



# Infectious Disease Challenge Studies: Ethical Issues in Causing Disease for Medical Knowledge

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*Infectious disease “challenge” studies, in which healthy participants are deliberately infected with pathogens to investigate the cause, prevention, and treatment of infectious diseases, hold great potential for delivering high-quality data about new interventions. Infectious challenge studies may be used to address a variety of scientific questions, such as demonstrating a causative role for a specific infectious agent in a particular disease, testing the ability of a drug to prevent or ameliorate disease, or testing the efficacy of a prophylactic vaccine.*

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## How Challenge Studies Address Difficulties with Standard Trial Designs for Infectious Diseases

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Infectious disease challenge studies may be employed to investigate both prophylactic measures (prevention of infections), and treatment of illness after the infection has occurred. First, we’ll address studies of prophylactic measures.

In order to study whether an investigative agent prevents infection, the researchers need to know the expected infection rate that would occur without prevention. This is referred to as the “attack rate”—the percentage of the population who become infected. If the natural attack rate is low, meaning only a small percentage of the population would be expected to be infected over the study duration, assessing the efficacy of any prophylactic measures will be difficult.

### Example 1: Neuraminidase Inhibitors for Influenza

Over a period of decades, more than 50 independent studies have enrolled over 1000 human volunteers in influenza infectious challenge protocols for a broad variety of experimental aims. In the late 1990s two parallel double-blind, placebo-controlled trials were carried out to determine the utility of the neuraminidase inhibitor oseltamavir as a prophylactic and a therapeutic treatment respectively<sup>1</sup>. One hundred seventeen volunteers were each housed in individual hotel rooms in isolation for one day, and then inoculated with a defined dose of cultured virus. Oseltamavir was given one day before (in the prophylactic study) or one day after (in the therapeutic study) the viral challenge. In the prophylactic study 67% of placebo and 38% of oseltamavir-treated subjects developed infection, with 50% of placebo and 0% of oseltamavir-treated subjects developing respiratory disease. In the therapeutic study, oseltamavir treatment resulted in a significant decrease in viral load and disease symptoms. These and similar studies played a significant role in determining best practices for management of influenza infection.

A very large number of subjects would have to be enrolled to get valid results, and the study may be very long. However, if the attack rate can be increased by intentional exposure to the infectious agent such that a difference in infection rates in the investigational agent arm and control arm can be more easily detected, both the sample size and the study duration can be

### **Example 2: A Vaccine to Prevent Cholera**

Several challenge studies were conducted to determine the ability of a single dose of live, oral cholera vaccine CVD 103-HgR to protect against various clinically significant strains of cholera. In dose-finding studies, volunteers were given increasing doses of a challenge strain to determine an appropriate challenge dose to induce disease. In one study, volunteers were randomized to receive vaccine or placebo and three months later 51 volunteers were orally challenged with a virulent clinical strain of cholera. Ninety-one percent of placebo-dosed volunteers developed diarrhea compared to 18% of vaccine-dosed volunteers (protective efficacy 80%). Thirty-nine percent of placebo-dosed subjects developed severe diarrhea, compared to 4% of vaccine-dosed volunteers (protective efficacy 91%)<sup>2</sup>. These data played a significant role in the eventual licensure of the vaccine for travelers.

decreased significantly. Importantly, the study can be carried out in a controlled or inpatient setting where subjects can receive intensive clinical oversight for treatment of the infection if necessary.

The safest and most effective public health intervention for many infectious diseases is preventive treatment with an attenuated, altered, or modified version of the pathogen to induce a protective immune response (vaccine). Unsurprisingly, vaccine safety and efficacy testing account for a large portion of proposed

infectious disease challenge studies. To estimate vaccine efficacy, one usually needs, at minimum, two groups of subjects, each with equivalent risk of infection. The efficacy of a preventive vaccine can be reported as the percentage reduction in number of subjects in a vaccine arm compared to a placebo/control arm who become infected over the course of the trial. The accuracy, and thus the practical utility, of efficacy estimates depends on the degree to which the two arms are truly at equal risk and on the number of subjects who become infected in the control arm—more infections mean more confidence in the reported efficacy. By carefully choosing a challenge dose of wild-type virus after study vaccine, the trial can achieve a nearly 100% attack rate, resulting in adequate statistical power with a much smaller enrollment.

### **Example 3: A Vaccine to Prevent Zika Virus Infection.**

Two DNA vaccines are in preliminary safety testing to determine whether they may be potential candidates for the prevention of Zika virus infection. How long the virus remains in infected people, and how they experience the stages of infection and recovery, are not well understood. In preparation for studies to assess the efficacy of the vaccines, researchers first plan to conduct a study in which volunteers are infected with varying amounts of the virus. The natural history and course of their infection is monitored closely, to understand better what the design and endpoints of the prevention study should be.<sup>3</sup>

Infectious disease challenge studies are also relevant in the development of treatment for infections. A number of different factors may impact the disease course of an infection and the response to infection therapy including the duration of infection, route of infection, quality and type of supportive medical care, and exact strain of infectious agent. In a general medical setting, enrollment of patients with infections that occur as a result of natural exposure would require controlling for all these variables in the analysis of data about the treatment efficacy. However, if the infection is intentionally caused, these factors are all known and consistent across subjects. Therefore, the outstanding question of whether the treatment is effective can be answered with much cleaner data. Because the infection can be induced at a specific time, the study can also be much shorter in duration.

### Agent Considerations

Not all infectious diseases are appropriate for deliberate challenge studies, and various criteria must be met for an infectious challenge to be ethically permissible. First, the infection must be curable or self-limiting. For example, because infection with human immunodeficiency virus (HIV) is currently incurable, deliberate infection of a human subject with HIV is unethical. Second, even if curable (e.g. with antibiotics or antivirals), the disease process must not cause unacceptable harm to study participants. However, harms can be managed in some cases. If an appropriate clinical test can detect surrogate

biomarkers before serious disease symptoms, it allows intervention with a curative treatment before subjects experience unacceptable harm. There are currently over twenty human infectious challenge agents in use, encompassing viral, bacterial, and parasitic pathogens. In the USA, challenge agents are treated as active agents and require the filing of an Investigational New Drug application with the Food and Drug Administration (FDA).

PATHOGEN TYPE	EXAMPLES
Viral	norovirus <sup>4</sup> , influenza <sup>5</sup> , dengue <sup>6</sup> , rhinovirus <sup>7</sup> , respiratory syncytial virus <sup>8</sup>
Bacterial	cholera <sup>9</sup> , typhoid <sup>10</sup> , <i>shigella</i> <sup>11</sup> , enterotoxigenic <i>E. coli</i> <sup>12</sup> , <i>Helicobacter pylori</i> <sup>13</sup> , gonorrhea <sup>14</sup> , campylobacter <sup>15</sup> , <i>Streptococcus pneumonia</i> <sup>16</sup> , <i>Haemophilus ducreyi</i> <sup>17</sup> , <i>Mycobacterium bovis BCG</i> <sup>18</sup>
Parasitic	malaria <sup>19</sup> , hookworm <sup>20</sup> , cryptosporidium <sup>21</sup> , giardia <sup>22</sup> , leishmania <sup>23</sup>

TABLE 1: Examples of Pathogens Currently in Use in Human Infectious Challenge Studies

An important factor in study design is the choice of the pathogen strain. Questions addressed in the clinical protocol about the pathogen strain chosen for the study should include:

- **How virulent is the strain?** Would it be possible to achieve the project goals with a less virulent strain or a deliberately attenuated strain? For example, dengue and cholera

challenge studies have used attenuated pathogen strains that cause less serious disease than wild strains. *Mycobacterium bovis* BCG is a non-virulent strain of *Mycobacterium* that is being used as a surrogate challenge for tuberculosis, whereas deliberate infection of subjects with *M. tuberculosis* would involve risks to subjects and to the public difficult to justify.

- **Is the strain resistant to any clinically-relevant drugs?** The use of any drug-resistant strain should be carefully justified. Drug sensitivity is important to allow rescue treatment of study participants and to manage the potential harm of any unintended secondary transmission.
- **Is the strain genetically or antigenically distinguishable from wild circulating pathogen strains?** It is desirable for the challenge strain to bear a genetic “fingerprint” that will easily distinguish the challenge strain from clinical strains that occur as natural infections. This allows tracking of the experimental pathogen in case of secondary transmission. It also protects researchers and institutions from adverse public perceptions if natural infections occur in the vicinity of the trial, by demonstrating that they were not the result of the trial conduct.

## Biosafety Considerations

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The use of infectious agents in the clinical study may create risks that apply to other persons beyond the study volunteer. The protocol should consider and—if applicable—describe appropriate protections for study personnel, personal contacts of the study volunteers, and the general public. Factors to be considered include the route, duration, and magnitude of pathogen shedding. Appropriate procedures to reduce risk to others might include a specific duration of confinement, restriction of subjects’ personal contacts, and/or vaccination of study staff.

The most important components of any biocontainment program are awareness, education, and training. It is important that any persons who may be at risk of secondary transmission in a challenge study are informed of the risk, trained on exposure control, and educated about how to respond to suspected exposures or secondary transmissions. Information on the pathogen, strain, diagnostic criteria, and drug sensitivity should be readily available for medical personnel handling any potential secondary transmission cases.

## Ethical and Informed Consent Considerations

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Deliberately infecting a healthy person with an





## Institutional Biosafety Committee Review

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* require that each institution receiving relevant NIH funding must register an Institutional Biosafety Committee (IBC) with the NIH. An important requirement of the *NIH Guidelines* is that an IBC should review all human gene transfer clinical trial research that takes place at the institution. Many institutions have policies that require IBC review of other studies involving infectious agents, even if those studies do not involve recombinant or synthetic nucleic acids. They consider that biosafety professionals and infectious disease specialists who sit on the IBC are well positioned to provide advice and oversight of clinical trials involving both recombinant and wild-type (most commonly occurring in nature) infectious agents. If the agent was derived using recombinant genetic technology, then experiments involving deliberate transfer into a human subject usually fall under Section III-C of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. Such studies require extra oversight by the NIH Office of Science Policy and the local IBC.

infectious disease purely in the interest of scientific advancement raises serious ethical questions. Because challenge studies are unique in giving people diseases in order to study how to prevent or treat those diseases, they create a strong ethical duty for researchers. Key features of ethical consideration should be explicitly and clearly addressed in the protocol, with quick response and appropriate modifications to the protocol should the study conduct encounter unexpected situations. The Belmont report<sup>24</sup> provides three key points of beneficence, justice, and respect for persons. To address these in infectious challenge studies requires particular consideration of risk/benefit analysis, selection of subjects, and informed consent. Since the infections being studied are caused for the purpose of research—no one is being treated for an illness they had before study participation—the significant risks to subjects are only balanced by the potential for benefit to society. An honest but full case for the benefits to society and a reasonable estimate of that potential benefit in the face of sometimes limited data are crucial. The protocol should include explicit discussion of the measures taken to minimize risks for the unique issues associated with infectious agents. This may include study design factors such as data collection and attention to long-term sequelae of infection that may extend long past the exposure—sometimes for months or even years. In the face of limited information, the study may need to anticipate revisions to the follow-up period as information is learned or address it as unknown.

Ensuring that participation in research is truly voluntary protects the individual regardless of whether there is a potential for high societal benefit. Key components of the informed consent process are assuring that subjects are fully informed and that they have sufficient time to discuss questions to make a considered choice. Additional measures might be appropriate in the informed consent process to ensure both of these are true. In some cases, involving more virulent or contagious pathogens or extended study durations, it may be appropriate for the consent process to be conducted in a series of discussions rather than asking for consent at the time the initial information about the study is conveyed. This ensures that the potential subject has the time to consider information and to ask questions. As with many complicated or potentially high-risk studies, supplemental materials to ensure comprehension of the study and study information (comprehension tests, graphics, videos, etc) can be useful.

Challenge studies present a unique ethical consideration in that shedding of the infectious agent may allow subjects to infect others, including close contacts. Confining subjects to special facilities during the period of contagion to reduce this risk is a frequently used approach; however, subjects must be allowed to withdraw from a study at any time if they change their mind about participation. Therefore, treatment and appropriate referral for follow-up procedures depending on the timing of subject termination, and measures that may be taken to locate subjects lost to follow-up, should be included in the protocol and clearly described in the informed consent

process. With the potential for spread, the consent process should be clear about the potential risks to subject contacts. The consent document should remind subjects of requirements, and provide information relevant for the subject to share with those contacts during consideration of participation. In some cases, conducting the consent process with, and documenting consent of, close contacts might be required.

## Conclusions

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The intentional infection of study participants, at first glance, seems difficult to justify from either an ethical or scientific perspective. However, there are circumstances in which studies that include deliberate infection (or attempted infection) of participants can be both ethically and scientifically valid. Clear communication of the scientific and ethical considerations can support the maximal benefit for society while ensuring the value of the individual volunteer.

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