**Ethical challenges posed by human infection challenge studies in endemic settings**

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Abstract

Human infection challenge studies (HCS) involve intentionally infecting research participants with pathogens, often with the ultimate aim of developing new interventions against infectious diseases. Despite ethical concerns about research involving vulnerable populations, there are both scientific and ethical reasons to consider conducting more HCS in low- and middle-income countries where neglected diseases are often endemic. HCS researchers can reduce the risks to participants (and the risks of transmission from participants to others) by controlling multiple factors (e.g. related to the laboratory environment, participant selection, the pathogen, and the timing of treatment); but HCS nonetheless raise important ethical issues, some of which may be particularly pertinent to HCS in endemic settings. This article provides background on HCS in general, as well as recent HCS in low- and middle-income countries, and an overview of the ethical issues associated with HCS in endemic settings.

Introduction

Human infection challenge studies involve the intentional infection of research participants with pathogens with the aim to (i) test (novel) vaccines and therapeutics, (ii) generate knowledge regarding the natural history of infectious diseases and/or host-pathogen interactions, or (iii) develop “models of infection”—i.e., reliable methods (to be used in studies with aims (i) and/or (ii)) of infecting human research participants with particular pathogens. Modern human challenge studies (HCS) are sometimes referred to as “controlled human infection studies,” because they involve *controlling* the pathogen strain and the timing, route, and/or dose of infection; infection in a *controlled* environment; and/or (with the aim to avoid serious harm to research participants) infection with pathogens causing disease that is self-limiting and/or can be (and is) *controlled* with effective cures or treatments.

The potential public health benefits of HCS include the development of beneficial drugs and vaccines that are urgently needed for pathogens endemic to low- and middle- income countries (LMICs) in particular. Since HCS could lead to such benefits being realised in a shorter timeframe and/or to benefits that might not otherwise be feasible (e.g., given the greater expense of larger studies), and since HCS involve exposing fewer participants to potentially risky experimental interventions than field trials, appropriately low-risk HCS might, under certain circumstances, reasonably be considered not just ethically permissible, but ethically required(1). Furthermore, since the results of HCS in non-endemic populations may not be entirely applicable in endemic populations (for example, due to genetic differences, immunity from prior infection, etc.), there may be important scientific reasons to conduct HCS in endemic settings. Because they are nonetheless ethically sensitive, this article provides an overview of ethical issues associated with HCS, with a particular focus on HCS in endemic regions.

Human challenge studies

HCS can provide an especially powerful scientific method for the testing of vaccines and therapeutics; they can be substantially smaller, shorter, and less expensive than other kinds of studies(2). Among other benefits they can, for example, significantly reduce the number of participants that must be exposed to an experimental vaccine in order to determine its efficacy. This is because (at least in cases where correlates of protection are unknown) determination of experimental vaccine efficacy requires that a sufficient number of research subjects who receive it, and those (in a comparator arm of a trial) who do not, are actually exposed to—i.e., “challenged” by—the pathogen in question. To ensure that a sufficient number of participants in field trials are exposed, such trials may need to be very large and/or may require impractically long follow-up periods(3). HCS are commonly used in early stage research for the selection of candidate interventions worthy of further investigation in larger studies. For example, the results of separate human challenge studies helped (i) to select among malaria vaccine candidates, leading eventually to the first licensed malaria vaccine (4) and (ii) to support the recent licensure of a new typhoid vaccine(5). Thus, both because HCS involve smaller numbers of volunteers in shorter studies, and because new drugs or vaccines that are ineffective can be ‘ruled out’ and not tested in larger studies, HCS potentially represent a highly cost-effective way to advance infectious disease research – meaning that they may be more attractive in resource limited settings. Similarly, where there are no existing vaccines or treatments for neglected pathogens, HCS can accelerate research programs with the aim of more rapid development of effective interventions for use in at-risk populations. The financial benefits of HCS can be especially important in the context of neglected diseases in particular—because their neglect often reflects inadequate financial motivation on the part of industry to invest in expensive R&D when profit potential is limited (as is commonly the case for diseases primarily affecting populations in low- and middle-income countries).

Though numerous infamous historical cases of unethical research involved the intentional infection of human subjects with pathogens(6, 7), the (sparse) existing bioethical ethical discourse on modern HCS(1, 8-14) appears to reflect consensus that intentional infection of human research participants *per se* is not ethically unacceptable—whereas grossly unethical challenge studies of the past were wrong for other reasons (e.g., they involved *uncontrolled* infection with especially dangerous and/or deadly pathogens; lack of voluntary informed consent, and sometimes violent force; exceptionally vulnerable populations, such as prisoners; etc.).

HCS are nonetheless ethically sensitive—and, *inter alia*, they raise complex questions concerning (1) the acceptable limit of risks to which healthy volunteers may be exposed,

(2) appropriate financial payment/compensation of participants, (3) the potential need for special review procedures (e.g., involving dedicated committees and/or the involvement of infectious disease experts), (4) the need for protection of third-parties from infection (transmitted by participants), and (5) appropriate criteria and processes for participant selection/exclusion.

Researchers involved in modern HCS have been especially careful to avoid (severe and/or irreversible) harm to participants and reduce the risk of transmission from participants to others in the community. This has been achieved through, for example, the control of challenge strains (i.e., avoiding especially dangerous ones) and assurance of early access to treatment once infection is confirmed and/or symptoms develop. Care has also been taken to exclude vulnerable participants – either those who may be physiologically vulnerable (e.g. due to comorbidities, co-infections including HIV, etc.), or those who are vulnerable for other reasons including poverty or lack of education(15, 16). This is a major reason why modern HCS have been conducted almost entirely in wealthy developed nations, even for pathogens/diseases that are usually only present (or endemic) elsewhere. This is unfortunate because—due to population differences regarding naturally acquired immunity, co-infections, genetics, microbiome, nutrition, and so on—research conducted in high-income settings may not always translate well to low- and middle-income countries (LMICs) where neglected diseases (for which research and development of new interventions are especially needed) are endemic(17).

Challenge studies in endemic settings

For this and other reasons, there have been increased calls for HCS in endemic settings(17). A limited number of such studies—involving diarrhoeal disease(18-20) and malaria(21-27) – have recently taken place (or commenced) in countries such as Thailand, Columbia, Tanzania, Kenya, Gabon, Mali, and Equatorial Guinea. Despite the potential scientific benefits of conducting HCS in endemic countries, HCS in such countries may raise particular challenges regarding informed consent (due to language barriers and/or limited educational background of potential participants) and/or concerns about “undue inducement” (e.g., if financial compensation is “too high”, in light of socio-economic status of potential participants) in addition to more general worries about potentially risky research involving vulnerable human subjects and fair participant selection. Children in endemic regions represent one particularly vulnerable group that is frequently excluded from research that may be associated with, or perceived to involve, higher than minimal risk – including some challenge models. Yet, because children would benefit from new vaccines and treatments for many neglected pathogens, and since the pathophysiology of disease in children may differ from adults (meaning that challenge studies of new interventions in adults may not predict safety or efficacy in children), excluding children from such research may lead to longer delays in developing appropriate prevention and treatment, which could result in greater avoidable harms to children more generally.

Despite the above challenges, there may be cases where infection during HCS is less risky/harmful to participants in endemic settings than participants in high-income countries—e.g., if the former have naturally acquired (partial) immunity to the pathogen under study (making resultant illness less severe) due to prior infection, or innate (partial) resistance due to genetic factors (e.g. thalassemia and sickle traits as protective factors against severe malaria(26, 28, 29)[[1]](#footnote-1)) whereas the latter do not. Furthermore, innate or acquired immunity of local population members may also reduce third-party risks of HCS conducted in endemic settings (if there is any chance of transmission from participants to the wider population, for example in an outpatient challenge model). Participation in HCS may sometimes even have *direct benefits* for healthy participants in endemic, developing countries (which is usually not the case for participants from wealthy developed nations) if/when (1) controlled infection leads to *protective* *immunity* against endemic diseases that otherwise would have put them at risk and/or (2) HCS involves infection with a locally prevalent pathogen participants would have otherwise likely been infected with later, but *controlled* infection (yielding immunity) leads to *less* *severe illness* than would otherwise be expected (in light of monitoring of, and care provided to, participants)(30). HCS participants in endemic settings may in some cases thus directly benefit from immunity gained from a less severe bout of illness than otherwise would have been likely and/or required for them to gain immunity. Such potential benefits of HCS participation were appealed to as part of the justification for Walter Reed’s famous yellow fever challenge studies in Cuba(14); and they have recently been acknowledged in discussion of potential HCS with Zika virus(10).

Conversely, there might be cases for which being part of a challenge study in endemic settings would be especially risky/harmful to participants. In the case of dengue, for example, the first infection usually leads to mild or no illness, and the greatest risk of severe dengue is associated with the second infection (with a second strain of the dengue virus). Participation in a dengue human challenge study in an endemic/high prevalence setting would thus be especially dangerous for both those who have never been previously infected with dengue and those who have been infected just once before. If an individual were infected with dengue for the first time in a challenge study this would make them more vulnerable to severe dengue if infected after the study (i.e. natural infection would be more dangerous for them than it would have been prior to their participation in the study). Individuals who had previously been infected just once, on the other hand, would be at especially high risk of severe dengue resulting from infection during a challenge study—because this would be their second infection. Human challenge studies with dengue in endemic/high prevalence settings might thus only be ethically acceptable, if at all, if participation is limited to those who have been infected with dengue at least two times before—i.e., both those who have never been infected before and those who have been infected just once before should presumably be excluded. Whether or not a study with such participation inclusion/exclusion criteria would be feasible in practice would depend on the availability of sufficiently sensitive and reliable testing (that would determine how many times, if at all, one has been infected before)—and the availability of such testing might be especially unlikely (in the short- and perhaps long-term) in low- and middle-income countries where dengue is endemic.

Likewise, local factors may influence assessments of the risks of transmission to third parties. For example, the design of challenge studies involving diarrhoeal and other pathogens spread via sewerage should pay careful attention to appropriate sanitation at research facilities (especially in settings where local sewerage infrastructure may not be adequate) and HCS involving vector-borne disease should consider the likelihood and/or significance of transmission (via local vectors, if any) from participants to other local residents.

Establishing HCS research programs in India and other countries with relevant endemic pathogens will require building on existing scientific infrastructure and/or developing new research organisations as well as ensuring that there is the capacity for appropriate local ethics and regulatory review of such studies. In terms of building on existing governance mechanisms, clinical trials registries (e.g. the Indian Clinical Trial Registry <http://ctri.nic.in/Clinicaltrials/>) could be expanded to include challenge studies (to prevent unnecessary duplication and promote publication of research findings). Existing ethics review committees could also be adapted (for example, by appointing a special sub-committee including an infectious diseases specialist to review HCS designs(1)) or refer HCS to a national / central ethics committee specifically appointed to ensure best practice in HCS research(11). Such capacity building in both scientific infrastructure and ethics expertise should ideally be sustained to ensure long-term benefits of more research, especially on pathogens (and other research programs) of relevance to the local community.

Since HCS are ethically sensitive, community engagement activities should begin early; among other benefits, this may allow study design and recruitment processes to be adapted to the relevant population (including issues of appropriate compensation and management of adverse events) and to local health research priorities. Publication of endemic HCS should ideally include the results of such community engagement activities(25) alongside scientific results(24) so that future research programs may be further improved.

Conclusions

There are many compelling ethical and scientific reasons to consider conducting more HCS in endemic countries, with the ultimate goal of developing new interventions against neglected diseases--and thereby improving the health of local people and those in other endemic countries. Yet there are also reasons to proceed cautiously, and each country will need to develop governance mechanisms appropriate to local circumstances. In other words, in India and other LMICs where HCS are being considered, policymakers, ethics committees and regulators should make decisions appropriate to their local setting, taking the relevant (and ethically salient) factors into account. In general, these would include (i) the scientific rationale for conducting research locally and/or the local importance of the knowledge gained, (ii) local regulation, ethical review, and trial pre-registration processes (iii) community engagement efforts, (iv) trial design, (v) pathogen selection, (vi) participant recruitment, selection and enrollment procedures (including issues of consent and financial compensation), (vii) potential benefits to participants and/or communities (viii) risks to participants and third parties (including the degree to which these can/should be minimized), (ix) reporting and management of adverse events, (x) post-trial follow-up of participants, and (xi) future access to the benefits of new interventions arising from such research. The current issue of this journal provides an opportunity to begin to address these ethical issues in order to assist policymakers in making decisions regarding existing or potential future HCS research programs in endemic settings.

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