THEME: DEVELOPING THE ETHICS OF CONTROLLED HUMAN INFECTION MODELS IN LMICS

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 (eg those 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"—ie 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. Although addressing social and environmental risk factors remains important (and often highly cost-effective), it is widely acknowledged that novel safe and effective interventions for neglected diseases can provide powerful tools for improving public health, especially in underprivileged populations. Since HCS could lead to such benefits being realised in a shorter timeframe and/or to benefits that might not otherwise be feasible (eg 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. As 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—ie "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

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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 sometimes be "deselected" (ie ruled out) for further testing in larger studies, HCS can provide a highly cost-effective way to advance infectious disease research–meaning that they may be especially attractive in resource limited settings. Similarly, where there are no existing vaccines or treatments for neglected pathogens, HCS can accelerate research programmes 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), this does not mean that intentional infection of healthy volunteers is necessarily ethically unacceptable. Grossly unethical challenge studies conducted by Nazi and Imperial Japanese Army researchers during World War 2, for example, are rightfully condemned for multiple reasons: they involved *uncontrolled* infection with especially dangerous and/or deadly pathogens; lack of voluntary informed consent, and violent force; and exceptionally vulnerable subjects (ie prisoners). In contrast, carefully controlled experiments involving intentional infection often pose only minor risks to which many (free and informed) participants would be (and are) willing to consent, and many such studies have been reviewed and approved by research ethics committees. Indeed, 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 impermissible.

HCS are nonetheless ethically sensitive—and, *inter alia*, they raise complex questions concerning (i) the acceptable limit of risks to which healthy volunteers may be exposed, (ii) appropriate financial payment/compensation of participants, (iii) the potential need for special review procedures (eg dedicated committees and/or the involvement of infectious disease experts), (iv) the need for protection of third-parties from infection (transmitted by participants), and (v) 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 (ie avoiding especially dangerous ones) and assurance of early access to treatment once infection is confirmed and/or symptoms develop (including through the use of inpatient challenge designs where participants are kept in healthcare settings or hotels staffed by healthcare professionals for the duration of the study in order to reduce risks to them and to others–even though this involves other kinds of burdens for participants, ie social isolation and time away from usual activities). Care has also been taken to exclude vulnerable participants–either those who may be physiologically vulnerable (eg due to comorbidities and/or co-infections including HIV–although two recently designed HCS are aiming for careful recruitment of individuals with well-controlled HIV (15)), and/or those who are vulnerable for other reasons including poverty or lack of education (16, 17). This is presumably 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 (i) it may perpetuate a lack of infrastructure and capacity in LMICs that could enable more locally relevant research and (ii) research conducted in high-income settings may not always translate well to LMICs (eg due to population differences regarding naturally acquired immunity, co-infections, genetics, microbiome, nutrition, etc) where neglected diseases are endemic (18). Indeed, for HCS to benefit LMICs they should ideally be designed in such a way that their findings are generalisable to the "target population(s)" ie those who are at highest risk of (severe) disease from the pathogen in question and stand to benefit most from new interventions.

Challenge studies in endemic settings

For this and other reasons, there have been increased calls for HCS in endemic settings (18, 19); and a limited number of such studies—involving diarrhoeal disease(20-22) and malaria (23-29) – have recently taken place (or commenced) in countries such as Thailand, Colombia, Tanzania, Kenya, Gabon, Mali, and Equatorial Guinea (15). 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 educational background of potential participants) and/or concerns about "undue inducement" (eg if financial compensation is "too high", in light of the 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 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.

Potential benefits in endemic settings

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—eg 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 (eg thalassemia and sickle traits as protective factors against severe malaria – both of which have been tested in challenge studies (28, 30, 31)) whereas the latter have not. Furthermore, innate or acquired immunity of members of the local population may also reduce risks to third-parties 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 (i) controlled infection leads to *protective immunity* against endemic diseases that otherwise would have put them at risk and/or (ii) HCS involves infection with a locally prevalent pathogen which participants might otherwise have been infected with later; but *controlled* infection (yielding immunity) leads to *less severe illness* than would otherwise be expected (in light of the controlled timing of infection, early diagnosis, monitoring, and care provided during the study) (32). HCS participants in endemic settings may in some cases thus directly benefit from immunity gained from a less severe bout of illness than would otherwise 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). Whether or not, or the extent to which, such benefits arise will depend upon facts about the particular pathogen, immune mechanisms (including the degree and duration of immunity gained during an HCS), and local epidemiology which may vary from study to study (and over time).

High risk cases

Conversely, in some cases challenge studies in endemic settings could be especially risky/harmful to participants. In the case of dengue, for example, the first infection usually leads to mild or no illness. The greatest risk of severe dengue–which can lead to a potentially life-threatening illness requiring intensive care and/or death (33)–is associated with the second infection (with a second strain of the dengue virus). The probability of severe dengue with second infection has been estimated to be around 2-5% (and is influenced by the timing and sequence of strains with which a person is infected, among other factors). Participation in a dengue human challenge study in an endemic/high prevalence setting could 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 (with a second strain of dengue) after the study - ie natural infection would then be more dangerous for them than it would have been prior to their participation in the study.

On the other hand, individuals who had previously been infected just once might be at especially high risk of severe dengue resulting from infection during a challenge study—because this would be their second infection. The magnitude of this risk would depend upon the challenge strain, and the use of a low-virulence strain might significantly reduce risks to participants. Infection with such a strain during a challenge study might actually benefit participants who would otherwise have been likely to be naturally infected with a higher virulence strain. Regardless of the strain used, for those who would otherwise have been likely to be infected naturally, challenge study participation could be beneficial because their second infection would then involve early diagnosis and supportive care. Alternatively, such studies of second dengue infection could be conducted among returned travellers in non-endemic countries who had been infected once during travel (thus avoiding endemic-country participants, who might be considered more vulnerable; and potentially decreasing risks, if better care is likely to be available in the non-endemic country).

Since the ethical acceptability of dengue HCS partly depends on the (net) risks entailed for participants included in the context in question, such risks should be systematically assessed and/or quantified as far as possible. Even if there is little or no net increase in risks for participants, it should be kept in mind that if severe cases of dengue end up being causally linked to HCS participation, this could hamper public acceptance of such studies.

Given the concerns raised above, some might argue that HCS with dengue in endemic/high prevalence settings might only be considered ethically acceptable, if at all, if participation is limited to those who have been infected with dengue at least twice before—ie both those who have never been infected and those who have been infected just once before would be excluded in order to reduce the risk of severe dengue resulting from a challenge study. Whether or not a study with such 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 previously infected)—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. In any case, excluding those who have never been infected, or those infected just once, with dengue could significantly reduce the value of a challenge

study design by making its findings less generalisable (eg because such a study might not sufficiently advance the understanding or prevention of severe dengue arising due to second infection, which is the outcome of greatest public health concern). Likewise, while the use of low virulence strains would reduce the risks to participants (34), it could also reduce the generalisability of the results of HCS to wild-type infection.

Generalisability

Rather than being unique to dengue, the issue of generalisability warrants consideration for all HCS designs–since their ethical acceptability partly depends on their findings being useful (and used, eg to select potential vaccine candidates for larger field trials) in terms of leading to public health benefits. On the one hand, there may be good ethical reasons to use certain strains that minimise risks to participants. If the use of such strains compromises the public health benefits of the study (because the results are not generalisable to wild-type infection–eg do not accurately predict the success or failure of vaccines in subsequent field trials), on the other hand, then the ethical rationale for using HCS rather than an alternative study design could be undermined.

Risks to third parties

With regard to the potential risks of transmission (of challenge infections) to third parties, local factors (eg in endemic as opposed to non-endemic regions) may influence study design and risk assessments. For example, the design of challenge studies involving diarrhoeal and other pathogens' spread via sewage should pay careful attention to appropriate sanitation at research facilities (especially in settings where local sewerage infrastructure may not be adequate, thus raising concerns of the spread of the challenge strain and/or the transfer of genes from the challenge strain to other pathogens) 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. One further consideration is the choice of challenge strain: although (in endemic settings) there may be high rates of acquired immunity to local pathogen strains, if different strains are used in a challenge study (to which the local population is not immune), then any third-party transmission could pose significant risks.

Capacity building for HCS

Establishing HCS research programmes 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 (eg 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 infectious diseases experts 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 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 (27) alongside scientific results (26) so that future research programmes 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 minimised),
(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.

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