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What risks should be permissible in controlled human infection model studies?

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Abstract

Controlled human infection model (CHIM) studies involve the intentional exposure of healthy research volunteers to infectious agents. These studies contribute to knowledge about the cause or development of disease and to the advancement of vaccine research. But they also raise ethical questions about the kinds of risks that should be permissible and whether limits should be imposed on research risks in CHIM studies. Two possible risk thresholds have been considered for CHIM studies. The first suggests constraining ethically permissible risks according to a minimal risk threshold and the second endorses a higher risk threshold that excludes irreversible or fatal infections. I argue that neither of these thresholds is persuasive and situate questions about risk thresholds in CHIM studies within a broader debate about permissible risks in research. I argue that risks in CHIM studies should be constrained according to limits on research risks that do not offer corresponding benefits in all studies rather than developing a unique risk threshold for CHIM studies. I then propose five recommendations for the ethical assessment of risk in CHIM studies.

KEYWORDS

challenge studies, clinical trials, controlled human infection model studies, ethics, research ethics, risk, risk threshold

1 | INTRODUCTION

Controlled human infection model (CHIM) studies are studies that involve the intentional exposure of research subjects to an infectious agent. CHIM studies contribute significantly to pathology and immunology research and are valuable for vaccine development.[1] But they also raise difficult ethical questions about whether and when it is permissible to deliberately infect a human subject with a pathogen. Most commentators agree that deliberate infection is ethically justifiable in some circumstances,[2] but not enough has been said about which circumstances are permissible and why.

One area of controversy concerns the degree of risk that should be ethically permissible. CHIM studies expose healthy volunteers to pathogens such as typhus, malaria, cholera, and

[1]Academy of Medical Sciences (2005). Controlled human infection model studies. Workshop summary; Academy of Medical Sciences (2018). Controlled human infection model studies. Workshop summary.

[2]Hope, T., & McMillan, J. (2004). Challenge studies of human volunteers: Ethical issues. *Journal of Medical Ethics*, *30*(1), 110–116; Bamberry, B., Selgelid, M., Weijer, C., Savulescu, J., & Pollard, A. (2016). Ethical criteria for human challenge studies in infectious diseases. *Public Health Ethics*, *9*(1), 92–103; Murdoch, B., & Caulfield T. (2017). The challenge of human challenge research models: A Canadian perspective. *Medical Law International*, *16*(4), 273–284; Miller, F., & Grady, C. (2001). The ethical challenge of infection-inducing challenge experiments. *Clinical Infectious Disease.* 33(7), 1028-1033. Anomaly, J. & Savulescu, J. (2019). Compensation for cures: Why we should pay a premium for participation in 'challenge studies'. *Bioethics* (early view). DOI: 10.1111/bioe.12596.

influenza that may involve considerable risks. Participation can also involve significant burdens such as mandatory isolation, multiple check-ups, and close monitoring. These potential risks are high enough to warrant concerns about the possibility of CHIM studies compromising public trust in research.[3] But it is not clear what limits (if any) should constrain the risks of CHIM studies.

One way to constrain risks in research is by invoking a moral threshold for allowable risk. Two possible risk thresholds have been considered for CHIM studies. The first suggests limiting ethically permissible risks according to a minimal risk threshold[4] and the second endorses a higher risk threshold excluding the possibility of irreversible or fatal infections.[5] In the following, I examine what risks should be permissible and what role a risk threshold should play in the ethical analysis of CHIM studies.

I argue (1) that existing proposals for risk thresholds are unsuccessful, and (2) that there may be no persuasive reason to develop a unique moral threshold for CHIM studies. (3) Instead, I situate questions about permissible risks in CHIM studies within a broader debate about the ethical permissibility of constraining research risks that do not offer corresponding benefit in research involving healthy, competent, fully informed, non-vulnerable subjects. (4) I argue that research risks without corresponding benefit should be constrained in CHIM studies as in other research studies. (5) Drawing on two case examples, I then propose recommendations for assessing permissible risk in CHIM studies.

2 | BACKGROUND

CHIM studies have been around for almost 300 years[6] and have enrolled thousands of volunteers, who have been exposed to over 60 different challenge strains,[7] including malaria, influenza virus, and typhoid.[8] They are used for a range of reasons,[9] including the understanding of pathogenesis and immunogenicity, establishing proof of concept, and guiding down-selection in vaccine research. They have played a central role in the development of vaccines for the prevention of cholera, typhoid, and malaria[10] and contributed to advances in vaccines for flu and dengue.[11]

Several rationales have been described for selecting CHIM studies. In vaccine development, they offer the advantage of increased speed and efficiency, since they facilitate the identification of both vaccine candidates that should be stopped and those that should be sped up at an early stage.[12] This allows researchers to limit field-testing of ineffective vaccine prototypes, which is expensive and requires a larger number of participants.[13] CHIM studies also play an important role in examining pathogens when there is no appropriate animal model[14] or when natural conditions are prohibitive, such as with rarely occurring infections.[15] Further, CHIM studies may offer a more rapid means of gathering data about vaccine candidates during emerging epidemics.[16]

CHIM studies also offer safety advantages. They allow researchers to monitor volunteers' safety more closely by controlling the timing, route, dose of infection, and by infecting volunteers with self-limiting or treatable diseases.[17] Further, the controlled settings (often involving in-patient settings) facilitate the identification of signs of infection before symptoms begin[18] and minimize the risk of infection being transmitted to third parties.[19] Furthermore, CHIM studies can be completed with smaller numbers of volunteers (10–40 participants) than other trials.[20]

There is little question that CHIM studies offer scientific and social benefits. But they also raise ethical concerns. These studies deliberately expose research subjects to pathogens. Clinicians are generally understood as responsible for treating and curing infection, rather than inflicting it[21] and avoiding harm is central to the Hippocratic oath. Inducing infections in healthy people may be viewed as counter-intuitive or distressing.

Perhaps the most similar research design is Phase I drug studies. These studies involve the exposure of healthy volunteers to experimental drugs in order to determine toxicity levels. They are similar to CHIM studies in that they impose risks that do not offer corresponding medical benefit.[22] But Phase I studies often use a dose escalation

[3]Hope & McMillan, op. cit. note 2; Bamberry et al, op. cit. note 2.

[4]Academy of Medical Sciences (2005), op. cit. note 1; Hope, T. et al., op. cit. note 2.

[5]Bamberry, B. et al., op. cit. note 2, p. 98.

[6]Darton, T., Blohmke, C., Moorthy, V., Altmann, D., Hayden, F., Clutterbuck, E., … Pollard, A. (2015). Design, recruitment, and microbiological considerations in human challenge studies. *Lancet Infectious Disease*, *15*(7), 840–851.

[7]Shah, S., Kimmelman, J., Lyerly, A. D., Lynch, H. F., McCutchan, F., Miller, F.G., … Zorilla, C. (2017). Ethical consideration for zika virus human challenge trials. Report and recommendations, p. 9. Retrieved from: https://www.niaid.nih.gov/news-events/ethical-considerations-zika-virus-human-challenge-trials

[8]Miller & Grady, op. cit. note 2.

[9]Ibid; Selgelid, M., & Jamrozik, E. (2018). Ethical challenges posed by human infection challenge studies in endemic settings. *Indian Journal of Medical Ethics*, *3*(4), 263–266.

[10]Gordon, S. B., Rylance, J., Luck, A., Jambo, K., Ferreira, D. M., Manda-Taylor, L., … Mlombe, Y. (2017). A framework for controlled human infection model (CHIM) studies in Malawi: Report of a Wellcome Trust workshop in CHIM in low income countries held in Blantyre, Malawi. *Wellcome Open Research*, *2*(70), 1–11; Selgelid & Jamrozik, op. cit. note 9.

[11]CHIM studies also provided the primary effectiveness required for the FDA to license Vaxchora, a live oral, cholera vaccine (Gordon, S. B. et al., op. cit. note 10).

[12]Bamberry, B. et al., op. cit. note 2; Darton, T. et al., op. cit. note 6.

[13]Darton, T. et al., op cit. note 6.

[14]Ibid.

[15]Ibid.

[16]Ibid.

[17]Bamberry, B. et al., op. cit. note 2; Darton, T. et al., op. cit. note 6; Selgelid & Jamrozik, op. cit. note 9.

[18]Bamberry, B. et al., op. cit. note 2.

[19]Shah, S. et al., op. cit. note 7, p. 8.

[20]Bamberry, B. et al., op. cit. note 2, p. 93.

[21]Miller & Grady, op. cit. note 2.

[22]Ibid.

model in which the dosage level of an experimental drug is stopped when the effects reach a certain level. In CHIM studies, risks may be mitigated in advance through the careful selection of pathogen strains and during the study through close monitoring, but insofar as they involve intentional exposure to pathogens, these studies raise the possibility of exposing research volunteers to significant disease symptoms.

The possibility of exposing research subjects to high levels of risk that do not offer corresponding benefit raises difficult questions about the circumstances under which the efficiency, scientific, and social value of CHIM studies should justify exposure to pathogens. Commentators have recently called for further attention to complexities about risk in CHIM studies.[23] In what follows, I address the following questions: Should there be a risk threshold constraining the degree of risk? Should this threshold be unique to CHIM studies? Should limitless amounts of risk that do not offer corresponding benefit to research subjects be permissible? How should risks be assessed in CHIM studies?

3 | RISK THRESHOLDS

Risk thresholds are part of a broader network of requirements for the ethical conduct of clinical trials. The permissibility of a clinical trial depends on a number of requirements, including that the risks of research stand in reasonable relation to the knowledge to be gained.[24] While most agree that risks and benefits must be balanced, it is not clear what this balance should look like. National and international guidelines offer guidance[25] and several competing frameworks for risk assessments appear in research ethics commentary.[26] One shared feature of most risk frameworks is their use of risk thresholds.

A risk threshold operates as a sorting mechanism that serves several functions.[27] First, it sets an upper limit on the amount of risk that should be permitted in research with particular kinds of research subjects. Members of the National Commission for the Protection of Human Subjects of Biomedical Research (1979) argued that research subjects with limited ability to protect or promote their own interests should receive additional protections when they participate in research.[28] Consequently, when vulnerable research subjects participate in health research, the amount of risk they may be exposed to in research interventions that do not offer corresponding benefit is often constrained to no more than minimal risk or a minor increase over minimal risk.[29] Debate surrounds the appropriate interpretation of the thresholds[30] and the meaning and identification of vulnerable populations,[31] but there is much agreement that some risk threshold is ethically required for non-therapeutic interventions on vulnerable subjects. The first function of a risk threshold is perhaps best understood as offering special protections for vulnerable populations in research.

The second role of risk thresholds is to identify research that poses such a low degree of risk that it should be eligible for expedited review. If a research protocol poses risks that are thought to be no more than minimal and does not involve a vulnerable population, then ethics committees often have more discretion in expediting the review process and, at times, in waiving the requirement to obtain informed consent.[32] More generally, risk thresholds can be understood as a sorting mechanism that helps identify protocols that merit additional scrutiny by ethics committees and those that require less attention.

3.1 | Risk thresholds in CHIM studies?

Should risk thresholds be invoked in CHIM studies involving healthy, competent, fully informed, and non-vulnerable adult volunteers? If a CHIM study poses more than minimal risk, but does not propose to involve a vulnerable population, then it seems that the first two functions of risk thresholds described above are not applicable. Nonetheless, recommendations for risk thresholds for CHIM studies have been considered.[33] In what follows, I analyse proposed thresholds and argue that they are not persuasive. I then examine the implications of this for risk analysis in CHIM studies. I situate proposals for risk thresholds in CHIM studies within a

[23] Murdoch & Caulfield, op. cit. note 2, p. 284; Selgelid & Jamrozik, op. cit. note 9; Palacios, R., & Shah, S. (2019). When could human challenge trials be deployed to combat emerging infectious diseases? Lessons from the case of a zika virus human challenge trial. *Trials*, *20*(2), 702.

[24] Emanuel, E., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *JAMA*, *283*(20), 2701–2711; Weijer, C., & Miller, P. (2004). When are research risks reasonable in relation to anticipated benefits. *Nature Medicine*, *10*(6), 570–573.

[25] Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (2016). International ethical guidelines for health related research involving humans. Geneva, Switzerland. Retrieved from http://cioms.ch/ethical-guidelines-2016/WEB CIOMS EthicalGuidelines.pdf; U.S. Department of Health and Human Services (HHS) (2009). 45 C.F.R. Part 46.

[26] Weijer & Miller, op. cit. note 24; Wendler, D., and Miller F. (2007). Assessing research risks systematically: The net risks test. *Journal of Medical Ethics*, *33*(8), 481–486; Rid, A., & Wendler, D. (2011). A framework for risk-benefit evaluations in biomedical research. *Kennedy Institute of Ethics Journal*, *21*(2), 141–179; Bernabe, R., Van Thiel, G., Raaijmakers, J., & Van Delden, J. (2012). The risk-benefit task of research ethics committees: An evaluation of current approaches and the need to incorporate decision studies methods. *BMC Medical Ethics*, *13*(6), 6.

[27] Rid, A. (2014). Setting risk thresholds in research: Lessons from the debate about minimal risk. *Monash Bioethics Review*, *32*(1), 63–85; Resnik, D. (2018). *The Ethics of Research With Human Subjects. Protecting People, Advancing Science, Promoting Trust*. Gewebestrasse, Springer. p. 171–172.

[28] Belmont Report, 1979. National Commission for the Protection of Human Subjects. The report to the Secretary of the Department of Health, Education and Welfare. Retrieved from https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/.

[29] Weijer & Miller, op. cit. note 24.

[30] Kopelman, L. M. (2004). Minimal risk as an international ethical standard in research. *Journal of Medicine and Philosophy*, *29*(3), 351–378; Wendler, D. (2005). Protecting subjects who cannot give consent: Toward a better standard for "minimal" risks. *Hastings Center Report*, *35*(5), 37–43; Binik, A. (2014). On the minimal risk threshold in research with children. *American Journal of Bioethics*, *14*(9), 3–12.

[31] Hurst, S. A. (2008). Vulnerability in research and health care: Describing the elephant in the room? *Bioethics*, *22*(4), 191–202; Luna, F. (2009). Elucidating the concept of vulnerability: Layers not labels. *International Journal of Feminist Approaches to Bioethics*, *2*(1), 121–139; Mackenzie, C., Rogers, W., Dodds, S. (Eds.) (2014). *Vulnerability: new essays in ethics and feminist philosophy*. Oxford: Oxford University Press; Rogers, W., Mackenzie, C., & Dodds, S. (2012). Why bioethics needs a concept of vulnerability. *International Journal of Feminist Approaches to Bioethics*, *5*(2), 11–38.

[32] Kopelman, L. op. cit. note 30.

[33] Bamberry et al., op. cit. note 2; Hope & McMillan, op. cit. note 2; RCP (1996); Academy of Medical Sciences (2005), op. cit. note 1. The most recent revision to Academy of Medical Sciences (2018) does not support a minimal risk threshold for CHIMs.

broader debate about the permissibility of constraints for research risks that do not offer corresponding benefits (sometimes called non-beneficial, net risks, or non-therapeutic risks) in research with healthy, competent, fully informed adults. I argue that while there should be no unique risk threshold for CHIM studies, broader constraints on the risks of non-therapeutic interventions should also apply to CHIM studies.

3.2 | First proposal

One prominent contender for a risk threshold constraining CHIM studies is the minimal risk threshold. The meaning of "minimal risk" is the subject of controversy,[34] but a number of interpretations understand minimal risk as referring to the risks of daily life or everyday experiences.[35] A minimal risk threshold for CHIM studies appeared in the 2005 version of the Academy of Medical Sciences guidelines, which claim that "however valuable the research, the degree of risk of harm can be no more than 'minimal'".[36] The guideline cites a recommendation from the Royal College of Physicians (1996),[37] but does not elaborate on the explanation for the risk threshold. The 2018 revision of the guideline drops the recommendation for a minimal risk threshold.[38]

A minimal risk threshold for CHIM studies has also been considered within a broader debate about the permissibility of risk thresholds for competent adults participating in all research.[39] Hope and McMillan argue that restricting risk in all research to no more than minimal risk may help to protect the public's trust in the research enterprise.[40] Their concern is that studies—including CHIM studies—may expose research participants to significant harm, which in turn, would lead to a negative public reaction against research. They write: "If significant numbers of people were to die as a result of taking part in medical research, then this would be likely to have the effect of bringing such research into disrepute (even though all those who died knew the risks and gave valid consent). The result of this would be to reduce the amount of research that could take place because of a public reaction against such research."[41]

Preserving public trust in research is essential, but it is not clear that a minimal risk threshold for CHIM studies is an ideal way to promote this goal. As Hope and McMillan recognize, this is a pragmatic, rather than a principle-based reason for an upper limit of reasonable risk. It relies on the assumption that CHIM studies are likely to cause significant harm, that the public will react in a certain way, and that this reaction will have broad negative consequences for the research enterprise. One problem with a pragmatic approach is that it does not explain whether the threshold is ethically necessary.

Another pressing problem is that it is not clear that a minimal risk threshold would resolve challenges related to public trust. The unique concern for CHIM studies is the deliberate exposure of healthy volunteers to a pathogen, which seems to run counter to the belief that physician researchers should act in the interests of patients. Insofar as this concern focuses on a physician researcher's duties to a research subject, constraining the degree of risk involved in the deliberate infection may not mitigate the problem.

Further, questions concerning public trust in the research enterprise are not unique to CHIM studies. Challenges in preserving this relationship may be present in all clinical trials. Limiting or preventing research that might compromise public trust risks imposing unnecessary delays on the research enterprise and may not be the most beneficial way to build, maintain, and improve the relationship between the public and scientific enterprise. Perhaps a more promising solution might include efforts to engage with prospective research participants, communities, and other stakeholders complemented by the development of a clear system for assessing the permissibility of risks in CHIM studies. These initiatives may contribute to a better understanding of what is involved in CHIM studies, their purpose, and the risks faced by participants. Moreover, they would provide an opportunity for stakeholders to engage with and contribute to the proposed research and to voice any concerns. More generally, the suggestion is that a minimal risk threshold is not justifiable for CHIM studies; this threshold should be reserved for protecting vulnerable populations.

3.3 | Second proposal

A second candidate for a risk threshold can be found in Bamberry and colleagues' ethical framework for CHIM studies.[42] They find minimal risk overly restrictive and propose another option. They suggest that "under no circumstances the research exposes volunteers to risks of irreversible, incurable or possibly fatal infections."[43] This threshold aims to protect research volunteers from serious risks while permitting important research to proceed.

This proposal has several appealing features, but also contains ambiguities that merit elaboration. For instance, it is not clear how to understand the restriction on the possibility of a fatal infection. If any (or a very low) risk of a fatal infection (including a one per hundreds of thousands) should be prohibited, then the threshold might be comparable to a minimal risk threshold. Similarly, some mild infections (such as the common cold) may not be cured but run their course without

[34] Kopelman, L., op. cit. note 30; Wendler, D., op. cit. note 30.

[35] DHHS, op. cit. note 25; National Human Research Protections Advisory Committee (NHRPAC) (2001). Final draft children's workgroup report, in response to PL (106–310); Freedman, B., Fuks, A., & Weijer, C. (1993). In loco parentis: Minimal risk as an ethical threshold for research upon children. *Hastings Center Report*, *23*(2), 13–19; Binik, A. (2017). A defense of the risks of daily life. *Kennedy Institute of Ethics Journal*, *27*(3), 413–442.

[36] Academy of Medical Sciences (2005), op. cit. note 1, p. 18.

[37] Royal College of Physicians of London (1996). Guidelines on the practice of ethics committees in medical research involving human subjects. Salisbury: Royal College of Physicians, p. 28.

[38] Academy of Medical Sciences (2018), op. cit. note 1.

[39] Hope & McMillan, op. cit. note 2.

[40] Ibid:113.

[41] Ibid.

[42] Bamberry, B. et al., op. cit. note 2.

[43] Ibid: 98.

incurring significant risks. If the threshold is understood as prohibiting these kinds of risks in CHIM studies, it would be overly restrictive.

This proposal is perhaps better understood as aiming to limit the exposure of healthy volunteers to *serious risks* that are irreversible, incurable, and *likely* to include the risks of mortality. But this understanding would benefit from further analysis of the notions of "serious risks" and "likely harms." The CIOMS guidelines suggest something similar. Commentary on the guidelines prohibits research risks involving a "very high mortality risk due to the absence of effective treatments" and draws on deliberate infection with anthrax or Ebola as examples of unacceptably high risks to competent adult volunteers.[44]

Ruling out CHIM studies that are likely to cause fatal infections is an important way of protecting research subjects from facing overly serious risks. But it is not clear whether this understanding of the threshold offers sufficient protection. For instance, should research risks that fall immediately below this threshold be considered permissible? And should all risks that fall below this threshold be assessed in the same way? For instance, should a dengue CHIM study proposing to expose participants to the risk of severe and prolonged fever be assessed in the same way as a lower risk malaria CHIM study? On this understanding, the proposed threshold would effectively rule out some studies involving overly high degrees of risk, but it is less clear whether it offers sufficient restrictions on high risks that fall just short of this mark.

Nonetheless, these proposals offer valuable insights. A minimal risk threshold would be overly restrictive without offering clear protections for public trust in research, but this proposal raises an important point—that limitless amounts of risk without the prospect of corresponding medical benefit are problematic. Bamberry and colleagues' suggestion that exposure to infections likely to pose serious risks, including risk of mortality, should be prohibited is also persuasive.

3.4 | Another look at risk thresholds

How does this bear on the analysis of ethically permissible risk in CHIM studies? I have argued that neither of the existing proposals for risk thresholds is persuasive. I have also suggested that CHIM studies involving competent, healthy, non-vulnerable subjects do not seem to meet two commonly recognized criteria for invoking risk thresholds. This might be understood as suggesting that, in the absence of evidence or a persuasive argument that some unique feature of CHIM studies warrants additional protections, they should not be treated exceptionally. That is, their risk profile should be assessed much like other research protocols that do not propose to include vulnerable subjects. But does this mean that limitless amounts of risk without corresponding benefit should be permissible?

The answer to this question and the implications of the suggestion that CHIM studies should not be treated exceptionally is not obvious. There is an ongoing debate over whether there should be limits to the risks of non-therapeutic interventions in research involving competent, healthy, fully informed, non-vulnerable adult volunteers. Determining whether CHIM studies should be subject to risk limitations depends on these broader questions about risk constraints.

Some defend the idea that there should be no absolute risk limits in research proposing to involve competent, fully informed adult subjects. They argue that an upper limit on risk is unjustifiably paternalistic and fails to show adequate respect for people's autonomous choices and preferences.[45] For instance, David Shaw argues that "institutional review boards should never reject a study because it poses too high a risk to participants … Everyone should have the right to participate in research without paternalistic decisions about risk being made on their behalf."[46] Robert Steel agrees, arguing that "there is no level of risk, no matter how high, that inherently mistreats a participant."[47] Attempting to protect people from their own decisions (even those that may compromise their welfare) is not a justifiable reason for invoking a risk threshold for competent adults because people may autonomously choose very high degrees of risk.[48] In examining the limits of his view, Steel draws on a hypothetical example of a CHIM study proposing to involve the infection of healthy young people with HIV. He argues that if enough healthy adults willing to participate could be found, if there were a sufficiently low likelihood of prospective participants taking on the risks non-autonomously, and if there were a sufficiently strong scientific rationale for the study, then even a study involving deliberate infection with HIV could, in principle, be justifiable.[49]

Others argue that limitless degrees of non-therapeutic risks should not be offered, even if the research proposes to involve competent, healthy, adults. For example, Joanna Rozynska argues that endorsements of a right to undertake high degrees of non-therapeutic risk mistakenly attribute primacy to the concept of autonomy.[50] On her view, some limits to autonomous decisions to undertake risk are justifiable, and one instance of a justified limitation is when a risky undertaking involves the help of another. Given that research involves a researcher in addition to an individual making an autonomous decision to accept a risk for herself and because there are complexities and

[44] CIOMS, op. cit. note 25, p.10.

[45] Miller, F. G., & Wertheimer, A. (2007). Facing up to paternalism in research ethics. *Hastings Center Report*, *37*(3), 24–34; Shah, D. (2014). The right to participate in high-risk research. *Lancet*, *383*, 1009–1011; Steel, R. (2019). Reconceptualising risk-benefit analyses: The Case of HIV cure research. *Journal of Medical Ethics*. Epub ahead of print. Doi: 10.1136/medethics-2019-105548.

[46] Shaw, op. cit. note 45.

[47] Steel, op. cit. note 45. Steel's argument focuses on HIV cure research, which involves brief, closely monitored, antiretroviral treatment interruptions. This research differs from CHIM studies, but also addresses questions about permissible risk limits in research with competent adult volunteers.

[48] Ibid: 6.

[49] Steel's arguments against risk ceilings are limited to considerations about paternalism and autonomous choice. That is, he argues that limiting risks in order to protect prospective research participants from making poor decisions would be unjustifiably paternalistic. But he suggests that his argument is consistent with there being other normative reasons that may contribute to risk limits, including legal liability or a possible loss of trust.

[50] Rozynska, J. (2015). On the alleged right to participate in high-risk research. *Bioethics*, *29*(7), 451–461.

inequities in the relationship between researchers and subjects, role-related duties of researchers give rise to the need for risk limits.[51] With respect to where to draw the line for acceptable risk, Rozynska endorses a process approach, in which the upper limit on the risks of non-therapeutic interventions is left to the judgment of an ethics committee. This approach offers the advantage of allowing differing risk judgments and promotes context sensitivity in risk determinations.[52]

Alex London also endorses constraints to the degree of risk that may be offered to research participants. When procedures pose incremental risks to people's basic interests that are not offset by direct corresponding benefit, the imposition of limits on permissible risk is justified by an underlying commitment to equal moral concern for all people.[53] London's cap on reasonable risks appeals to the notion of a comparator activity. He proposes that non-therapeutic research risks should not exceed those risks involved in other socially sanctioned activities that have a similar structure to clinical research.[54] Determining reasonable risk levels by appealing to a comparator activity is a useful strategy that aims to draw on risks of activities considered acceptable in similar circumstances, to determine the levels of risk acceptable in research.[55] London suggests volunteer public service professions—such as paramedics and firefighters—as relevant comparator classes of socially sanctioned activities.[56]

The arguments above make a persuasive case that protecting people's basic interests and respecting their equal moral worth does not necessarily give rise to a right to undertake any degree of research risk without corresponding benefit. It may be reasonable to constrain choices because of the nature of the research enterprise, the involvement of researchers, and because of inequities in the relationships between researchers and subjects. Further, these arguments offer several valuable insights about how to constrain risks that do not offer corresponding benefits. I agree with Rozynska that ethics committees should play a central role in making judgments concerning appropriate limits on reasonable non-therapeutic risks. Their multi-disciplinary membership and potentially diverse risk perceptions mean they are well placed to consider contextual complexities when making risk determinations. But additional guidance may help promote procedural consistency and clarity. To this end, drawing on socially sanctioned comparator activities involving risks undertaken for the benefit of others,[57] is a promising strategy.

While a detailed analysis of relevant comparator activities cannot be offered here, the debate over risk limits in all non-therapeutic research interventions involving competent healthy adults has important implications for the analysis of ethically permissible risk in CHIM studies. I suggest that while there may be no unique, CHIM study specific risk threshold, broader constraints on non-therapeutic risks should be applied. It follows that limitless amounts of risk should not be offered to prospective research participants in CHIM studies.

While the debate over risk limits in research with competent, healthy adults has only been sketched, it has important implications for permissible risks in CHIM studies including the following. CHIM studies involving non-vulnerable adults should not be subject to a unique or exceptional CHIM study specific risk threshold. This is consistent with the idea that the risks of non-therapeutic interventions should be constrained. Establishing these risks limits should draw on ethics review committees whose judgments may be informed by appeal to comparator activities for permissible risk (which would rule out interventions that cannot be controlled and involve a high risk of mortality). In what follows, I propose how these suggestions may be applied to CHIM studies, drawing on two case examples.

4 | CASE STUDIES AND RECOMMENDATIONS

Consider the following two examples, chosen to reflect a range of risks encountered in CHIM studies. Both are conducted in non-endemic setting and involve participants who would not otherwise be likely to be exposed to the pathogens being studied. The analysis will consequently focus on CHIM studies conducted in high income countries and non-endemic settings, but I will identify areas in which there may be morally relevant differences for CHIM studies conducted in endemic settings including low- and middle-income countries.

4.1 | Example 1: Malaria

Malaria is a severe public health challenge. The WHO estimates that in 2017, there were 219 million cases of malaria leading to roughly 435 000 deaths.[58] The *Plasmodium falciparum* parasite causes one of the most severe types of malaria (CDC) and is difficult to protect against. To examine whether immunity can be induced, researchers designed a CHIM study testing a potential vaccine.[59] The study recruited 15 healthy volunteers aged 18–45 living in non-endemic settings who had no history of malaria.

Participation involved a number of procedures, risks, and burdens. To determine eligibility, prospective participants underwent

[51] Ibid: 454–459.

[52] Ibid: 461.

[53] London, A. J. (2006). Reasonable risks in clinical research: A critique and a proposal for the integrative approach. *Statistics in Medicine*, *25*, 2869–2885; London, A. J. (2007). Two dogmas of research ethics and the integrative approach to human-subjects research, *Journal of Medicine and Philosophy*, *32*(2), 99–116.

[54] Ibid.

[55] CIOMS, op. cit. note 23, p. 12. See also Miller and Joffe (2009) for a partial endorsement of using comparator activities to assess limits on permissible risk (Miller, F., & Joffe, S. (2009). Limits to research risks. *Journal of Medical Ethics*, *35*(7), 445–449).

[56] For other analyses of candidates for risk thresholds, see: Miller, F., & Joffe, op. cit. note 55; Resnik, D. (2012). Limits on risks for healthy volunteers in biomedical research. *Theoretical Medicine and Bioethics*, *33*(2), 137–149.

[57] London (2006), op. cit. note 53; London (2007), op. cit. note 53.

[58] World Health Organisation (2018). *World malaria report*. Geneva. License: CC BY-NC-SA 3.0 IGO.

[59] Roestenberg, M., McCall, M., Hoopman, J., Wiersma, J., Luty, A., Gemert, G., … Sauerwein, R. (2009). Protection against a malaria challenge by sporozoite inoculation. *New England Journal of Medicine*, *361*(5), 468–477.

routine physical exams, hematologic, and biochemical screening. Once enrolled, study participants were randomized to either a vaccine group (10 participants) or a control group (five participants). Participants in both groups received a prophylaxis called chloroquine for 13 weeks. During this time, the experimental group were exposed to bites from mosquitos infected with *P. falciparum* once a month for three months and the control group were exposed to the same number of bites from uninfected mosquitos. The chloroquine prophylaxis was then discontinued and all subjects were exposed to bites from infected mosquitoes. During this time, subjects were monitored closely (checked twice daily) on an outpatient basis for symptoms and signs of malaria. When tests were positive, subjects received a standard curative regimen and were monitored closely to ensure a complete cure.[60] Adverse events recorded during the trial included headaches, severe fever, severe malaise, myalgia, and nausea.[61]

The study, published in the *New England Journal of Medicine*, found a more effective way of protecting research subjects from a challenge with *P. falciparum* malaria. These results are of significant value, the study received ethics committee approval, and all subjects provided informed consent.[62]

4.2 | Example 2: Cholera

A second example concerns a CHIM study examining cholera.[63] Cholera is a potentially epidemic and life threatening diarrheal illness caused by infection with the bacteria *Vibrio cholerae*.[64] It is a significant public health challenge, with roughly 2.9 million cases reported each year resulting in 95 000 deaths.[65] Until the early 1990s, there was one strain of epidemic cholera (the 01 serogroup), but in 1992 a new type—the Bengal serotype (serotype 0139)—emerged in Bangladesh and parts of India.[66] CHIM studies in which volunteers are challenged with cholera were identified as an important step towards the development of an effective vaccine to prevent the second strain of cholera. But in order for these studies to produce consistent and reproducible results, a sufficiently large quantity of the frozen bacteria was needed with which to challenge volunteers.[67] The CHIM study I will consider aimed to validate the frozen sample of the new cholera strain.[68]

The study recruited 25 healthy adult volunteers (between 18 and 40 years old) for an in-patient dose-escalation study. Volunteers who passed screening measures were admitted as in-patients to a clinical research center and received the challenge of live virulent cholera.[69] One of the study's goals was to ensure that the challenge would replicate the symptoms of cholera,[70] which suggests that if the challenge is successful, participants in this study are likely to face significant levels of risk and discomfort. Typically, cholera may last two to seven days, during which symptoms may include an abrupt onset of diarrhea, with litres of fluid loss within hours, often accompanied by vomiting, muscle cramps, and possibly leading to hypovolemic shock.[71]

The most prominent symptom reported in this study was diarrhea, including severe cases. For instance, in one study group, the mean diarrheal stool volume was 7,804 grams (with a range of 1,337–20,370 g) lasting for an average of 82.8 hours.[72] In addition, study participants experienced a number of potentially uncomfortable procedures, including multiple daily examinations, continuous monitoring of fluid intake and output, nausea, vomiting, and diarrhea, and stool collection for inspection.[73]

Both of the above studies contributed to the generation of valuable knowledge about disease prevention. They also included risks, burdens, and significant discomforts to participants. Interventions resulting in litres of diarrheal loss or multiple days of fever and vomiting exceed minimal risk but are not life-threatening. How should the risks of these studies be assessed?

4.3 | Recommendations

What justifies the risks of infection with *Vibrio cholera* or *Plasmodium falciparum*? The challenge in these studies offers no corresponding medical benefit; it is administered purely in the interests of answering the study question. In the first example, healthy participants not otherwise at risk of malaria were infected with *P. falciparum* to learn about the efficacy of chloroquine for malaria prevention. The goal in the second example is to deliberately infect healthy participants with the pathogen to test the viability of the cholera sample. Given that these interventions are not administered with therapeutic warrant, their risks cannot be justified by balancing them against the potential medical benefits to be gained. The risks of non-therapeutic interventions in CHIM studies require a different set of constraints.

Drawing on the discussion of risk limits above, I suggest five recommendations for the ethical assessment of risk in CHIM studies. These recommendations draw on existing ethical guidance for research, which reflects the way in which questions about risk in CHIM studies are situated within broader debates about ethically

[60] Ibid.

[61] Ibid.

[62] Ibid.

[63] Cohen, M., Giannella, R., Losonsky, G., Lang, D. R., Parker, S. P., Hawkins, J. A., … Schiff, G. A. (1999). Validation and characterization of a human volunteer challenge model for cholera by using frozen bacteria of the new *Vibrio cholerae* epidemic serotype, 0139. *Infection and Immunity*, *67*(12), 6346–6349.

[64] Finkelstein, R. A. (1996). Cholera, Vibrio cholerae 01 and 0139, and other pathogenic Vibrios. In Baron, S. (Ed.), *Medical microbiology* (4th ed.) (chapter 24). Galveston (TX): University of Texas Medical Branch; Center for Disease Control and Prevention; (2018). Cholera – Vibrio cholerae infection. Retrieved from: https://www.cdc.gov/cholera/general/index.html

[65] CDC, op. cit. note 64.

[66] Cohen, M. et al., op. cit. note 63.

[67] Ibid.

[68] Ibid.

[69] Ibid.

[70] Ibid.

[71] Finkelstein, R. A., op. cit. note 64.

[72] Cohen, M. et al., op, cit. note 63.

[73] Ibid.

permissible risks. But the focus will be on the bearing of recommendations and their specification for the CHIM study design.

4.3.1 | Distinguish research risks and burdens

The first recommendation is to identify the risks and the burdens of a protocol. Risks and burdens are often combined in research ethics review, but distinguishing between them can help draw attention to the under-appreciated impact of research burdens in CHIM studies. Research burdens are often experienced as significantly as the harms of deliberate infection, but they are less well recognized.

Two recent interview studies found that research participants significantly underappreciate burdens and discomforts, such as close monitoring, significant time commitments, required confinement, the need to change work schedules, feeling trapped or isolated, and the discomforts of frequent blood draws.[74] Based on these findings, investigators called for increased attention to participant awareness of the burdens of research during the informed consent process for CHIM studies.[75] I support this recommendation, but would like to emphasize that concerns about the impact of burdens should not be discharged to the consent process alone. Instead, they should be identified and assessed independently of the risks.

The cholera example demonstrates the impact of burdens. Discomforts of this study include screening measures, living in a clinical centre, careful monitoring of fluid intake and output, and multiple daily examinations. Participants should be carefully informed of these burdens, but an ethics committee should also factor them into their determinations by considering whether they stand in reasonable relation to the social value of the study and whether they change a harm-benefit determination before any prospective participants are approached for research participation.

4.3.2 | Risk minimization

Recommendation two is to ensure that risks have been minimized consistent with sound scientific design. In all research studies, risk minimization requires that procedures be limited to those required by the design and that procedures already being performed for diagnostic or treatment purposes be substituted for research procedures whenever possible.[76]

But meeting this requirement for CHIM studies requires additional measures. Research participants should be given genetically modified strains of pathogens in CHIM studies that are less severe than wild type and ideally single drug susceptible. By modifying or carefully selecting the infection, researchers can help to ensure that infections in these studies will not be incurable or pose irreversible harms.[77]

To meet this requirement, the pathogen selected for the challenge should be examined in addition to the procedures involved in study recruitment, participation, and follow-up.[78] The malaria study reports selecting a strain of *P. falciparum* that is chloroquine sensitive,[79] suggesting that measures were taken to minimize risks consistent with sound scientific design.

4.3.3 | Vulnerability

When research involves vulnerable populations, additional protections should be invoked. The risks of non-therapeutic procedures with vulnerable populations should be subject to a low risk threshold. Both the definition of vulnerability[80] and the appropriate risk threshold for non-therapeutic interventions on vulnerable subjects[81] are controversial, but a number of persuasive suggestions have been offered. In identifying vulnerable populations, care should be taken not to focus uniquely on populations traditionally labeled as vulnerable (e.g., children),[82] but on those at increased likelihood of incurring additional wrongs.[83] Taxonomies of vulnerability may usefully be drawn on to identify a range of possible vulnerabilities in research,[84] including unemployment, underemployment, and illness. The case studies above enroll adults in non-endemic settings, which contributes to the mitigation of some vulnerabilities,[85] but in all prospective CHIM studies a range of sources of vulnerability should be considered in making determinations about whether to invoke low risk threshold.[86]

[74] Kraft, S., Duenas, D., Kublin, J., Shipman, K., Murphy, S., & Shah, S. (2019). Exploring ethical concerns about human challenge studies: A qualitative study of controlled human malaria infection study participants' motivations and attitudes. *Journal of Empirical Research on Human Research Ethics*, *14*(1), 49–60; Njue, M., Njuguna, P., Kapulu, M., Sanga, G., Bejon, P., Marsh, V., … Kamuya, D. (2018). Ethical considerations in controlled human malaria infection studies in low resource settings: Experiences and perceptions of study participants in a malaria challenge study in Kenya. *Wellcome Open Research*, *3*(39), 1–17.

[75] Ibid.

[76] Weijer & Miller, op. cit. note 22; DHHS, 45 CFR 46.111(a)(1)(ii).

[77] Bamberry, B. et al., op. cit. note 2.

[78] Risk minimization determinations should also consider whether conducting preventive vaccine trials with at-risk populations (rather than CHIM studies with healthy volunteers) would lower risks to research subjects without exacerbating other potential or existing vulnerabilities.

[79] Roestenberg, M. et al., op. cit. note 59, p.470.

[80] Hurst, S. A., op. cit. note 31; Luna, F., op. cit. note 31; Rogers & Dodds, op. cit. note 31.

[81] Kopelman, L., op. cit. note 30; Wendler, D., op. cit. note 30.

[82] Luna, op. cit. note 31.

[83] Hurst, op. cit. note 31.

[84] Rogers, W. et al., op. cit. note 31.

[85] There is growing interest in the conduct of CHIM studies in endemic settings (Selgelid & Jamrozik, op. cit. note 9; Gordon et al., op cit. note 10) and additional work is needed to examine the implications of this requirement for CHIM studies in endemic settings. Of central concern to this analysis would be the understanding of vulnerability, the identification of vulnerable research subjects, and considering whether conducting CHIM studies in endemic settings or with at risk populations increases or decreases vulnerabilities.

[86] A related concern, which is not examined here is whether significant financial compensation may contribute to people undertaking high degrees of risk in CHIM studies. For analyses of compensation and subject selection in CHIM studies, see Bamberry, B. et al., op. cit. note 2; Selgelid & Jamrozik, op. cit. note 9; and Palacios & Shah, op. cit. note 23.

4.3.4 | Assess risks and burdens in relation to social value

The fourth requirement is to assess whether risks and burdens are reasonable in relation to the social value of the knowledge to be gained. Non-therapeutic risks cannot be counterbalanced by medical benefits (they offer none), but they do aim to generate socially valuable knowledge. Consequently, their justification depends at least in part on the potential social value of the knowledge to be gained. Social value is a widely recognized ethical requirement[87] that appears prominently in the current CIOMS guidelines[88] and helps to ensure that research examines interventions that have the capacity to improve health or well-being[89] and also helps to offset non-therapeutic research risks.[90]

How should the risks be balanced against the social value? Determining whether the social value requirement has been met involves a judgment call about whether a study's level of significance is sufficient to counterbalance the risks of non-therapeutic interventions. To make this call, an ethics committee should consider whether the protocol involves a research question of social importance. Appraising social priorities is benefitted by drawing on the multidisciplinary expertise of an ethics committee, including that of community members.[91] This assessment should also consider whether the study's hypothesis has been adequately addressed in previous studies, and whether there are any pressing challenges for study completion.[92] This assessment should also consider whether conducting preventative vaccine trials with at-risk populations at risk for the disease would offer greater social value and if so, whether there are other persuasive reasons (e.g., limited infrastructure or safety concerns) that favor non-endemic settings.[93]

Should risks in CHIM studies offering considerable social value be limited? Drawing on the discussion above, I suggest that even if the research offers the prospect of considerable social value and proposes to include competent, healthy adults, some risks should not be offered.[94] Determining where to draw the line should appeal to ethics committees' deliberations, which may be guided by reference to comparator activities of socially sanctioned activities[95] and should aim to rule out infections that cannot be controlled or are likely to pose serious risks. This does not offer a comprehensive specification of the range of acceptable non-therapeutic risks, but supports limits on permissible risks and rules out CHIM studies proposing to deliberately infect healthy participants with infections such as HIV or Ebola.

In the malaria study, the potential social value of the research may be drawn from its purpose. The study aimed to determine whether immunity could be induced for one of the most severe types of malaria. Background information provided by the researchers included that immunity to *P. falciparum* is difficult to acquire and that at the time of the study, there was only one vaccine candidate, which was still under Phase III testing.[96] The risks of the malaria study include the harm associated with malaria infection, including symptoms such as headaches, severe fever, severe malaise, myalgia, and nausea. To make a determination about whether these risks are reasonable with respect to the potential social value, an ethics committee might appeal to the high burden of malaria and the limited options for protection at the time of the study. Given these realities of malaria, in combination with the assurance that participants would be carefully monitored and cured from the strain proposed in the study, a committee might reasonably argue that the potential social value of this study stands in reasonable relation to its risks.

The cholera study falls earlier in the research trajectory and aims to determine whether a frozen sample of the virus could be validated for use in future CHIM studies. This study has less direct application to a cure or prevention and exposes participants to significant symptoms of cholera disease. But the study is a necessary step in the trajectory of research aiming to develop an effective vaccine. Given that the cholera study addresses an outbreak of considerable and growing concern, is required for additional vaccine research that aims to save thousands of lives, and is not likely to cause high risk, such as the risk of mortality, a committee might reasonably determine that the risks stand in reasonable relation to the potential knowledge to be gained.

4.3.5 | Risks to the community

Potential risks to the community, including risks to third parties who are not research subjects should also be taken into account. CHIM studies give rise to the risk of potentially transmitting the pathogens under investigation to non-research subjects who come into contact with the subject.[97] This potential risk to third parties who are not research subjects is problematic because the broader community

[87] CIOMS, op. cit. note 25; Weijer & Miller, op. cit. note 24; Emanuel, E. et al., op. cit. note 24; Wendler, D., & Rid, A. (2017). Assessing research risks systematically: The net risks test. *Journal of Medical Ethics*, *33*(8), 481–486; Wenner, D. (2017). In defense of a social value requirement for clinical research. *Bioethics*, *31*(2), 77–86; Wenner, D. (2018). The social value requirement in research: From the transactional to the basic structure model of stakeholder obligations. *Hastings Center Report*, *48*(6), 25–32.

[88] CIOMS, op. cit. note 25.

[89] Emanuel, E. et al., op. cit. note 24.

[90] Weijer & Miller, op. cit. note 24; Wendler & Rid, op. cit. note 87.

[91] Weijer & Miller, op. cit. note 24.

[92] Binik, A., & Hey, S. P. (2019). A framework for assessing scientific merit in ethical review of clinical research. *Ethics & Human Research*, *41*(2), 2–13. These considerations need not rule out studies offering low social value. Low value studies may be permissible provided that the non-therapeutic risks of the research are correspondingly low. The kinds of studies that would be excluded include clinical research with non-generalizable results, studies replicating already proven results (e.g., certain me-too drugs), or very expensive studies that have little social value (Emanuel et al., op. cit. note 24, p. 2703; Wendler and Rid, op. cit. note 87).

[93] A comprehensive analysis of whether CHIM studies offer greater social value in endemic settings and with populations at risk of the disease as subjects cannot be addressed here. For analyses of the ethical concerns emerging for CHIM studies in endemic settings, see Selgelid & Jamrozik, op. cit. note 9 and Palacios & Shah, op. cit. note 23.

[94] CIOMS, op. cit. note 25.

[95] London, op. cit. note 53.

[96] Roestenberg, M. et al.. op. cit. note 59.

[97] Miller & Grady, op. cit. note 2; Kimmelman, J. (2005). Medical research bystanders. *IRB: Ethics & Human Research*, *27*(4), 1–6.

TABLE 1 Summary of recommendations for ethical risk assessment in CHIMs

Recommendation	Questions for ethics Review	Malaria study	Cholera Study
Identify risks and burdens of study participation	What risks of harm are associated with study participation? What inconveniences and burdens are associated with study participation?	Harm associated with malaria infection, including symptoms such as headaches, severe fever, severe malaise, myalgia, and nausea Time commitments, multiple appointments, close monitoring	Exposure to cholera, including symptoms such as severe discomfort, including acute and consistent diarrhea Screening measures, in-patient setting, careful monitoring, multiple daily examinations
Minimize risks consistent with sound scientific design	Are there any unnecessary procedures? Can any study procedures be combined or replaced by diagnostic or treatment interventions? Have the risks of the pathogen strains been modified/selected to minimize risks?	None found N/A – healthy volunteers A less severe strain of P. falciparum was selected	None found N/A – healthy volunteers
Vulnerable populations should be adequately protected	Does the study propose to enroll a vulnerable population? If yes, risks should be constrained by a risk threshold (e.g., minimal risk or minor increase over minimal risk)	Proposes to enroll healthy, competent adults in a non-endemic settings The possibility of other potential sources of vulnerability should be examined in ruling out the need for a lower risk threshold	Proposes to enroll healthy, competent adults in a non-endemic setting The possibility of other potential sources of vulnerability should be examined before ruling out the need for a lower risk threshold
Assess risks and burdens in relation to social value	What is the potential social value of the study? Are both the risks and burdens reasonable in relation to the knowledge to be gained? Does the study involve risks without corresponding benefit that are unjustifiably high? Pass judgment concerning balance between harms and potential social value	Potential to determine how to build immunity against severe form of malaria Risks are curable, can be carefully monitored, and do not pose a high risk of mortality High burden of malaria and limited options balanced against risks and burdens of participation	Validate a frozen sample of the virus to proceed with additional CHIM studies examining a vaccine Does not pose very high risks, such as the risk of mortality Risks of outbreak of considerable and growing concern, combined with necessary step in scientific process, balanced against risks and burdens to participants
Assess risks to the community	Does the study pose risks to bystanders? Who are the relevant bystanders? Are these risks likely and have they been minimized? Does the community of relevant stakeholders support the research?	Risk of malaria transmission via mosquito Community Risks of transmission in non-endemic setting are very low	Risks of cholera transmission Community Infectivity of cholera generates risk of transmission Risks minimized by isolating study participants (in-patient setting)

may not know about the study and has not consented.[98] To minimize the impact of risks to the community, proposed CHIM studies should identify those individuals who a CHIM study is likely to put at risk (including research participants, non-participants, and communities) and examine whether these risks have been minimized as much as possible. This assessment can be made by considering a pathogen's modes of transmission, duration of infectivity, and whether there is a need for a mandatory isolation period.[99]

Assessment of the risks to the community should involve engagement, consultation, and discussion with key stakeholders. Community engagement prior to the research can help to ensure that the social value of the proposed research is relevant, that the risks (including risks to third parties) are acceptable to the host population, and may help to promote transparency.[100] Furthermore, community engagement may help to determine whether non-research subjects should be warned about the risks of transmitting the pathogens and the best way to issue these warnings.[101]

[98] Shah, S., Kimmelman, J., Lyerly, A. D., Lynch, H. F., McCutchan, F., & Zorilla, C. (2018). Bystander risk, social value, and ethics of human research. *Science*, *360*(6385), 158–159.

[99] Shah, S. et al., op. cit. note 7.

[100] Ibid: 32.

[101] The impact of local and environmental factors on risks to third parties should also be taken into account. In endemic settings, this may involve examining local conditions and infrastructure, such as the sanitation capacities and requirements at research facilities conducting CHIM studies on pathogens that may be spread via sewage. In non-endemic settings, the assessment may involve considering whether local factors such as water supplies or common modes of transportation are likely to have an impact on the risk of pathogens in CHIMs spreading within a community.

With respect to the case studies, an ethics committee might consider the likelihood of transmitting malaria to a broader community fairly low, given that infected mosquitos are carefully monitored. Insofar as cholera is more readily transmitted through contact and infected water supplies, this study may pose somewhat higher risks to third parties. This may be taken into account in determining whether to use an in-patient setting used the cholera study. Taken together, these recommendations (summarized in table 1) help to ensure that the risks of a CHIM study protocol are ethically permissible.

5 | CONCLUSION

Most agree that CHIM studies deliberately infecting volunteers with pathogens should be permissible in some circumstances, but it is unclear whether they should be subject to different ethical considerations. Some have endorsed risk thresholds to protect research participants and public trust from the risks of deliberate infection, but little has been said about whether and why risk thresholds might be justifiable. I have argued that existing risk thresholds are unpersuasive and that there is no clear reason to develop a risk threshold uniquely for CHIM studies. But this is not an endorsement of the possibility of limitless risk. Instead, I suggested that the same constraints that should apply to the risks of non-therapeutic procedures in other research designs, involving competent, healthy, fully informed adults, should also be invoked for CHIM studies. I then proposed five recommendations drawing on broader ethics guidance, the particular characteristics of CHIM studies, and two case examples.

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