Chapter 1
Introduction

Infectious diseases cause a large burden of morbidity and mortality worldwide, with a disproportionately high burden in low- and middle-income countries (LMICs). For example, many vector-borne diseases (e.g., malaria, dengue, schistosomiasis, Zika, etc.) and diarrhoeal diseases (e.g., cholera, *Shigella*, typhoid, etc.) are primarily endemic in LMICs among populations where social, economic, and physiological vulnerabilities are common and/or severe. Furthermore, many other pathogens with a wider global distribution nevertheless cause a disproportionate disease burden in LMICs (e.g., pneumococcus, streptococcus, *Neisseria*, respiratory syncytial virus, etc.). In addition to improvements in public health measures and social determinants of health, new medical interventions (e.g., vaccines and treatments) are urgently needed for many such pathogens. This is because (i) in some cases, no effective interventions exist and (ii) in others, existing interventions are becoming less effective (e.g., due to antimicrobial resistance) and/or are associated with unacceptable risks (e.g., drug toxicities).

Human infection challenge studies (HCS) involve the intentional infection of research participants with pathogens (or other micro-organisms) and primarily aim to (i) test (novel) vaccines and therapeutics, (ii) generate knowledge regarding the natural history of infectious diseases (and/or asymptomatic infection), 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 infection challenge studies are sometimes referred to as "controlled human infection studies," because they involve *controlling* the selection and/or production of the micro-organism strain(s) 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 micro-organisms causing no disease or disease that is self-limiting or can be (and is) *controlled* with effective cures or treatments; and/or *controlling* who is being infected (and/or subjected to other experimental interventions) (Selgelid and Jamrozik 2018).

HCS involving reliable models of infection provide an especially powerful scientific method for the testing of vaccines and therapeutics; and they can be

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substantially smaller, shorter, and less expensive than other kinds of studies. Among other benefits, they can significantly reduce the number of participants that must be exposed to an experimental intervention 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 (which may only be a small proportion of participants in field trials).

HCS are commonly used in early stage research for the selection of candidate interventions worthy of further investigation in larger studies. Well-designed HCS can thus lead to significant public health benefits being achieved sooner than would otherwise be possible, meaning that there is sometimes a strong ethical rationale for conducting such studies. In some cases, there may also be strong scientific and ethical justification to conduct HCS in LMIC populations in particular—especially if this would help to generate findings (e.g., regarding immune mechanisms and/or vaccine efficacy) that are more relevant to populations with the highest burden of relevant diseases.

Though numerous infamous historical cases of unethical research involved the intentional infection of human subjects with pathogens, the (sparse) existing bioethical ethical discourse on modern HCS (Miller and Grady 2001; Hope and McMillan 2004; UK Academy of Medical Sciences 2005; Lederer 2008; Miller and Rosenstein 2008; Gutmann and Wagner 2012; Bambery et al. 2015; Shah et al. 2017) 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 (i) the limit of acceptable risks to which healthy volunteers may be exposed, (ii) appropriate financial payment/compensation of participants, (iii) the potential need for special review procedures (e.g., involving dedicated committees and/or the involvement of infectious disease experts), (iv) the need for protection of third-parties from infection (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, in part via exclusion of vulnerable individuals. This is a major reason why modern HCS have been conducted almost entirely in wealthy developed nations, even for infections/diseases that are usually only present 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 LMICs where neglected diseases (for which research and development of new interventions are especially important) are endemic. For this

and other reasons, there have been increased calls for HCS in endemic settings (Gordon et al. 2017; Baay et al. 2018; Elliott et al. 2018).

In a review of the literature for this project, we identified 13 LMIC HCS published between 1992 and 2018 that were conducted in Thailand, Colombia, Tanzania, Kenya, and Gabon—countries in which the pathogens used (malaria, cholera, and *Shigella*) are endemic. These studies recruited around 400 individuals in total, which is less than 1% of the >40,000 volunteers who have participated in HCS in high income countries (HICs) in since World War II (Kalil et al. 2012; Evers et al. 2015).

Despite the potential scientific benefits of conducting HCS in endemic countries, HCS in such countries may raise (or be perceived to 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. Furthermore, the risks of spreading infections from study participants to third parties may be higher in some endemic areas and/or underprivileged populations (e.g., because of the presence of vectors for vector-borne diseases, or the absence of adequate sanitation to prevent the spread of diarrhoeal disease).

On the other hand, there may be cases where infection during HCS is less risky/harmful to participants in endemic settings than participants in wealthy developed countries—e.g., if the former have naturally acquired (partial) immunity to the pathogen under study (making resultant illness less severe) whereas the latter do not. Participation in HCS may sometimes even have *direct benefits* for healthy participants in endemic countries (which is usually not the case for participants from non-endemic wealthy 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 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) (Selgelid and Jamrozik 2018) and/or (iii) HCS participants receive an experimental vaccine that turns out to protect against subsequent infection (after the study) with locally prevalent strains of the pathogen in question.

Weighing the potential benefits and burdens (including risks to participants and third parties) associated with HCS requires careful attention to scientific and ethical aspects of study design, and should also involve learning from local communities regarding local priorities and the public acceptance of potential research designs etc. In any case, HCS should be conducted according to appropriate requirements of ethical and regulatory review, which may need to be adapted to this relatively complex and (in some settings) novel area of scientific research.

1.1 Focus of This Report

This report aims to fill a gap in the current literature by focusing particularly on ethical and regulatory issues that are specific and/or highly salient to challenge studies conducted in LMICs (where many pathogens of interest are primarily endemic). Having reviewed relevant scientific and bioethical literature, constructed case studies of LMIC HCS, and conducted qualitative interviews with relevant experts in LMIC HCS, we ultimately sought to identify (i) areas of consensus regarding ethical issues and regulation in the context of LMIC HCS, as well as (ii) unresolved issues that require further study/analysis.

1.2 Methods

1.2.1 Literature Review

Our review of academic literature and regulatory documents was particularly focused on identifying (i) primary scientific papers detailing LMIC HCS, (ii) relevant historical examples of (other) HCS, (iii) regulatory documents or policy consultations specific to HCS (whether HIC or LMIC), and (iv) bioethical analyses of HCS and/or ethical issues relevant to HCS in LMICs.

Relevant articles published between 1700 and 31st December 2018 were identified through searches in the authors' personal files, Google Scholar, and PubMed. Articles arising from these searches and citations within those articles were reviewed. For LMIC HCS, we included primary publications that gave details of HCS methods and results; conference abstracts were excluded due to lack of detail. Searches were conducted in English and articles published in English were the primary resources. Where articles in other languages had translations of their abstract or article available in English, these were also reviewed. The search strategy included the terms: bioethics, dengue, ethic*, cholera, challenge model, challenge study, controlled human infection model (CHIM), controlled human malaria infection (CHMI), histor*, human challenge, human infection study, malaria, regulat*, schistosomiasis, shigella, typhoid, Zika.

1.2.2 Qualitative Interviews

Our research team conducted qualitative interviews with 45 participants. We initially recruited informants based on involvement in the conduct of recent HCS in LMICs, expertise related to HCS, expertise in research ethics, and/or involvement in the regulation and/or funding of HCS research. Many interviewees currently working in HICs had been involved in and/or had expertise related to LMIC HCS in particular.

Table 1.1 Characteristics of 45 qualitative interview participants

	n	%
Primary area of expertise		
Science	33	73.3
Ethics	7	15.6
Regulatory representative	4	8.9
Funder representative	1	2.2
Primary location of work		
HIC	26	57.8
LMIC	19	42.2
Africa	6	13.3
Asia	9	20.0
North America	15	33.3
South America	4	8.9
UK/Europe	11	24.4
Sex		
Female	20	44.4
Male	25	55.6
Total	45	100

Further informants were recruited via "snowball" sampling, based on suggestions from the above informants at time of interview. As detailed in (Table 1.1), we recruited a diverse group of participants with a wide range of expertise. Deidentified interview transcripts were coded thematically with a combination of pre-set and open coding. The research team, informed by the main aims of the study, agreed upon an initial code list. Coding then progressed openly and iteratively as emergent codes arose and coding categories were further refined as agreed by the research team. Data were organised and cleaned for use in the final analysis. Coded data were analysed to identify overarching themes and sub-themes (that were validated through initial member checking in subsequent interviews and via the mechanisms discussed below) with validated themes being used to inform the structure of this Final Report. As part of the consent processes, interview participants consented to be quoted anonymously (by pseudonym) in this report and other relevant publications and/or to waive the right to anonymity and be quoted by name.

1.2.3 Synthesis and Validity Checking

The findings of the literature review and thematic analyses of qualitative data were synthesised in this Final Report. Draft copies of the Final Report were shared with (i) a subset of participants who provided feedback to the research team (enabling

an assessment of internal validity) and (ii) participants at two international meetings of researchers and policymakers with relevant expertise (enabling an assessment of external validity and transferability).[1] Comments were incorporated, in most cases with de-identified acknowledgement in light of participants' wishes.

References

Baay, M.F.D., T.L. Richie, P. Neels, M. Cavaleri, R. Chilengi, D. Diemert, S.L. Hoffman, R. Johnson, B.D. Kirkpatrick, and I. Knezevic. 2018. Human challenge trials in vaccine development, Rockville, MD, USA, September 28–30, 2017. *Biologicals*.

Bambery, B., M. Selgelid, C. Weijer, J. Savulescu, and A.J. Pollard. 2015. Ethical criteria for human challenge studies in infectious diseases. *Public Health Ethics* 9 (1): 92–103.

Elliott, A.M., M. Roestenberg, A. Wajja, C. Opio, F. Angumya, M. Adriko, M. Egesa, S. Gitome, J. Mfutso-Bengo, and P. Bejon. 2018. Ethical and scientific considerations on the establishment of a controlled human infection model for schistosomiasis in Uganda: Report of a stakeholders' meeting held in Entebbe, Uganda. *AAS Open Research* 1.

Evers, D.L., C.B. Fowler, J.T. Mason, and R.K. Mimnall. 2015. Deliberate microbial infection research reveals limitations to current safety protections of healthy human subjects. *Science and Engineering Ethics* 21 (4): 1049–1064.

Gordon, S.B., J. Rylance, A. Luck, K. Jambo, D.M. Ferreira, L. Manda-Taylor, P. Bejon, B. Ngwira, K. Littler, and Z. Seager. 2017. A framework for controlled human infection model (CHIM) studies in Malawi: Report of a Wellcome Trust workshop on CHIM in low income countries held in Blantyre, Malawi. *Wellcome Open Research* 2.

Gutmann, A., and J. Wagner. 2012. Ethically impossible STD research in Guatemala from 1946 to 1948. *Presidential Commission for the Study of Bioethical Issues.*

Hope, T., and J. McMillan. 2004. Challenge studies of human volunteers: Ethical issues. *Journal of Medical Ethics* 30 (1): 110–116.

Kalil, J.A., S.A. Halperin, and J.M. Langley. 2012. Human challenge studies: A review of adequacy of reporting methods and results. *Future Microbiology* 7 (4): 481–495.

Lederer, S.E. 2008. Walter Reed and the yellow fever experiments. In *The Oxford textbook of clinical research ethics*, 9–17.

Miller, F.G., and C. Grady. 2001. The ethical challenge of infection-inducing challenge experiments. *Clinical Infectious Diseases* 33 (7): 1028–1033.

Miller, F.G., and D.L. Rosenstein. 2008. Challenge experiments. In *The Oxford textbook of clinical research ethics*, 273–279.

Selgelid, M.J., and E. Jamrozik. 2018. Ethical challenges posed by human infection challenge studies in endemic settings. *Indian Journal of Medical Ethics.*

Shah, S.K., J. Kimmelman, A.D. Lyerly, H.F. Lynch, F. McCutchan, F.G. Miller, R. Palacios, C. Pardo-Villamizar, and C. Zorilla. 2017. Ethical considerations for Zika virus human challenge trials. *National Institute of Allergy and Infectious Diseases.*

UK Academy of Medical Sciences. 2005. *Microbial challenge studies of human volunteers.* London: Academy of Medical Sciences.

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