The Ethical Challenge of Infection-Inducing Challenge Experiments

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Challenge experiments that induce infections in healthy volunteers are an important method for initial efficacy testing of candidate vaccines and for study of the pathogenesis of infectious diseases. Although these studies can be conducted safely for selected infectious diseases that are either fully treatable or self-limiting, they raise significant ethical issues. An ethical framework is offered for evaluating infection-inducing challenge experiments, which focuses on the scientific and public health rationale for conducting these studies, the risks that they pose and the ways in which these risks can be minimized, the symptoms experienced by healthy volunteers that may cause discomfort or distress, the exclusion of vulnerable research subjects, the informed consent process, the payment of volunteers, and the use of isolation of volunteers to prevent infection of others.

Infectious diseases continue to cause substantial morbidity and mortality. The world's biggest killer of children and young adults, infectious diseases are responsible for >13 million deaths annually, most of which occur in less developed countries [1]. Continued research is critical to finding safe and effective ways to prevent and treat infectious diseases. The challenge experiment is an important method that is sometimes used to study the pathogenesis of infectious diseases and, especially, to evaluate initial efficacy of vaccines before large-scale field tests are conducted. In challenge experiments, infections are deliberately induced under carefully controlled and monitored conditions, usually in inpatient settings. Research volunteers are exposed to bacteria, viruses, or parasites, including *Vibrio cholerae*, agents that cause malaria, influenza viruses, endotoxin, and *Salmonella* serotype Typhi [2–6]. Induced infections are usually either self-limiting or can be fully treated within a relatively short period of time.

Experiments conducted by physician-investigators designed to cause infections that have uncomfortable symptoms in human subjects are likely to evoke serious moral concern. Some might argue that physicians, who ought to be dedicated to avoiding the deliberate infliction of harm on patients, should never undertake research that induces infections in healthy volunteers. Although these experiments, by their very nature, are ethically troubling, we contend that they are not necessarily unethical and that they may be ethically justified when conducted by competent investigators according to scientifically sound protocols that incorporate safeguards to ensure the safety of volunteers. Clinical research commonly involves risks to subjects that are not compensated by medical benefits, but that are justified by the potential value of the knowledge to be gained. Infection-inducing challenge experiments are not necessarily any more ethically problematic than are phase I trials aimed at the determination of the maximum tolerated doses of investigational agents. Such trials typically enroll healthy volunteers who are exposed to potential side effects and complications without any compensating medical benefits.

The ethics of this experimental paradigm in the field of infectious disease research have been considered by investigators, institutional review boards (IRBs), the US Food and Drug Administration (Rockville, Maryland), and the National Institutes of Health (Bethesda, Maryland) [6]; however, they have not been examined systematically in the medical or bioethics literature. We offer a framework for

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evaluating the ethical acceptability of particular infection-inducing challenge experiments.

FRAMEWORK FOR EVALUATING THE ETHICS OF INFECTION-INDUCING CHALLENGE EXPERIMENTS

The following questions, which are summarized in table 1, are pertinent to evaluating the ethics of infection-inducing challenge experiments. This framework draws primarily on the Nuremberg Code and on federal regulations in the United States that govern research with human subjects [7, 8]. Similar guidance can be derived from the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects [9, 10].

Is the scientific rationale for using a particular human infection–inducing challenge model acceptable? Infection-inducing challenge models have been used for many years to study the pathogenesis of infectious diseases and to evaluate the preliminary efficacy of investigational vaccines. For example, in a report of a typical challenge study, 25 healthy adult volunteers received an experimental cholera vaccine candidate [11]. Five weeks later, 18 of the vaccinees and 8 of the unvaccinated control subjects were challenged with wild type El Tor Ogawa *V. cholerae*. Three vaccinees and 7 control subjects developed diarrhea, which demonstrated preliminary efficacy of the vaccine (80.9%).

In another study, Sack et al. [2] administered a strain of frozen cholera bacteria to 40 volunteers in an attempt to establish a standardized inoculum of *V. cholerae* for future challenge and vaccine studies. According to the authors, "The goal of the study was to determine a dose of bacteria which would consistently induce diarrhea in $\geqslant$80% of volunteers. Additionally, it was important that many of the illnesses should be moderate or severe (i.e., that the geometric mean of the total diarrhea was at least 3 liters)." Induction of severe diarrhea was important to ensure that the cholera challenge approximated the disease in its natural state and thus is useful in future testing to determine whether candidate vaccines provide adequate protection.

Thirty-four (85%) of the 40 volunteers developed diarrhea, which was "severe" in 10 subjects. Ten volunteers (25%) vomited, and 15 (38%) had fever (temperature, >40.8°C) that lasted <24 h. The volunteers were carefully monitored; they received fluids, to prevent dehydration, and antibiotic treatment, when their symptoms met the criteria for severe cholera or 4 days after administration of the bacteria. The study successfully demonstrated a method of cholera challenge for use in testing the efficacy of candidate vaccines.

Vaccine development is a long, complex, and costly process that involves multiple steps to demonstrate that a vaccine is safe, immunogenic, and protective before it is licensed for widespread use [12]. Usually, basic research is done to identify and characterize the causative agent, describe the host's immune response, and develop candidate vaccines for testing. Then, ideally, an animal model that mimics human infection and response can be used to test safety and efficacy before researchers begin testing in humans. Animal experimentation raises its own set of ethical issues, however, and for many studies of serious infectious diseases, animal models are not available or have limited utility [13]. Nonetheless, human challenge experiments should not be undertaken if the knowledge could be obtained by means of ethical research with animals.

Human testing of vaccine candidates occurs in sequential phases; it begins with evaluation of safety and immunogenicity and subsequently involves protective efficacy. Expeditious development of effective vaccines can help spare many people from morbidity or death associated with infectious diseases. Preliminary evidence of the effectiveness of a vaccine candidate obtained through a challenge model could limit the exposure of thousands of human subjects in field trials to only the most promising vaccine candidates. In addition, by weeding out vaccine candidates that do not demonstrate the ability to protect challenged subjects, and by identifying possible confounding variables in the measurement of outcomes, the use of a challenge model could significantly increase the efficiency and reduce both the time and the cost of vaccine development [12, 14].

Certain infection-inducing challenge models, therefore, are scientifically valuable in the generation of useful knowledge that is not otherwise readily obtainable, which can expedite development of vaccines to prevent serious illness. However, each proposed study that makes use of an infection-inducing challenge model should be evaluated on its own merits to determine whether it is an appropriate method for answering an important research question. Assessment of the study's scientific rationale should always precede assessment of its risks and discomforts.

Are the risks of infection-inducing challenge studies acceptable? When infection-inducing challenge experiments, conducted by qualified investigators, are confined to infectious diseases that either are self-limiting or can be fully treated, and when volunteers are carefully monitored and treated to prevent or counteract potentially serious complications, such as dehydration, these experiments do not pose risks of lasting harm. For example, according to a retrospective review of 18 challenge experiments that involved the infection of 118 healthy volunteers with malaria, no subjects had lasting sequelae. However, 97% of the subjects experienced $\geqslant$1 symptoms. The most common symptoms were arthralgia or myalgias (in 79% of subjects), malaise or fatigue (in 79%), headache (in 77%), chills (in 68%), and fever (temperature, >38°C; in 61%), which had a median duration of 2 days [3].

Although infection-inducing challenge

Table 1. Framework for ethical evaluation of infection-inducing challenge experiments.

Ethical issue	Specific questions and considerations
Rationale for using human challenge model	What the are scientific aims of study?
	What is the justification for using infection-inducing challenge model?
	Have alternative methods of answering the research question been considered?
	Has the model been used in animals?
Risks	Is there possibility of serious risk or harm?
	How will volunteers be screened or evaluated before enrollment?
	Are the induced infections self-limiting or reversible?
	Are the symptoms of infection treatable or tolerable?
	What is the plan for management of infection or symptoms?
	How will the volunteers be monitored?
	Are there potential risks of transmission to others?
	How will these risks be minimized?
Discomforts	What are the expected symptoms (type, duration, magnitude) from induced infection?
	How will discomforts be minimized?
	How will symptoms be monitored?
	When and how will symptoms be treated?
Vulnerable subjects	How will vulnerability be assessed?
	Are proposed volunteers competent adults?
Informed consent	Is there adequate information about purpose, procedures, (including isolation, if relevant), risks, discomforts, lack of benefit?
	How will volunteers be provided with information?
	Will there be adequate opportunity for questions and discussion?
	How will the capacity for making decisions and comprehension of information be assessed?
Financial compensation	Does the amount of financial compensation constitute undue inducement?
	Is it commensurate with the time and effort required?
	Is it calculated according to institutional policy or standard formula?
Right to withdraw from research	Is the time and method of isolation limited to that necessary to protect others?
	How will research team assess whether or not volunteers are adequately informed about the need for isolation and the possible limitations on leaving the research facility?

experiments can be conducted safely and without the risk of lasting adverse consequences, volunteers are exposed to symptoms of infectious diseases that may be uncomfortable. How, then, should the level of risk that is posed by infection-inducing challenge experiments be characterized? The concept of "minimal risk" in studies that involve human subjects is widely regarded as marking a threshold between those studies that can be readily justified from those that require more rigorous scrutiny and a determination of substantial potential benefits to the subjects or valuable knowledge to be gained. In the United States, the regulations that govern research using human subjects at institutions receiving federal funds define "minimal risk" as follows: "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" [8]. Infection-inducing challenge experiments with such diseases as malaria, cholera, and typhus do not pose a probability and magnitude of harm that make their risk more than minimal. With respect to discomfort, however, the more severe symptoms experienced by a substantial proportion of subjects in these experiments fall outside of the range of those ordinarily encountered in daily life, especially when the volunteers would not otherwise be exposed to the diseases under investigation. Therefore, these studies typically are more than "minimal risk."

Federal regulations in the United States, however, do not limit research that involves healthy adult volunteers to minimal risk studies. In fact, many examples of studies that have involved healthy volunteers could arguably be classified as carrying risk that is greater than minimal, such as phase I drug studies or studies that involve liver biopsies, bronchoscopies, or other invasive procedures. In contrast, a 1986 report of the Royal College of Physicians of London, "Research on Healthy Volunteers," stipulated that "A risk greater than minimal is not acceptable in a healthy volunteer study"

[15]. That report defines "minimal risk" as including the following 2 types of situations: "The first is where there is a small chance of a recognized reaction which is itself trivial, e.g., a headache or feeling of lethargy. The second is where there is a very remote chance of a serious disability or death" [15]. Challenge experiments that induce infections with agents of malaria, typhoid, and cholera may qualify as minimal risk, with respect to the second criterion, but they do not satisfy the first. Severe diarrhea induced by challenge with *V. cholerae* [2] or 2 days of high fever, along with arthralgia or myalgia, malaise or fatigue, headache, and chills, induced by challenge with *Plasmodium falciparum* [3], although they are predictable and reversible reactions, are not "trivial." Indeed, the infections and symptoms that are induced by these experiments are judged to be sufficiently severe to warrant inpatient supervision, supportive care, and antibiotic treatment for all subjects. Although the risk is more than minimal, challenge studies can be conducted safely for a circumscribed range of induced infections. To avoid causing serious or irreversible harm, induced infections should be self-limiting, or effective therapies to treat or easily reverse symptoms should be available. These experiments must be accompanied by IRB-approved plans for monitoring the well-being of volunteers and for reporting adverse events.

Infection-inducing challenge experiments also may pose risks to persons who are not research participants, because volunteers may transmit infectious diseases to others with whom they come into contact. Careful screening of prospective volunteers can reduce the risk of disease transmission to those persons who are most vulnerable to infection; for example, pregnant women and volunteers who live in households with infants could be excluded. Furthermore, volunteers must practice adequate contraception while they are capable of transmitting infection. Infection control procedures for research and clinical staff, who come into contact with volunteers, and isolation of volunteers, while they remain infectious, may be indicated for some challenge experiments. Isolation, however, presents additional ethical problems, which are addressed below.

Are the discomforts of infection-inducing challenge experiments acceptable? Although the risks of lasting harm from infection-inducing challenge experiments may be minor, we contend that these studies deserve serious ethical scrutiny because of the probability and magnitude of discomfort that they can produce. The symptoms produced by induced infections can cause significant distress lasting a few days or more; accordingly, they should not be considered "mere inconveniences" [16]. The evaluation of discomfort or distress that is not associated with risks of lasting harm has not received the attention it deserves in the literature on the ethics and regulation of research that involves human subjects. The Nuremberg Code states, "The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury" [7]. Federal regulations mention discomfort in the definition of minimal risk, quoted above, and in the general requirements for informed consent, which include "a description of any reasonably foreseeable risks or discomforts to the subject" [8].

There are no agreed-upon criteria to determine what degree of research-related discomfort is acceptable in research without the prospect of benefit for individual subjects. Some would argue that there should be no limit on how much discomfort is allowed in such research, because competent adults who are presented with adequate information about an infection-inducing challenge study have the right to decide how much discomfort or inconvenience they are willing to accept [17]. Others, including the authors, contend that some studies might be likely to produce such a magnitude of discomfort that it would be unethical to recruit volunteers. In any case, the discomforts anticipated in a challenge study should be addressed by investigators and IRBs and minimized, by means of careful monitoring and control of symptoms, in a manner consistent with the scientific purpose of the research. Reports of infection-inducing challenge studies typically describe the physical symptoms that are experienced by the volunteers, but not the accompanying subjective distress. Empirical research on the assessment of discomfort experienced by volunteers in infection-inducing challenge experiments would illuminate the level of tolerable discomfort from the perspective of the volunteers and thus contribute to ethical appraisal of this experimental paradigm.

Does the challenge experiment enroll subjects from a vulnerable population? In view of the level of discomfort and lack of benefit posed by infection-inducing challenge experiments, this type of research should not be conducted with groups of subjects who may be particularly vulnerable to exploitation. Accordingly, children and incompetent adults, as well as prisoners, should not be recruited for these studies. Economically disadvantaged persons could be vulnerable to "undue inducement" in some cases from the offer of financial compensation; however, exclusion based solely on income is discriminatory. The potential for exploitation can be reduced by a careful process of informed consent and determination of financial compensation, as discussed below.

Does the informed consent process, including the consent documents, adequately inform potential subjects about the risks and discomforts associated with the challenge experiment? A thorough process of information disclosure before research enrollment is critical to ensure that prospective volunteers understand the purpose of challenge experiments; the procedures involved, including isolation,

if it is relevant; the risks of the induced infection and the measures undertaken to minimize these risks; the type, level, and duration of discomfort likely to be experienced; what can or will be done to alleviate discomfort; and the fact that there are no individual health-related benefits from research participation. To ensure subjects' capacity to give voluntary informed consent for infection-inducing challenge studies, certain strategies, such as multiple information sessions and discussions with time for questions, written tests of comprehension, and possibly a psychological evaluation, might be appropriate [18, 19].

Does the amount of financial compensation offered to volunteers for challenge experiments constitute "undue inducement" that interferes with voluntary consent? Volunteers for these experiments usually receive financial compensation, as is typical for research with healthy volunteers that offers no potential health benefits. Although altruism may motivate some volunteers, it is believed that recruitment for infection-inducing challenge experiments would not be sufficient without payment for research participation. Ethical concern about paying research subjects is based on the possibility that the need or desire for money will unduly induce prospective volunteers to discount the risks and discomforts of research participation [20]. On the other hand, persons who contribute their time and effort to the conduct of important but often uncomfortable research should be compensated appropriately for their participation and not asked to make financial sacrifices. IRBs should assess the level and methods of compensation for challenge experiments, within the context of plans for ensuring informed consent, to evaluate the potential for undue inducement. The amount of compensation should be determined on the basis of the time and inconvenience of research participation, not on the level of risk, and should be comparable to other local unskilled employment opportunities [20]. Compensation should be calculated and prorated according to time and procedures completed.

Is the conduct of infection-inducing challenge experiments compatible with the right of human subjects to withdraw from research participation at any time without penalty? In some studies, volunteers are isolated for a period of time after infectious challenge to prevent infection of others [21]. Such restriction on the freedom of research volunteers should not be permitted unless it is judged by investigators and IRBs to be necessary to protect public health. Isolation or constraints on the ability to leave the research facility conflicts with the norm of research ethics, which is that volunteers are able to withdraw from research participation at any time without interference or penalty. However, restrictions on freedom to withdraw from research participation or a research facility are not unique to infection-inducing challenge experiments. In studies that involve experimental bone marrow transplantation, for example, once subjects have received prior whole body radiation, they must continue to participate in the protocol for their own safety, until transplantation and associated treatment have been completed. In a closer analogy to infection-inducing challenge experiments, psychiatric patient volunteers in studies that withdraw subjects from medication may not be free to leave the research facility if they are judged to be a danger to themselves or others.

Challenge experiments that involve isolation should limit the time volunteers spend in isolation to what is necessary to eliminate the risk of infecting others. The need for isolation places an added burden on the process of informed consent. All volunteers must be fully cognizant of and agree voluntarily to the isolation requirements. Whereas subjects may not be allowed to leave the research facility for a specified period, this does not preclude their right to withdraw from further exposure to infectious agents and/or other unwanted research procedures.

SPECTRUM OF CANDIDATE DISEASES FOR HUMAN CHALLENGE MODELS

In exploring the ethical justifiability of particular challenge experiments, it may be helpful to consider infection-inducing challenge models as falling along a continuum from those that are legitimate to those that are clearly unacceptable. In between lies a border zone of more controversial potential experimentation. At one end of the spectrum, legitimate challenge models might include those experiments that induce infections with a rapid onset of tolerable symptoms and those that are self-limiting or that can be adequately treated and eradicated with certainty. Examples include challenge experiments investigating the common cold, cholera, and malaria. At the other end of the spectrum, and considered unacceptable, according to current knowledge, would be challenge models in which infections are induced for which treatment is nonexistent or ineffective, symptoms are intolerable, and/or serious morbidity or mortality is likely to result—for example, HIV or hepatitis C virus. In between the extremes lie potential challenge models that would expose subjects to infections that are characterized by less-than-full confidence in eradication, the possibility of chronic disease, and/or an increased, but still small, risk of serious morbidity or mortality. Current examples might include challenge models for Lyme disease or *Helicobacter pylori* infection. Decisions about the acceptability of proposed models in this middle area require the considered judgment of thoughtful people by means of an ethical framework, such as the one proposed here. As the state of biomedical knowledge and treatment progresses, the location of possible challenge models along this spectrum is likely to shift.

CONCLUSIONS

We have raised questions and offered suggestions concerning the ethics of human infection–inducing challenge experiments with the aim of providing an ethical structure for carefully considering these studies. Such research poses significant moral issues, but it may be ethically justifiable. The complex and demanding task of determining whether, and under what conditions, infection-inducing challenge experiments are morally acceptable rests with funding institutions, investigators, IRBs, and regulatory authorities. Whereas the need to improve public health is compelling, it is imperative to ensure that all research adequately protects human subjects and complies with shared moral values.

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