 7. Does the study satisfy other ethical requirements?

The steps outlined above aim to ensure the study will have sufficient benefit to the population. However, alongside beneficence there are other ethical criteria that are relevant. The Belmont Report highlighted three criteria for ethical research with human participants; beneficence, respect for persons and justice (The National Commission for the Protection of Human Subjects of Biomedical Research, 1979). We agree that respect for persons and justice are important components of ethical research and should be satisfied by proposed CHIM studies. Drawing on previous discussion of the ethics of CHIM studies (Miller and Grady, 2001; Bambery et al., 2016; Shah et al., 2017; Academy of Medical Sciences, 2018; World Health Organization, 2021) we suggest the following criteria must be met for CHIM studies to be considered ethical.

- Is there a fair and comprehensive system of compensation?
- Is there a process to ensure voluntary and sufficiently informed consent?
- Is the recruitment process fair and protect the interests of vulnerable groups?
- Are the interests of the local community around the study site protected?
- Is there a comprehensive plan for communication with stakeholders?

#### 7.1 Is there a process to ensure voluntary and sufficiently informed consent?

Voluntary, informed consent is required for all CHIM studies. This is a key component of ensuring that the study involves respect for persons, as it is for other types of human subjects research that involves significant risk to the participants.
As mentioned, an issue that arises with CHIM studies for novel pathogens is the uncertainty about the level of disease risk following infection, particularly the long-term consequences. Some have suggested that such uncertainty precludes informed consent (Dawson, Earl and Livezey, 2020; Kahn et al., 2020; Spinola et al., 2020). However, others have argued that if the uncertainty is communicated clearly, the participant can still be sufficiently informed to consent to the study (Steel, 2020). It is also worth noting that there are a range of other activities that carry high uncertainty in risk that we allow people to choose to do, including cosmetic surgery and many extreme sports.

7.2 Is there a fair and comprehensive system of compensation?

As noted earlier, we agree with existing work that suggests that payment is appropriate for participation in CHIM studies. We see payment as necessary to meeting the ethical requirements of respect for persons and justice. Failing to compensate participants for their time, the burdens they experience and the risk they are taking on would be failing to show them adequate respect. Similarly failing to provide appropriate payment would be unjust as failing to include all the relevant costs of research when deciding on payment amounts would be unfair. It would also be unfair to fail to pay for risk in research when payment for risk is considered standard in employment as ‘hazard pay’.

It would be important to determine a payment amount that is fair but is not so high that it could be considered unduly coercive (Fernandez Lynch and Largent, 2020). We suggest following the framework provided by Grimwade et al., which suggests that payment for participation in CHIM research should have three components: payment for participation, payment for risk, and a system for compensation for harms if they occur (Grimwade et al., 2020). Payment for participation should include payment for participants’ time with a standard base rate of payment augmented for the pain and discomfort of study procedures and for risk. The amount of payment increase for pain and risk could be guided by hazard payments in the UK armed forces (McConnell and Wilkinson, 2021). Alternatively, appropriate payment for risk could be calculated using existing value of a statistical life estimates or through reference to existing rates of hazard pay (Grimwade et al., 2020).

The compensation for harm the occurs should, at a minimum, cover their healthcare costs for treatment of the condition and compensate for expected wages lost due to the condition. Ensuring adequate follow-up of participants would be important from a scientific perspective as well as ethically. A robust system of follow-up would ensure that participants who have experienced harm from the study can be appropriately treated and compensated.

7.3 Is the recruitment process fair and does it protect the interests of vulnerable groups?

For a CHIM study to be considered just it must have a fair recruitment process and take measures to prevent harms to vulnerable populations.

Historical instances of exploitative research with groups who had an impaired ability to consent or lower social or economic power has contributed to caution of research in groups that might be considered vulnerable (The National Commission for the Protection of Human Subjects of Biomedical Research, 1979). The concept of ‘vulnerability’ has been the subject of substantial discussion (Bracken-Roche et al., 2017; Gordon, 2020). The CIOMS guidance suggests that vulnerable people are those who have reduced capacity for protecting their own interests, or people for whom circumstances make it less likely that others will adequately consider their interests (Council for International Organizations of Medical Sciences, 2016). Although it may be common to think of vulnerability categorically in terms of groups – e.g. children, incarcerated people, and people with mental illness and cognitive impairment, and those experiencing socially disadvantage – it is also important to consider vulnerability on a spectrum, and to consider how characteristics can combine to influence vulnerability (Gordon, 2020).

Protecting vulnerable groups may require avoiding including them as research participants. However, as in other areas of research, blanket exclusion of some groups from being considered in CHIM research may not be in their overall best interests (Murphy et al., 2020). The exclusion of some groups from research may contribute to poorer population health outcomes in those groups, as health advice is based on research that may not represent them. As such, it is necessary that research recruitment processes be fair and avoid unnecessary exclusion of particular groups.

In situations where it’s thought that a CHIM study with vulnerable participants may be appropriate then additional protection measures ought to be taken. This might include requiring a smaller degree of expected harm to participants or a greater degree of expected population benefit, additional tests to ensure that consent is adequately informed and voluntary, including participant assent when consent is more appropriately obtained by a guardian, and potentially special changes to the research environment or protocol to accommodate additional needs.

Although it is important not to exclude groups from participating in research for irrelevant reasons, care needs
to be taken when the study population comprises people from groups experiencing disadvantage in society.

7.4 Are the interests of the local community around the study site protected?

In some circumstances, a CHIM study may pose risks to the local community around the study site. This would be the case when the study involved a highly transmissible pathogen which was not circulating in the local community. In these situations, respect for the people in the local community would be satisfied if the study is in the interests of the local community, i.e., that it carries expected benefit to this local population. If the study is not expected to bring benefit to the population, then respect for the population could be satisfied by gaining community approval for the study to go ahead.

It would be impractical to gain the explicit consent of all members of the local community around the study site. However, local government could act as proxy for their collective assent in this instance. Mackay and Chakrabarti suggest that in situations where it is impractical to gain consent from all members of a population, the authorization of the research a government institution with a right to rule over the relevant spheres of policy should be considered sufficient for the research to be conducted (Mackay and Chakrabarti, 2019). Determining the appropriate government institution would require input from the UK Health Security Agency and the National Health Service but may be local health protection teams.

7.5 Is there a comprehensive plan for communication with stakeholders?

Respect for persons requires that all those affected by the research receive communication about the plans for the research and progress. There should be a clear communications plan for all research, including CHIM studies. This would be particularly important in an emergency outbreak scenario. Depending on the circumstances, it would likely be appropriate to communicate with:

- Local and national policymakers – to ensure that the study is answering the most important research questions to inform policy, and so the results can be used promptly to inform policy.
- International policymakers – to ensure that the results can be used internationally to inform policy.
- The global scientific community – to ensure that research is coordinated, and to share experiences that may be helpful for other researchers including methods and results to inform research directions.

There should be a plan in place for rapid dissemination of results.

It may also be appropriate to liaise with the local community around a CHIM site if the study may pose an infection risk to the local community. If there is substantial community-transmission in the area this will be less important. But if there is no community transmission it would be important to ensure that local healthcare providers were aware of the study and so could be alert to any presenting cases that may have illness compatible with the disease under study.

8. An example model for determining when expected population benefits justify expected participant harm

The key question for determining when it’s ethically appropriate to conduct CHIM studies is whether the expected benefits to the population are justified by the expected harms to the participants, and whether these expected harms are acceptable.

In some instances, it will be very clear that a study is ethically inappropriate, namely if the expected harm to participants is high and the expected population benefits are low. In some instances, it will be obvious that a study ought to proceed, and it may even be ethically required to allow a study to proceed if the expected harm to participants is low and the expected population benefits are very high.

We think it is important that a consistent approach to answering this question be developed ahead of an outbreak. This will avoid decisions being made without guidance in emergency situations where the time and attention of important decision makers is limited.

Approaches and metrics for deciding if a study is permissible or required should be determined ahead of time. This would require further analysis with involvement of analytic ethicists, virologists, clinical trials specialists, and epidemiologists. The views of the public would also be important to include – this may take place through citizen juries, or other techniques that allow for informed preferences of the community to be elicited, and should utilise existing processes used by the UK Health Research Authority (Health Research Authority, no date).

In this section we describe one possible approach, but this is intended as a starting point for discussion. The process of developing an approach for use in decisions about CHIM research in the UK should involve ethicists, scientists, policymakers and members of the public.
8.1 A possible model

Here we outline one possible model for determining whether participant expected harms are justified by population expected benefits. It involves defining categorical levels of risk, based on the expected harm to participants, and using these as a guide to the required degree of expected population benefit for the study.

Requiring a greater amount of expected population benefit and greater confidence in the assessment when there is greater risk to participants can help to ensure appropriate respect to participants who are taking on greater personal risk. Studies that pose low risk to participants may be justified by any population benefit, and could be considered required (i.e. efforts made to conduct the study if there are people voluntarily seeking participation in such a study) if the expected population benefit is high. Studies that pose higher risk would only be considered if the benefits were sufficiently high. A representation of this model is shown in Table 2.

It may also be appropriate to have more stringent requirements for studies that have moderate or high expected participant harm. For example, it may be appropriate to have higher standards for consent for these studies. This might take the form of formal tests of comprehension or requiring a minimum education level for participants. It may also be appropriate to require rapid and open access of data from studies with higher risk, to ensure that benefits are maximized. It may also be appropriate to compensate participants more highly for study participation.

Table 2: Comparing expected population benefit to expected participant risk

<table>
<thead>
<tr>
<th>High participant expected harm</th>
<th>Moderate participant expected harm</th>
<th>Low participant expected harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high expected benefit</td>
<td>High expected benefit</td>
<td>Moderate expected benefit</td>
</tr>
</tbody>
</table>

However, this model requires an assessment of what constitutes each level of expected benefit and harm. This assessment could be made qualitatively, possibly by the consensus of a specially formed committee. However, there may be value in exploring quantitative models that could be used to inform assessments. This would include quantitative models to assess the amount of expected harm to participants, expected benefits to the population, and how to compare these.

8.1.2 Defining level of risk

We propose the following as possible definitions of low-, moderate- and high expected harm for participants in CHIM research. We have used mortality risk as a proxy for overall expected harms, but there would be value in developing a more sophisticated model that could account for all the expected harms and benefits outlined above. Qualitative research could help to develop a more nuanced assessment of risk that takes into account the variation of how risk is valued across the population.

- Low expected harm would be comparable to risks that are commonly encountered in everyday life, such as the yearly risk of dying in a road traffic accident, which was roughly 1 in 40,000 in the UK in 2019. We could consider this risk, 1 in 40,000, to be the upper limit of low expected harm considering mortality risks only.
- Moderate expected harm would be consistent with levels of risk that are accepted for other altruistic acts, including organ donation. Moderate expected harms defined by mortality risk could be considered 1 in 40,000 to 1 in 500.
- Studies that carry a mortality risk of above 1 in 500 could be considered high expected harm.

8.1.3 Determining benefits required by risk level

A possible approach to determine when benefits justify risks is to require benefits to increase non-linearly as expected harms to participants increase. In situations of low expected harm, we would only require there to be an expected population benefit as justification. In situations of moderate expected harm, we would require the expected benefits to be substantially greater than the participants and the general population would require consideration of a far greater number of factors. It would be appropriate to develop interactive models that allow many factors to be considered together to provide a qualitative or quantitative assessment of expected harms and benefits that can then be compared. These models should include consideration of the uncertainty of estimates. It would also be necessary to consider the effects of waiting to gain more information before deciding whether or not to conduct the study. Ideally these estimates would be provided in quality-adjusted life years, or well-being adjusted life years.

Development of these models would be a complicated task and is beyond the scope of this report. Here we outline factors to be included in these models and discuss how the results may be presented and compared. Equations that may be helpful for generating these estimates are provided in Appendix D.
expected harm, perhaps continuing to rise linearly, but at a steeper gradient than for studies with low expected harm. For studies with high expected harm, we might expect the benefits to increase non-linearly with greater risk.

It might be possible to develop a quantitative approach to comparing levels of risk to participants with the required expected benefits to the population. As an example, we might say that the ratio of expected population benefit to expected participant harm only needs to be 1:1 in low-risk studies, needs to be 100:1 in medium-risk studies, for high-risk studies should be 10000*x:2:1 where x is the ratio of risk to 1% (or 1000:1 when the risk to participants is considered high but below 1%). For example, this would result in a study with a 10% mortality risk requiring a benefit to harm ratio of 100,000:1.

These multipliers on the required population benefit, to account for greater personal participant risk and for the risk to public trust, are shown in Table 3.

Table 3: Possible model for determining when population expected benefits justify participant expected harms

<table>
<thead>
<tr>
<th>Comparable risks</th>
<th>Ratio of expected benefits to expected harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Dying in a road traffic accident in the UK</td>
</tr>
<tr>
<td>Medium risk</td>
<td>Organ donation</td>
</tr>
<tr>
<td>High risk</td>
<td>Climbing Mt Everest and other higher risk activities</td>
</tr>
</tbody>
</table>

It would also be appropriate to decide when studies should be considered required, rather than just permissible. One option would be to consider studies that meet the level of expected benefit for higher risk levels ought to be considered required (assuming that there are prospective participants who want to volunteer and there isn’t a better use of the resources required for the study). So, a study with low participant expected harm that has an expected population benefit to participant harm ratio of 1000:1 or greater should be considered required. The formula for required benefit for studies with high participant expected harm complicates the use of this approach for studies with a participant mortality risk below 1%, but we can use a risk of 10% as a conservative proxy, such that a study with moderate expected harm that has a population expected benefit to participant expected harm ratio of more than 20,000:1 should be considered required.

This approach suffers from a threshold problem. It seems strange to think that a study with a mortality risk of 1 in 39,000 should be considered dramatically different to a study with a mortality risk of 1 in 41,000. Therefore, it makes sense to have flexibility when using this approach and consider other factors such as population or participant enthusiasm for the study or the degree of uncertainty in estimates of benefit and harm.

8.1.4 Limitations of this approach

This approach has important limitations. Firstly, quantitatively estimating the expected benefits and harms of a study will be very difficult and there will be substantial uncertainty in all estimates. Unless care is taken in developing and interpreting the models there is a risk that decision-making might be negatively influenced by overly simplified models that do not include all the relevant considerations or communicate uncertainty sufficiently. Similarly, the model as described does little to incorporate the importance of uncertainty in decision-making. It seems likely that as well as requiring greater estimates of benefit, higher-risk studies should also require greater certainty in expected outcomes. The model would also need to account for how time would influence estimates, including values of effects and level of uncertainty. Finally, the value of many outcomes will vary between people, as will risk tolerance. Therefore, an important challenge would be developing an approach that reconciled a diversity of viewpoints.

We believe that the above comparisons of risks and benefits are plausible. However, the approach used to answer this question should be developed with input from ethicists, scientists, policymakers and members of the public.

8.2 Considerations for outside the context of an outbreak

The absence of pathogen circulation changes the risk scenario. In this context, the risk of precipitating an outbreak and the potential for enhancement of pathogen transmissibility become major components of the risk of a CHIM study. Conducting a study with a pathogen of pandemic potential runs the risk of generating a local outbreak or even a pandemic and as such there should be a strong presumption against conducting these studies.

Even when pathogens have lower transmissibility among humans there is a risk that a CHIM study may enable the pathogen to adapt to the human host and become more transmissible. Deliberate infection of humans with pathogens creates an opportunity for the pathogen to adapt to the human host. For this reason, we suggest that it would usually not be appropriate to conduct CHIM studies with pathogens that have high virulence that are not currently circulating in humans, regardless of the level of individual risk posed to participants. Even if there was a subset of the population that faces low individual risk, the population risk posed by a potential outbreak should prevent a study going ahead.

It may be possible that the potential benefit of conducting a CHIM study with a high virulence pathogen with pandemic potential is so great that it could be justified.
if suitable containment infrastructure existed, and extraordinary safety protocols were implemented.

This consideration would not preclude a CHIM study using a low-virulence prototype pathogen, or an attenuated version of the pathogen of interest.

9. Recommendations

Based on our analysis we make the following three major recommendations for ensuring appropriate and ethical use of CHIM research for mitigating pandemic risk:

1. Establish a clear 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

Each of these recommendations is accompanied by several sub-recommendations that suggest concrete actions to be taken in support of the major recommendations.

9.1 Establish a clear mechanism for determining when a CHIM study with a PPP is in the public interest

In our framework, determining when a CHIM study is in the public interest is a key question. It's a question that involves significant empirical uncertainty, especially in the setting of an outbreak of a novel pathogen, and normative uncertainty. It requires an estimation of the expected harms and benefits of conducting a CHIM study and an ethical judgement to be made on whether the expected benefits to the population justify the expected harms to participants. Having mechanisms in place ahead of time to make this decision would help to ensure that decision-making in an emergency is informed, well-reasoned, procedurally fair and efficient. Therefore, we make the following sub-recommendations, which we think will help achieve this aim.

Recommendation 1.1 – Establish a process to determine when expected benefits ethically justify expected harms

A key ethical question in CHIM research is when the expected benefits to society ethically justify the expected harms to participants. This is a question that should have a pre-determined approach for coming to an answer. We have presented one possible framework. However, given the importance of this criterion for ethical research, we recommend further work to develop an explicit, justifiable, reproducible approach to this question that is logically consistent, procedurally fair and informed by all relevant stakeholders. This should include ethicists, members of RECs, scientists, epidemiologists, public health specialists, policymakers and members of the public.

Recommendation 1.2 – Develop models to quantify benefits and risks of CHIM studies with PPPs

Making a judgment on whether a study is in the public interest requires an estimation of its expected benefits and harms. To provide this information, we suggest the development of computational models to assess the impacts of CHIM studies in different scenarios. These should be developed for different types of pathogens (e.g. airborne respiratory viruses, vector-borne viruses, etc.), and for studies in an outbreak scenario and in the inter-pandemic period.

Economic models should also be developed to allow for rapid estimation of the cost-effectiveness of conducting a CHIM study in different scenarios. This would require a costing exercise to systematically estimate the costs of conducting CHIM studies, which could be combined with an estimate of the study impacts to develop a cost-effectiveness estimate.

It would be important to recognize the limitations of these models and avoid putting too much weight on estimates that might seem highly precise but could be very inaccurate. It would also be important to include uncertainty in these models and ensure this was clearly communicated to decision-makers. This might call for results to be presented as confidence intervals rather than point estimates. However, despite their limitations, we believe that quantitative models can aid decision-making, especially when the alternative is to rely on intuitive judgments that might be poorly informed. Models can be helpful to clarify areas of uncertainty and elucidate the implicit assumptions driving intuitive judgements.

Recommendation 1.3 – Identify example scenarios where CHIM research would be appropriate in an outbreak setting

The models described in Recommendation 1.2 should then be used to identify scenarios where CHIM studies are likely to be in the public interest. Outbreak scenarios and scenarios in the inter-pandemic period should be considered. Details to include are pathogen and outbreak features, political and social factors, and mitigation measures, such as the availability of current vaccines, or the expected difficulty of developing an effective vaccine. Before conducting this research, careful thought should be given to the potential for malicious use of the results.
and steps taken to reduce this risk. After understanding the types of scenarios where CHIM studies may be useful, the likelihood of these scenarios occurring should be estimated.

**Recommendation 1.4 – Develop processes to understand and monitor public sentiment to CHIM research**

One of the key concerns raised about a CHIM study during the COVID-19 pandemic was the possible effect on public trust in vaccines and science. Being able to understand how public sentiment is changing in a dynamic situation like a pandemic would enable more informed estimates of the potential effect of a CHIM study on public trust. Understanding public sentiment may also be helpful for decision making. Although it ought not to play a deciding role in the decision of whether a study should go ahead, public sentiment should be one input into the decision.

This should build on existing structures to understand opinions of the UK public on health research, such as the NIHR Centre for Engagement and Dissemination. It may also build on processes used by the team responsible for the SARS-CoV-2 CHIM study to understand public sentiment. These procedures should be able to be used to monitor changes in public sentiment over the course of an outbreak.

**Recommendation 1.5 – Develop educational materials for policymakers and the public**

To ensure that decision-making is informed and minimize the risks of impairing public trust, policymakers and the public should have an understanding of the nature of CHIM research. Educational materials should be developed to inform the public of the nature and history of challenge studies, and their potential benefits. This may include comparison of the risks with other altruistic activities, such as organ donation, firefighting and military service.

**Recommendation 1.6 – Establish a group who would be charged with making the determination of when a CHIM study during a public health emergency would be ethically justified**

As outlined in Section 5, public health emergencies present special situations that call for changes to standard procedures. Due to the close involvement of research with government policies and the need for coordination across actors in this setting, we recommend that the determination of whether a CHIM study is in the public interest should be made by a group composed of representatives from relevant government agencies including the HRA, funders, ethicists, and scientists. This composition of this group and procedures for its conduct should be established ahead of time.

9.2 Establish procedures to streamline ethics review of CHIM studies with PPPs

While the ethics review process for the SARS-CoV-2 CHIM studies did not delay the research, we think additional measures could be taken to reduce the risk of CHIM research with PPPs being unnecessarily delayed, or of being conducted unethically. Therefore, we make the following sub-recommendations to help to streamline the ethics review of CHIM studies with PPPs.

**Recommendation 2.1 – Maintain a standing Specialist REC for CHIM research in an outbreak**

For the approval of the SARS-CoV-2 CHIM studies a Specialist Ad-hoc REC was assembled to ensure thorough and timely ethics review of the studies. We recommend that this Specialist REC be maintained as a standing group to ensure the relevant expertise is available to review proposals for a CHIM study in an outbreak. The composition of the standing group may change over time, and members should receive additional training on considering CHIM studies and the ethical issues they raise. The group should include ethicists, infectious disease experts, epidemiologists and modelers.

**Recommendation 2.2 – Adapt the HRA REC checklist to develop a special checklist for CHIM research with PPPs**

The HRA has a checklist for RECs to use when reviewing research proposals. We recommend adapting this checklist for CHIM research with PPPs. This would include adding additional questions on the involvement of policymakers, funders and regulators in determining whether the study is in the public interest, as well as details on special consent procedures, communications with local health authorities and plan for rapid release of results.

**Recommendation 2.3 – Create template protocols for CHIM studies with PPPs**

Template protocols should include plans for deciding on sample size, statistical analysis, recruitment procedures, informed consent procedures, study procedures including inoculation, monitoring, treatment, follow-up, management of adverse events and participants wishing to withdraw from the study.

**Recommendation 2.4 – Develop informed consent procedures for CHIM research**

CHIM studies with PPPs are likely to involve greater amounts of uncertainty in risks and benefits than most other types of research studies. In some instances, they may also carry greater risks of death or serious injury. Therefore, there should be special procedures developed
to ensure that the participants understand the risks they are volunteering to accept and the uncertainty in the risk estimates. This may include educational materials and a test for understanding, particularly for a quantitative understanding of risk and uncertainty.

**Recommendation 2.5 – Review the approach to compensation for higher-risk research in the UK**

Currently HRA recommends against including payment for risk in compensation for research participants. For reasons described above we believe that providing payment for risk is an important component of ensuring fairness in CHIM research. Therefore, we recommend the policy on compensation in research be reviewed.

A system of payment for CHIM research participation should be developed ahead of time. This should have an agreed upon approach to payment for study participation that includes the time, discomfort and pain of study participation, payment for risk, and a system of compensation for harms that may occur as a result of the study. Appropriate rates of payment for risk could be informed by rates of hazard pay in other types of employment in the UK, including the military.

Qualitative research should be conducted with prospective CHIM study participants to ensure that the rate of payment is considered fair but not unduly coercive.

**Recommendation 2.6 – Develop a template communications plan for CHIM research in an outbreak**

A communications plan should be developed. This should include plans for communication with national and international policymakers, other members of the CHIM research community, the local public health authority responsible for a CHIM site, and members of the public, including through media releases and social media communications.

The communications plan should include plans for publishing study results and data accessibility. Although open access to data and study materials should generally be encouraged, thought should be given to potential misuse of data and publication plans should be adjusted to mitigate this risk if relevant.

**9.3 Develop and maintain the infrastructure and expertise required to conduct high quality CHIM studies efficiently**

A key finding of our analysis was the importance of enabling CHIM research to happen efficiently in an outbreak. As we learned through COVID-19, in a rapidly spreading outbreak, delays can influence whether thousands of people die, and whether thousands of others lose their jobs or experience significant financial hardship. Therefore, there is important benefit from gaining information that could improve the pandemic response as quickly as possible.

Major factors influencing the speed with which a challenge study could be conducted were the speed with which sufficient stock of challenge agent could be produced, the availability of appropriate facilities and expertise to conduct CHIM studies. Our discussions with experts also highlighted the role the CHIM studies could play in developing medical countermeasures for PPPs ahead of time, which would also help to maintain readiness in a pandemic. Therefore, we make the following sub-recommendations that aim to improve the speed at which a CHIM study could be conducted.

**Recommendation 3.1 – Produce a report on the expertise and facilities available to conduct CHIM research in the UK and globally and the feasibility of maintaining this capacity**

The report should include information on the investment needed to conduct CHIM studies and the feasibility of sustaining the necessary investment. This should include the investment required to maintain readiness to conduct urgent CHIM studies upon detection of an outbreak with pandemic potential.

The report should include an analysis of the current CHIM research capacities in the UK and the impacts of increasing CHIM research on the research and clinical workforce. It should also include analysis of the requirements for manufacturing challenge strain and the impacts of diverting laboratory resources to this task during a major infectious disease outbreak.

**Recommendation 3.2 – Conduct a roundtable discussion to discuss the role of CHIM research in development of medical countermeasures against PPPs prior to another pandemic**

Several groups have highlighted the potential role of developing vaccines for prototype pathogens in reducing pandemic risk. The speed with which the COVID-19 vaccine was developed was partly due to previous research aimed at developing vaccines for the coronaviruses responsible for MERS and SARS-1. We recommend a roundtable discussion be held with key figures in the efforts to develop such prototype pathogens to discuss the role that CHIM research in the UK could play in these efforts. This should include scientists leading relevant research, CEPI and the WHO, as well as representatives from the UK government and major research funders.
Recommendation 3.3 – Review the procedures for manufacturing challenge agent and identify options for accelerating this process in an outbreak

Our analysis highlighted that the development of sufficient stock of challenge agent is one of the key determinants of how quickly a CHIM study could be conducted, and a key limit on the value of studies.

Procedures should be developed to ensure that challenge agent manufacture can begin as soon as there is an indication of an outbreak with a PPP or novel agent that may have pandemic potential. This should occur immediately and before any decision has been made on whether a CHIM study would be helpful. Options for speeding up the production of challenge agents should be explored, including the use of reverse genetics or synthetic biology. These options should be reviewed by biosecurity experts to assess their dual-use potential. Another possibility that would require further evaluation is developing a library of potential challenge viruses consisting of prototype pathogens that cause mild disease.

Consideration should also be given to when, if ever, it might be appropriate to use challenge agent that is not developed to GMP standards. It seems plausible that this would be appropriate in some circumstances, e.g. where the agent posed an urgent and significant threat to large numbers of people.

Recommendation 3.4 – Investigate the potential for conducting person-person transmission studies

Given that the time taken to develop sufficient challenge agent can be an impediment to CHIM studies, it would be worth exploring alternative study types that can be conducted more rapidly. Person-person transmission studies are one option. These retain many of the benefits of CHIM studies, but lack the level of control found in CHIM studies. For this reason, they are likely to be a second choice to CHIM studies, but may have a role to play in investigating highly transmissible pathogens when rapid answers are required.

Recommendation 3.5 – Develop a roadmap to ensuring CHIM research capacity for pandemic preparedness

A plan should be developed to ensure that capacity is developed to conduct research to a high standard and in a timely manner in the inter-pandemic period and at the onset of an outbreak with pandemic potential. A roadmap with necessary steps and timelines should be developed. This should integrate with existing pandemic preparedness plans.
References


Dawson, L., Earl, J. and Livezey, J. (2020) ‘Severe Acute Respiratory Syndrome Coronavirus 2 Human Challenge


Our World in Data (no date) *COVID-19 Data Explorer - Our World in Data*. Available at: https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=40..


### Appendices

#### Appendix A

**Search Strategy**

**Ethical issues in CHIMs**

- PubMed: (ethic*) AND (“controlled human infection”) OR (“human challenge”) OR (“controlled infection”) OR (“human infection challenge”) OR (“controlled human malaria infection”)
- PhilPapers: ethic* & “human challenge” | “controlled infection” | “controlled human infection” | “controlled human malaria infection”
- Google Scholar: (ethics OR ethical) AND (“controlled human infection”) OR (“human challenge”) OR (“controlled infection”) OR (“controlled human malaria infection”)

Additional references to be sourced from citations of relevant materials

#### Appendix B

**List of interview questions**

The specific questions that CHIM studies are well-placed to answer regarding PPPs.

- What questions are controlled human infection model studies well-placed to answer regarding pathogens with pandemic potential? This might include questions during the inter-pandemic period, or questions that arise once a pandemic has started or an outbreak of a novel pathogen has been detected.
- To what extent can CHIM studies (or controlled natural exposure CHIM studies) be used to evaluate efficacy of non-pharmaceutical interventions including those like ventilation, filtration, and UV light that could be put in place pre-pandemic?
- To what extent can CHIM studies be used on the pre-pandemic regulatory pathway for prototype or universal vaccines or therapies against PPPs, including both potential purchase for a stockpile and
for accelerating regulatory authorization during a pandemic?

- What hypotheses about PPPs (such as those concerning transmission, pathogenesis, and immunology) can be developed via CHIM studies and where can CHIM studies test hypotheses?

The benefits and risks of conducting CHIM studies for these questions, relative to alternative research approaches or not conducting this research.

- What are the benefits of answering these questions?
- Do you think other types of studies could be done to answer these questions? To what extent are other study methodologies (e.g. animal challenge, in vitro, ex vivo, natural history) substitutes or complements to challenge? How can challenge data be integrated into existing methodologies to enhance understanding?
- If so, what would be the advantages and disadvantages of using a controlled human infection study?

PPPs that are the most likely candidates for CHIMs in the pre-pandemic period.

- Which pathogens and pathogen families are candidates for controlled human infection studies in the pre-pandemic period?
- What makes these pathogens more suitable for this type of study?
- To what extent are there pathogens that may be too virulent to be candidates for pre-pandemic challenge but could potentially be attenuated so as to have acceptable levels of safety and scientific validity? Are there pathogen families where a less virulent member exists that can be used in a challenge model (e.g. endemic betacoronaviruses serving as a potential challenge)?

How benefits can be maximised and risks minimised.

- If you or another researcher were to undertake these studies (or other controlled human infection model studies using pathogens of pandemic potential) how could those benefits be maximised?
- How could the risks and harms be minimised?

Best practice for conducting CHIM studies.

- What features of these studies are important when considering best practice in conducting controlled human infection model studies?

Anticipated technical or regulatory challenges.

- What do you think the greatest barriers are to conducting useful controlled human infection model studies? This might include technical or regulatory challenges, or any other type of barrier.
- How can tradeoffs between safety and representativeness best be managed?

Requirements (including preparation, infrastructure, regulatory environment, financial and human resources) for conducting ethical CHIM studies.

- In your view, what requirements are there to conduct these studies ethically? This might include physical requirements, such as facilities and healthcare access, and may include other types of requirements, such as support from communities, or a regulatory environment that can act on results of these studies.

Ethical uncertainties in conduct of CHIM studies.

- Do you have any concerns or considerations about the ethics of controlled human infection model studies with pathogens of pandemic potential that we haven't discussed yet?
- To what extent is it common to have pathogens like COVID where population subsets (like young healthy people) have significant less risk than populations overall?
- What do you think the ceiling of individual risk should be? How do you think we should determine this?

List of interviewees

- 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

Appendix C

US NIAID list of pathogens of high pandemic and epidemic potential

**Coronaviridae**
- Including coronaviruses, such as SARS-CoV-2

**Orthomyxoviridae**
- Including influenza viruses

**Bunyavirales**
- Including viruses causing haemorrhagic fever, such as hantavirus

** Arenaviridae**
- Including viruses causing haemorrhagic fever, such as Lassa virus

**Filoviridae**
- Including viruses causing haemorrhagic fever, such as Ebola virus and Marburg virus

**Flaviviridae**
- Including the flavivirus family, such as Yellow fever virus, Dengue virus and Zika virus

**Paramyxoviridae**
- Including Hendra virus, Nipah virus and human parainfluenza viruses

**Picornaviridae**
- Including enteroviruses and rhinoviruses

**Togaviridae**
- Including Chikungunya virus and Barmah Forest virus

**WHO prioritized diseases for research and development in emergency contexts**

- COVID-19
- Crimean-Congo haemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle Eastern respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- “Disease X”

**CEPI Priority Diseases**

- MERS
- Lassa fever
- Nipah
- Disease X
- Rift Valley Fever
- Chikungunya
- Ebola

Appendix D

Equations for calculating expected participant harm and expected population benefit

The expected participant harm can be summarized as:

$$ - (((O_{inf})(RR_{care})+H_{study}) + ((O_{inf})(P_{ci})+(B_{ipr})(P_{study})) $$

Where $O_{inf}$ = the health outcomes from infection, $RR_{care}$ = the risk reduction from additional care provided in the study, $H_{study}$ = study harms, $P_{ci}$ = probability of infection in the community, $B_{ipr}$ = the personal benefits of an improved pandemic response and $P_{study}$ = the probability that the study will lead to the improved pandemic response.

Ideally this would be calculated in either quality-adjusted life years, or a measurement of wellbeing, such as well-being adjusted life years.

This expected population expected benefit of the study can be summarized as:

$$ (I_{goal})(P_{study}) - ((E_{hp})(N_{p})+(I_{sae})(P_{sae})+(I_{mu})(P_{mu})) $$

Where $I_{goal}$ = the expected impact of the goal of the study, $P_{study}$ = the probability that the study will achieve that goal, $E_{hp}$ = the expected harm for participants, $N_{p}$ = the
number of study participants, $I_{sae}$ = the expected impact of a serious adverse event, $P_{sae}$ = the probability of a serious adverse event, $I_{mu}$ = the expected impact of malicious use of the study results, and $P_{mu}$ = the probability of malicious use of the study results.

As with the participant expected harm, this should ideally be measured in quality- or well-being adjusted life years.

Appendix E

Checklist for ethical CHIM research

**Is there a clear scientific rationale for the study?**
- Does the study address a research question that is likely to lead to beneficial changes to public health policy?
- Are the methods of the study likely to answer the research question?

**Have the potential harms of the study been considered thoroughly?**
- Have all relevant harms to participants been considered?
- Have all relevant harms to the local population around the study site been considered?
- Have all relevant societal harms been considered?
- Have risks of misuse of study results been considered?
- Have the potential harms been minimized to the extent that the research aims can still be met?

**Have the potential benefits of the study been considered thoroughly?**
- Are the potential benefits of the study realistic?
- Is the method for estimating the potential benefits of the study appropriate?

**Do the expected benefits of the study justify the expected harms to participants?**
- Is the method for coming to the decision that the expected harms are justified clear?
- Has an explanation been provided for this method?

**Are there better methods to achieve similar benefits?**
- Have all relevant alternative research options been considered?
- Has an adequate explanation been provided for why the proposed study is preferable to alternatives?

**Is the process for gaining participant consent likely to yield adequately informed, voluntary consent?**
- What information has been provided to participants?
- How has participant understanding been assessed?
- Have procedures been developed to allow participants to withdraw from the study without compromising safety?

**Is the proposed compensation for participation fair?**
- How was payment calculated?
- Does payment cover participant time, study harms, and risk?
- Is there a system for providing compensation should an adverse event occur?
- Is there adequate follow-up to monitor for longer-term adverse events?

**Does the study involve vulnerable groups?**
- Does the study involve any of the following groups as participants?
  - People under the age of 18
  - People with cognitive impairment
  - People with mental illness
- Does the study target populations that are likely to experience social disadvantage?
- If yes to any of the previous two questions, is there a justification for this choice and have adequate protections been put in place to protect the interests of participants and ensure requirements for voluntary, informed consent are met?

**Is the study likely to benefit the community resident in proximity to the study site?**
- If it is unlikely to benefit this group, has approval from the relevant authority been obtained?
Is there a plan for communication with:

- Local public health authority
- Local healthcare services
- National policymakers
- Relevant international groups
- Participants and their families
- Members of the public

Has the study been reviewed by an independent expert group?

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About this report

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About the UK Pandemic Ethics Accelerator

The UK Pandemic Ethics Accelerator by the Oxford Uehiro Centre of 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.

About 1Day Sooner

1Day Sooner aims to reduce the global burden on infectious disease and avert future pandemics by working to accelerate the development and implementation of vaccines, treatments, and medical interventions. They do so as advocates for people who want to be in high-impact medical studies, including human challenge studies.