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Ethical Frameworks for Human Challenge Trials in Infectious Disease Research

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ABSTRACT

Human challenge trials deliberately infect healthy volunteers with a pathogen to accelerate vaccine development, and the practice moved from a research niche into public debate when a SARS-CoV-2 challenge model was proposed during the COVID-19 pandemic.

This review synthesizes the ethics literature on controlled human infection models, including the permissibility criteria built around treatable disease and scientific necessity, and the difficulty of informed consent when a study offers no direct benefit to the volunteer.

We examine the dispute over compensation, where higher payment is framed either as undue inducement or as fair recognition of risk, alongside the problem of risk to third parties who never consented, particularly for transmissible respiratory pathogens.

We also consider equity concerns raised when challenge models for diseases such as malaria and typhoid are sited in low- and middle-income countries, where the population bearing research risk may not see proportionate benefit.

We conclude that no single criterion renders a challenge trial permissible alone, and that a defensible study requires treatable disease, informed consent, fair compensation, third-party risk containment, and equitable siting together, which is why most candidates still fail to qualify.

Keywords: human challenge trials; controlled human infection models; research ethics; informed consent; vaccine development

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INTRODUCTION

A human challenge trial does something ordinary

clinical research studiously avoids: it deliberately infects a healthy volunteer with a pathogen in order to learn something faster than waiting for natural

exposure would allow. Controlled human infection models (CHIMs), as the broader class of studies is usually called, have been used for decades in malaria and typhoid vaccine development, but the practice moved from a specialist corner of infectious disease research into public view when researchers proposed deliberately infecting volunteers with SARS-CoV-2 to speed COVID-19 vaccine trials [1]. That proposal forced bioethicists, regulators, and the public to revisit questions that had mostly been settled by convention rather than by sustained argument: how much risk a volunteer may consent to on behalf of accelerating a public good, what counts as adequate understanding of a pathogen whose natural history is still being characterized, and whether the traditional case for challenge studies holds up when the disease in question has no reliable rescue treatment.

The ethical literature on human challenge trials did not begin with COVID-19, and it is worth being clear about that, because much of the recent commentary reads as though it did. Systematic reviews of the reasons researchers and ethicists actually give for permitting these studies find a fairly stable core of justifications going back well before 2020: the scientific value of controlled exposure, the practical impossibility of achieving equivalent knowledge through field trials in some settings, and the volunteer's own considered willingness to accept risk [2]. What changed with the pandemic was not the ethical architecture but the stakes attached to getting it right quickly, under public scrutiny, for a pathogen that killed people who caught it naturally. This review surveys that architecture as it stands today: the conditions under which challenge trials are considered permissible, the specific difficulties of consent and risk communication they raise, the long-running argument over paying participants, the problem of risk to people who never enrolled, and the equity concerns that arise when challenge models are proposed for use in lower-income settings.

THE ETHICAL CASE AND ITS LIMITS

The standard ethical case for human challenge trials rests on a comparison: relative to a conventional field efficacy trial, a challenge study can answer some scientific questions with a fraction of the participants, in a fraction of the time, because the researcher controls exposure rather than waiting for it. Proponents of this reasoning have argued that this efficiency is not merely a convenience but itself an ethical consideration, since faster answers about vaccine efficacy or pathogen biology can translate into earlier protection for populations at large during an outbreak [3]. Early proposals to use a human challenge model for SARS-CoV-2 leaned heavily on this argument, framing accelerated vaccine licensure as a benefit large enough to justify substantial individual risk to a small number of informed volunteers [1].

The limits of that argument became clearer once

commentators worked through what "acceptable risk" would actually mean for a virus whose long-term effects were, at the time, still poorly characterized and for which no reliably effective rescue treatment existed. A widely discussed set of ethical criteria for human challenge studies more generally holds that a permissible challenge trial needs, at minimum, a treatable or self-limiting disease course, a low risk of severe outcomes even without treatment, and a scientific question that genuinely cannot be answered as well another way [4]. Analyses written specifically for the SARS-CoV-2 proposal attempted to work out what risk threshold this standard would actually permit, generally concluding that a young, healthy volunteer population, careful pre-screening, and immediate access to the best available supportive care could bring individual risk down to a level comparable to other accepted research risks, though estimates of exactly how low varied considerably depending on the assumptions used [5]. When the SARS-CoV-2 challenge model was later extended to study emerging variants rather than the original strain, the ethical calculus had to be redone rather than assumed to carry over, since transmissibility and severity are not fixed properties of "the virus" once new lineages are circulating [6]. More recent efforts to formalize this reasoning have tried to build explicit risk thresholds and stopping rules into CHIM protocols themselves, rather than leaving the acceptable-risk judgment to case-by-case ethics committee discretion each time [7]. Table 1 summarizes how this permissibility framework has been applied, or found to strain, across several of the pathogens that have actually been used in challenge studies to date.

Table 1. Application of the standard permissibility criteria for human challenge trials across pathogens that have actually been used in challenge studies.

Pathogen class	Disease course	Rescue treatment available	Main permissibility concern raised in the literature
Malaria	Self-limiting if treated promptly	Yes, highly effective antimalarials	Long-standing precedent, but mosquito-vector containment still requires strict facility protocols
Typhoid	Self-limiting if treated promptly	Yes, antibiotics	Well-established model, though attenuated strains raise questions about translational validity
Influenza	Usually self-limiting	Yes, antivirals and supportive care	Containment of respiratory shedding to protect staff and household contacts

Pathogen class	Disease course	Rescue treatment available	Main permissibility concern raised in the literature
SARS-CoV-2	Variable, some severe/long-term outcomes	Limited at time of first proposals	Whether risk could ever be characterized well enough for genuine informed consent
Hepatitis C	Often asymptomatic acute phase, but chronic risk	Yes, direct-acting antivirals	Uncertain long-term natural history for models using novel strains

CONSENT, UNDERSTANDING, AND THE BOUNDARIES OF AUTONOMY

Standard informed consent doctrine assumes a participant can weigh a reasonably well-characterized risk against a reasonably well-characterized benefit. Human challenge trials complicate this on both sides of the ledger. The benefit to the individual volunteer is typically nonexistent or negligible -- these are not therapeutic interventions -- so the entire ethical weight rests on the volunteer's willingness to accept personal risk for a collective scientific gain, which raises the practical question of whether volunteers actually understand that distinction rather than half-believing, as therapeutic misconception research elsewhere has documented, that participation carries some personal medical upside [8]. On the risk side, a pathogen newly adapted for challenge-study use, as with early hepatitis C virus models, may carry genuinely uncertain long-term consequences that no consent document can characterize with confidence, because the relevant natural history data simply have not been collected yet.

This uncertainty is compounded when challenge trials are conducted in settings where researchers cannot assume the same baseline health literacy, language of consent documentation, or prior familiarity with clinical research that underpins much Western bioethics guidance. Work specifically addressing informed consent for controlled human infection studies in low- and middle-income countries has proposed a range of practical remedies -- community engagement prior to individual enrollment, iterative and staged consent processes, and independent local ethics oversight with genuine authority to halt a study -- precisely because a single consent conversation, however carefully conducted, may not adequately convey what a novel challenge model actually entails [9]. A recurring theme across this literature, echoed in the broader public-consultation research on challenge trials, is that ethics committees consistently rate the acceptability of a proposed study differently than members of the public do when both are shown the same protocol, which suggests that "informed consent was properly obtained" is a necessary but not sufficient marker of ethical soundness -- societal legitimacy is a separate

question from individual authorization [10].

COMPENSATION, RECRUITMENT, AND THE SPECTER OF EXPLOITATION

Because challenge trials offer no direct medical benefit, payment plays an unusually central and unusually contested role in recruitment. The core worry is not new to challenge studies specifically -- research ethics has argued for decades about when payment becomes "undue inducement," clouding a volunteer's judgment about risk rather than simply compensating their time -- but it becomes sharper when the risk being compensated is deliberate infection rather than, say, a blood draw or a day of clinic visits [11]. If payment must be high enough to attract volunteers willing to accept genuine infection risk, and if that population skews toward people with fewer other economic options, the study risks recruiting disproportionately from those for whom the payment functions less as fair compensation and more as an offer too costly to refuse.

A counter-argument, made by researchers who think the standard "undue inducement" framing is itself paternalistic, holds that treating higher payment as inherently coercive infantilizes participants who are capable of judging trade-offs for themselves, and that the more consistent ethical failure is actually underpaying people for meaningful risk while dressing the underpayment up as protection from exploitation [12]. Neither position has fully displaced the other in the literature, and the practical result in most challenge-trial programs has been a middle path: payment scaled to time and discomfort rather than explicitly to risk, disclosed transparently, alongside recruitment screening that does not deliberately target economically vulnerable populations. Whether that middle path actually resolves the underlying tension, or simply obscures it behind a compensation formula, remains an open question that resurfaces every time a new challenge model is proposed.

RISK BEYOND THE VOLUNTEER

A feature that distinguishes challenge trials from most other research is that the risk is not necessarily contained within the study population. A deliberately infected volunteer, particularly with a transmissible respiratory pathogen, can in principle infect household members, healthcare workers, or the wider community if containment measures fail, which is a risk category that standard individual-consent frameworks were never built to address, since the people put at risk by transmission never agreed to anything. Meeting reports from convenings on the influenza human challenge model have treated this containment question as a first-order design constraint rather than an afterthought, addressing quarantine duration, facility requirements, and viral shedding monitoring as core elements of any protocol rather than optional safety extras [13]. Reviews of controlled human

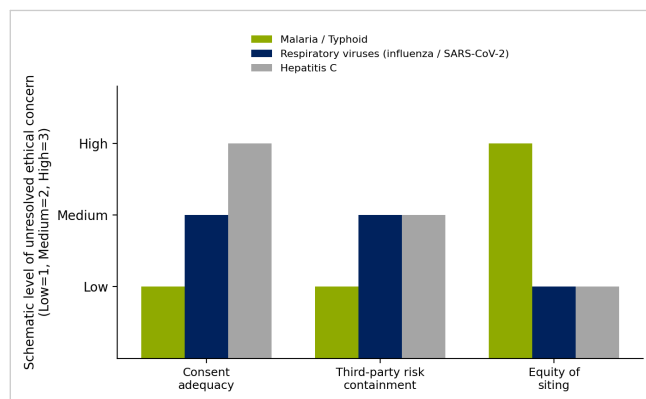
infection models used to accelerate vaccine development more broadly note that the pathogens that have been judged suitable for challenge work to date -- malaria, typhoid, certain respiratory viruses, and now hepatitis C under tightly controlled conditions -- are precisely those for which transmission risk to third parties can be reliably managed through isolation protocols, treatment on symptom onset, or biological features of the pathogen itself, such as malaria's dependence on a mosquito vector that a controlled inpatient setting simply removes from the transmission chain [14]. Where that containment cannot be assured with confidence, the ethical case for a challenge trial weakens considerably regardless of how favorable the individual risk-benefit calculation looks.

Stakeholder discussions convened specifically to refine the regulatory and ethical context for CHIMs generally have pushed toward standardizing exactly this kind of containment and monitoring requirement across institutions and jurisdictions, on the reasoning that ad hoc, study-by-study judgments about acceptable third-party risk produce inconsistent protections and make it harder for any single ethics committee to benchmark a novel proposal against established practice [15].

EQUITY IN THE USE OF CHALLENGE MODELS

Challenge studies for pathogens such as typhoid and malaria have long been conducted partly with an eye toward populations in low- and middle-income countries where those diseases remain endemic, since a vaccine candidate's real-world relevance depends on how it performs against locally circulating strains and in populations with different prior exposure histories [16] [17]. This raises a distinct equity question from the consent and payment issues already discussed: whether it is appropriate to site a challenge trial, with its attendant infrastructure and expertise requirements, in a setting where the eventual vaccine may or may not be made accessible to the population that bore the research risk. Jamrozik and Selgelid's influential analysis of this question argues that challenge studies conducted in endemic low- and middle-income settings are not inherently more ethically fraught than the same studies conducted elsewhere, provided the trial is genuinely responsive to local disease burden and local researchers have a substantive role in study design and governance rather than a purely administrative one [18].

Figure 1. Schematic comparison of how three recurring ethical concerns have been judged to resolve across three pathogen classes commonly used in human challenge research (illustrative synthesis of the qualitative literature discussed in this review, not a quantitative measurement).



Recent stakeholder consultations on siting a pneumococcal challenge study among people living with HIV in Malawi illustrate how this reasoning plays out in practice: the consultation process surfaced concerns not only about individual consent and third-party transmission but about whether a population already carrying a heavier burden of both infectious disease and structural health inequity should be asked to shoulder challenge-study risk at all, even with genuinely local input into the protocol [19]. Human challenge trials in vaccine development more broadly have been credited with real acceleration of typhoid and malaria vaccine candidates that might otherwise have taken years longer to reach field efficacy testing [20], which is precisely the kind of benefit that makes the equity question difficult rather than easy -- the same studies that raise legitimate exploitation concerns are also the ones most directly tied to protecting the populations bioethicists worry about exploiting. Figure 1 offers a schematic comparison of how three recurring ethical concerns -- consent adequacy, third-party risk containment, and equity of siting -- have been judged to resolve across three pathogen classes commonly used in challenge research.

CONCLUSION

Human challenge trials do not fit comfortably into the risk-benefit templates built for conventional clinical research, and the honest position emerging from two decades of ethical analysis, sharpened considerably by the pandemic-era proposals for SARS-CoV-2, is that no single permissibility criterion does all the necessary work on its own. A treatable or self-limiting disease course, genuinely informed consent that does not rely on unstated therapeutic misconception, fair rather than coercive compensation, reliable containment of risk to third parties, and equitable siting relative to who eventually benefits from the resulting vaccine are each necessary conditions, and none is sufficient in isolation. What the recent literature adds is not a formula that resolves these conditions into a

single test but a clearer sense of where the genuine trade-offs sit -- between speed and certainty, between individual autonomy and community consent, and between accelerating protection for a population and asking that same population to bear the research risk. Challenge trials will likely remain a valuable, tightly bounded tool for a specific class of pathogens rather than a general model for infectious disease research, precisely because the ethical conditions that make them defensible are demanding enough that most candidate pathogens and most proposed settings will continue to fail to meet them.

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Conflict of Interest

The authors declare no conflicts of interest relevant to this work.

Author Contributions

Kasper Larsen conceived the review and drafted the initial manuscript. Nils Mendes performed the literature synthesis on risk thresholds, compensation, and third-party transmission risk and critically revised the manuscript. Marius Eberhardt contributed the sections on equity and low- and middle-income country siting and provided final approval of the submitted version. All authors read and approved the final manuscript.

Ethics Statement

As a literature review synthesizing previously published, publicly available research and policy analysis, this article did not involve new data collection from human participants and did not require institutional ethics committee approval.

Data Availability

No new data were generated or analyzed for this review. All sources discussed are cited in the reference list and are publicly available through their respective publishers.

REFERENCES

- Eyal N, Lipsitch M, Smith PG (2020) Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure. *Journal of Infectious Diseases*.
- Katzer C, et al. (2023) Ethical Requirements for Human Challenge Studies: A Systematic Review of Reasons. *Clinical Pharmacology & Therapeutics*.
- Eyal N, et al. (2020) Ethics of controlled human infection to address COVID-19. *Science*, DOI:[10.1126/science.abc1076](https://doi.org/10.1126/science.abc1076).
- Ethical Criteria for Human Challenge Studies in Infectious Diseases (2016) *Public Health Ethics*.
- What risks should be permissible in controlled human infection trials? (2020) *Vaccine*.
- Ethics of Human Challenge Trials Using Emerging Severe Acute Respiratory Syndrome 2 Variants (2022) *Journal of Infectious Diseases*.
- Assessing Risk Thresholds in Controlled Human Infection Models (CHIM) (2025) *PMC*.
- Ethics of Controlled Human Infection Studies With Hepatitis C Virus (2023) *Clinical Infectious Diseases*, PMID:37579202.
- Informed consent for Controlled Human Infection Studies in low- and middle-income countries: Ethical challenges and proposed solutions (2022) *PMC*.
- Ethical acceptability of human challenge trials: Consultation with the US public and with research personnel (2024) *PLOS ONE*.
- When Does the Amount We Pay Research Participants Become "Undue Influence"? (2015) *AMA Journal of Ethics*.
- A Case for More Generous Compensation for Human Research Subjects in Non-Therapeutic Research (2021) *Columbia Journal of Bioethics*.
- Meeting report: Convening on the influenza human viral challenge model for universal influenza vaccines, Part 1 (2019) *Vaccine*.
- Controlled Human Infection Models To Accelerate Vaccine Development (2021) *Clinical Microbiology Reviews*, DOI:[10.1128/cmr.00008-21](https://doi.org/10.1128/cmr.00008-21).
- Refining the regulatory and ethics context of controlled human infection models -- a stakeholder meeting report (2026) *Vaccine*.
- Typhoid vaccine development with a human challenge model (2017) *PubMed*, PMID:28965714.
- Human challenge models: tools to accelerate the development of malaria vaccines (2019) *PubMed*, PMID:30732492.
- Jamrozik E, Selgelid MJ (2020) Ethical issues surrounding controlled human infection challenge studies in endemic low- and middle-income countries. *Bioethics*, DOI:[10.1111/bioe.12802](https://doi.org/10.1111/bioe.12802).
- Considerations in planning a controlled human infection model in at-risk groups in sub-Saharan Africa: the case for pneumococcal challenge in people living with HIV in Malawi and a report of stakeholder consultation (2025) *PMC*.
- Human challenge trials in vaccine development (2020) *PMC*.