Ethical Criteria for Human Challenge Studies in Infectious Diseases

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Purposeful infection of healthy volunteers with a microbial pathogen seems at odds with acceptable ethical standards, but is an important contemporary research avenue used to study infectious diseases and their treatments. Generally termed ‘controlled human infection studies’, this research is particularly useful for fast tracking the development of candidate vaccines and may provide unique insight into disease pathogenesis otherwise unavailable. However, scarce bioethical literature is currently available to assist researchers and research ethics committees in negotiating the distinct issues raised by research involving purposefully infecting healthy volunteers. In this article, we present two separate challenge studies and highlight the ethical issues of human challenge studies as seen through a well-constructed framework. Beyond the same stringent ethical standards seen in other areas of medical research, we conclude that human challenge studies should also include: (i) independent expert reviews, including systematic reviews; (ii) a publicly available rationale for the research; (iii) implementation of measures to protect the public from spread of infection beyond the research setting; and (iv) a new system for compensation for harm. We hope these additions may encourage safer and more ethical research practice and help to safeguard public confidence in this vital research alternative in years to come.

Background

Well-documented horrific medical experimentation conducted by the Nazi regime during World War II—without any form of consent or regulation—resulted in serious illness, injury and death among prisoners (Schaefer, 2004). Among other atrocities, Nazi research involved the intentional infection of vulnerable prisoners with live tubercle bacilli in order to observe the pathogenesis of tuberculosis and guide future vaccine development (Cohen, 1990). More than 200 individuals died as a result of these experimentally induced infections.

Though this Nazi research occurred almost three quarters of a century ago, many would be shocked to discover that medical researchers are still intentionally infecting healthy human volunteers with pathogens in order to advance knowledge about immunology and infectious disease. While such studies may be ethically acceptable when conducted in highly controlled environments, where well-informed research subjects consent freely and are effectively treated upon the development of infection, there has been little bioethical discussion about what this research involves or why it is important, and it is a potential concern that members of the public may continue to view challenge studies negatively because of the atrocities committed in the past.

This article will provide a comprehensive discussion of the relevant ethical issues associated with this contentious avenue of medical research and highlight the ethical issues in challenge studies as seen through a well-constructed framework. Though we believe challenge studies should generally adhere to the same stringent ethical standards as seen in other areas of medical research, we advocate setting higher levels of reasonable risk for challenge studies compared to other non-therapeutic research (which in some jurisdictions is not permitted for research involving greater than ‘minimal risk’, which is sometimes exceeded in challenge studies). We also argue for measures to protect against...
demonstrated that inoculation with cowpox protected Phipps with cowpox, a related but far less virulent virus, smallpox. In 1796, Jenner inoculated 8-year-old James Edward Jenner to develop the first vaccine—against intentional infection of a research subject enabled wars of that period (Oldstone, 2010).

In one of the great success stories of medical history, intentional infection of a research subject enabled Edward Jenner to develop the first vaccine—against smallpox. In 1796, Jenner inoculated 8-year-old James Phipps with cowpox, a related but far less virulent virus, and, after subsequently exposing Phipps to smallpox, demonstrated that inoculation with cowpox protected against smallpox infection (Riedel, 2005). Whilst Jenner’s experiment would likely be considered unethical by modern standards, his challenge study gave birth to the field of vaccinology, leading to the advent of vaccination in general and the vaccine that enabled eradication of smallpox in particular.

Infectious diseases continue to pose serious threats to human health. Though many successful vaccines and antimicrobial treatments have been developed, infectious diseases still cause more than 13 million deaths annually, mainly amongst children in the developing world. Continued research is vital for the development of novel and efficacious vaccines and antimicrobial treatments that could prevent millions of clinical cases and deaths every year. Challenge studies play an important role in infectious disease research by contributing to the study of pathogenesis and, particularly, vaccine development. In regards to the latter, researchers intentionally infect competent adult volunteers with diseases that are either self-limiting or fully treatable in order to gain insight into the potential of vaccine candidates, optimizing their development by more quickly advancing those that are effective and halting the progression of ineffective vaccines. Significant costs in terms of time and money are thus saved, and the likelihood of discovering and developing an effective vaccine is greatly increased.

Current ethical guidelines have great difficulty justifying challenge studies, despite their scientific importance and ongoing use. For example, paragraph 3 of the Declaration of Helsinki states: ‘The health of my patient will be my first consideration’, and the International Code of Medical Ethics declares that: ‘A physician shall act in the patient’s best interest when providing medical care’ (World Medical Association, 2015). Paragraph 8 of the Declaration of Helsinki notoriously states:

‘While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects’ (World Medical Association, 2013).

It is generally not in the interests of participants to take part in non-therapeutic research, including challenge studies, because it exposes them to risk without the prospect of direct benefit. It is nonetheless permissible to expose participants to necessary risks for scientific purposes provided those risks are reasonable (Savulescu and Hope, 2010), full compensation for any resulting harm is provided (Savulescu, 2001) and participants have the capacity to consent voluntarily to take part in the research.

Not only can challenge studies be permissible, there can be good ethical reasons to conduct them. By carefully documenting signs of infection before initial symptomatology, researchers can prioritize the safety of participants whilst ensuring that we invest only in the most promising vaccine candidates. Whereas phase II and phase III clinical trials test vaccine efficacy in endemic areas with sample sizes ranging from 100 to 100,000 participants, challenge studies allow preliminary testing of vaccine efficacy amongst 10–40 participants, often in an in-patient setting, in studies that are short and easily repeatable. Cost savings are substantial, and because larger numbers of candidate vaccines can subsequently be tested, the chances of discovering a potential breakthrough are heightened.

Though the scientific benefits of challenge studies are well understood, the ethical advantages of exposing fewer volunteers to the risks posed by vaccine candidates should not be overlooked. This becomes increasingly significant for research into complicated diseases like malaria, where less than 10 per cent of preclinical vaccines will progress to phase III clinical evaluation (Davis et al., 2010), and there are thus many potentially effective vaccine candidates in need of testing. Without the use of a preliminary challenge experiment(s), large-scale malaria vaccine trials would be the only alternative and would involve the exposure of large numbers of people to many ineffective vaccines, in less supervised conditions and with treatment less available than for human challenge studies. As all vaccine candidates may pose inherent risks (e.g. allergy), more people would be
placed at risk of rare, serious side effects of ineffective vaccines than would occur in human challenge studies, which involve far smaller sample sizes. Challenge studies might, for this reason, be considered ethically required (rather than merely ethically permissible).

Like other areas of medical research, we believe challenge studies may only be ethical if they are limited to study designs in which (i) they may generate important scientific knowledge; (ii) there are no satisfactory alternative methods; (iii) well informed competent adult volunteers consent freely to infection; (iv) they are subject to appraisal by an ethics review committee; (v) there is acceptable balance of benefits and harms; and (vi) there is equitable selection of study participants. However, above and beyond these common standards (which should apply to all clinical trials), we argue that human challenge studies should also include (vii) independent expert reviews, including systematic reviews; (viii) public availability of rationale for the research, to protect public confidence; (ix) implementation of measures to protect the public from spread of infection beyond the research setting; and (x) a new system for compensation for harm.

There are two main reasons why this research should be viewed differently from other non-therapeutic research on healthy volunteers, such as (phase 1) drug toxicity trials. First, challenge studies may not only pose risks to individual volunteers, but infection of research subjects may also be spread to others in the community, which warrants additional protocol to ensure public protection. Second, it is likely that the idea of purposely infecting healthy volunteers involved in medical research with a known pathogen may be so alien to the public’s expectations of the medical profession that any harm befalling volunteers (whether studies are ethical or not) has the potential to spark backlash, thereby jeopardizing the continuation of important medical research which may save many lives (Hope and McMillan, 2004). Appropriate methods should be put in place to protect public confidence, like making the study design and rationale publicly available and including an independent expert-based review of risk (e.g. by infectious disease physicians) to safeguard volunteer safety.

In any case, challenge studies involve intentional harming of participants—i.e. the intention of challenge studies is that (at least some) participants become infected, and infection is (usually) inherently harmful. Though this does not make challenge studies wrong, it arguably does at least make them morally problematic—hence warranting greater scrutiny. While drug toxicity studies may foreseeably harm participants, challenge studies will certainly harm participants if adequate protections are not taken. This may be seen as violation of the principle of non-maleficence, or as it is often put, ‘First do no harm’. This could be seen as the only example in current medical research of intentionally harming participants, though we will argue that this is not the case.

In light of these ethically salient factors, challenge studies warrant additional/novel regulatory safeguards to ensure volunteer and community safety. Given that decisions about whether proposed challenge studies are ethical or not are largely made at the discretion of funding agencies and research ethics committees, our ethical criteria, which include additional safeguards for volunteer safety, such as an independent, expert-based appraisal of the risks involved in the research that should be based on a comprehensive and systematic review of relevant existing evidence, may aid both investigators and research ethics committees in the design and review of human challenge studies in the future. Inter alia, we outline requirements for protection of public safety and publicity/education regarding participant protection to protect against potential public backlash.

**Ethical Criteria for Human Challenge Studies**

Our criteria (Table 1) expand on important contributions made by Miller and Grady (2001) and the Academy of Medical Sciences (2005) who have previously devised broad frameworks for ethical evaluation of infection-inducing challenge experiments.

We will now explore the origins and applications of our additions with a discussion of two case studies of separate challenge studies.

**Case 1. A Historical Perspective—Edward Jenner and Smallpox**

During the 18th century, smallpox was a devastating disease that had a mortality rate as high as 30 per cent (Riedel, 2005). Variolation—involving the exposure of the host to a milder form of infection with live smallpox virus, usually through cutaneous scratches in the skin—was widely practiced at the time. A local infection developed and, if the host recovered, immunity to subsequent infection was acquired. However, roughly 1 in every 100 patients developed such severe complications from the procedure that they died, meaning the mortality rate for variolation was high, at least by contemporary standards, at around 1 per cent.
### Table 1. Ethical Criteria for Human Challenge Studies in Infectious Diseases

#### Ethical requirements for a human challenge study

<table>
<thead>
<tr>
<th>Criteria common to all medical research</th>
<th>(Y/N)</th>
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<tr>
<td>1 Scientific rationale</td>
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<tr>
<td>– Will important knowledge be gained from the research?</td>
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<tr>
<td>– Has a systematic review of existing evidence been supplied? Are the methods of the review clearly defined?</td>
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<tr>
<td>2 Absence of alternative</td>
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<td>– Could the research be answered with other methods or by cell lines, ex vivo tissue and animal models?</td>
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<tr>
<td>– Is it clear why a challenge study is required to feasibly answer the research question?</td>
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<td>– Are the proposed methods appropriate to the stated objectives of the study?</td>
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<td>3 Informed consent</td>
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<td>– Are the participants competent adults acting freely?</td>
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<td>– Have they been informed about—and understood—the study’s purpose, procedures and benefits and risks, as well as their rights as study participants?</td>
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<tr>
<td>– Have they been provided with the opportunity to ask questions and voice concerns?</td>
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<td>– Has their comprehension of study information been tested?</td>
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<tr>
<td>– Have these procedures been documented and archived for future reference?</td>
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<tr>
<td>4 Benefits and harms</td>
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<tr>
<td>– Have risks been properly and accurately assessed?</td>
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<tr>
<td>– Have risks been minimized consistent with the scientific ends of the study?</td>
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<tr>
<td>– Are the risks acceptable considering the benefits to society and/or the individual?</td>
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<tr>
<td>– Can researchers ensure that volunteers will under no circumstances be exposed to the risks of irreversible, incurable or possibly fatal infections?</td>
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<tr>
<td>5 Selection of study participants</td>
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<tr>
<td>– Has the amount of financial compensation for participation been reviewed and approved by a research ethics committee?</td>
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<tr>
<td>– Do study recruitment procedures adequately protect vulnerable individuals, including the poor, those with low levels of education and the unemployed?</td>
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<td>– Are there measures in place to compensate volunteers in the event of research-related injury?</td>
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Criteria required specific to challenge studies

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<td>6 Independent review</td>
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<tr>
<td>– If the study involves a new challenge model, has it been reviewed and approved by two independent experts in infectious diseases?</td>
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<td>– Has the study been reviewed and approved by a research ethics committee? (Plus FDA if in USA)</td>
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<td>7 Publicly available rationale</td>
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<tr>
<td>– Has a clear publicly accessible rationale for the study been made available, explaining the nature of the benefits and risks, the inadequacy of alternatives and the adequacy of the measures to protect participants and the community from harm?</td>
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<tr>
<td>8 Protection of public</td>
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<tr>
<td>– Are there risks to others who come into contact with the volunteer? Have these risks been communicated? Will they be well-managed/mitigated?</td>
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<tr>
<td>– Are there measures in place to protect the community from spread outside the research setting?</td>
</tr>
<tr>
<td>9 Compensation for harm</td>
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<tr>
<td>– Are there measures in place to compensate volunteers in the event of research-related injury?</td>
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Edward Jenner hypothesized that inoculation with cowpox would be safer than variolation whilst still effective at immunizing the host against future smallpox infection. This hypothesis was based on qualitative observations regarding the low prevalence of smallpox amongst milkmaids. He noticed that milkmaids, unlike those from other professions, had less facial scarring, a typical sign of smallpox infection at the time, and believed this to be related to their regular exposure to milk, and most probably cowpox.

In 1796, Jenner inoculated 8-year-old James Phipps with cowpox and, several weeks later, exposed Phipps to smallpox in order to test if a cowpox injection could prevent smallpox infection. Though his hypothesis was correct and Phipps was unharmed, there are several reasons why Jenner’s study would be considered unethical in contemporary contexts.

**Justification**

For one, it is clear that research hypotheses for contemporary challenge studies would need to be supported by far more preliminary work than one self-assessed qualitative analysis. Investigators should be required to explicitly acknowledge (in a written undertaking) why a challenge study is necessary to answer their research question. Specifically, though Jenner did not have access to the advances in scientific research we enjoy today, investigators should outline why other related areas of immunological research may be insufficient for their particular area of research.

Though many investigators in the 21st century may be able to conduct research with cell lines, ex vivo tissue or animal hosts, we note that these methods are generally inferior to challenge studies because of their lack of immunological and genetic diversity (Pollard et al., 2012). Further, these alternatives often cannot emulate the influence of intestinal microbiota and other environmental factors that mediate the complex outcomes of infections within human hosts. However, challenge studies should be replaced by these alternatives wherever possible. This ensures that health risks are not unnecessarily imposed on healthy human volunteers in situations where the research may be possible without human participation. Challenge studies would not be justified in this context.

Moreover, the challenge study itself should not be used unthinkingly. Contemporary challenge studies should be limited to research that may generate scientific information of genuine importance. Only studies fulfilling a strong scientific rationale should be considered for approval. This may involve investigators clearly describing the methods used to review relevant literature systematically, as well as submission of a comprehensive literature review itself. It is important to remember the recent case of Ellen Roche—a healthy volunteer who died in a hexamethonium challenge study of asthma study at Johns Hopkins because of a simple failure to conduct a systematic review of existing literature in a drug study which would have revealed the lethal risk which hexamethonium presented (Savulescu and Spriggs, 2002). While this was not a microbial challenge study, it raises the same ethical issues of risk to healthy volunteers.

**Consent**

Jenner’s experiment was also ethically problematic because he was unable to gain valid consent from his research subject, Phipps, an 8-year-old child. While we do not know if his parents provided valid consent, or if he was told what was happening, contemporary challenge models should only include participation of well-informed, competent, adult volunteers. Children do not have the capacity to consent to take part in the research and it is unlikely that it would be ethical for parents to act as proxy decision makers in the context of enrolling children in research involving intended harm beyond minimal risk and no direct benefit to the child.

Criticisms of the infamous Willowbrook hepatitis experiments likewise attest to the importance of explicit consent procedures for human challenge studies. There was significant public outcry as a result of Saul Krugman’s intentional infection of mentally disabled children with hepatitis at the Willowbrook institution, in research involving problematic procedures of informed consent by parents. While it is commonly thought that the Willowbrook experiments are a paradigm example of unethical medical research, the problematic nature of this research arguably had more to do with inadequate informed consent and unacceptable risk exposure rather than intentional infection of research subjects per se. In other words, the fact that Krugman purposefully infected research participants was not a wrong in itself, but it was wrong that he did so on children without adequate consent or consideration of the risks involved.

Contemporary challenge models should limit participation exclusively to competent, healthy adults who are thoroughly informed about the study’s purpose, procedures and potential benefits and harms, as well as their rights as research participants. Adult volunteers should be competent and acting freely, and have sufficient opportunity to ask questions and voice concerns in a meeting scheduled prior to the commencement of the
study. Further, their understanding of the information provided to them should be formally tested and be made publicly available in a readily intelligible form. These procedures should be well-documented and archived for future reference.

**Benefits and Harms**

Perhaps what is most morally troubling about Jenner’s challenge model is the fact that the risks and benefits posed to Phipps were not properly or accurately assessed. Jenner had no clear understanding of the protection cowpox would confer on Phipps, which, if ineffective, may have resulted in his death.

Contemporary challenge models should involve risks that are demonstrated to be acceptable according to high standards of evidence. The Declaration of Helsinki explicitly states that ‘every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits’ (paragraph 17) (World Medical Association, 2013). Other research guidelines, like those supplied by the General Medical Council (UK), more specifically state that in non-therapeutic research (which includes challenge studies) investigators ‘must keep the foreseeable risks to participants as low as possible and the potential benefits . . . must far outweigh any such risks’ (General Medical Council, 2013).

Though it is clear that the risks in Jenner’s experiment were poorly defined, how ought investigators and research ethics committees put this guidance into practice for contemporary cases? First, the risks involved in challenge studies should, as much as is possible, be clearly and accurately defined. This requires that appropriate laboratory studies and studies in animal models, where such models are available, be completed prior to human testing, and that the results of these studies are presented in a systematic review of the literature. Second, risks must be minimized consistent with sound scientific design. In challenge studies, this may involve manipulation of the infectious agent (e.g. to ensure that it is highly sensitive to antibiotic treatment or through use of an attenuated strain or one which is less capable of passing to other humans) or changes to the study design (e.g. using less invasive or burdensome means of collecting study data).

Third, risk to participants and wider community must be deemed reasonable compared with study benefits, including benefit to the participant (if any) and the importance of the knowledge to be gained (Weijer, 2004). Since study participants are unlikely to benefit (unless, for example, a vaccine being tested turns out to be safe and effective), the benefit will typically be social benefit of knowledge gained. This needs to be clear to study participants, ethics committees and the public.

**Financial Compensation**

Financial compensation should be divided into compensation for risk (prior to commencing the study) and compensation for actual harm (following the study). While financial compensation for risk may be perceived as a benefit by study participants, it should not be part of the benefit–harm analysis of ethics review (as large amounts of compensation could thereby justify otherwise unacceptable levels of risk). For this reason, ethics committees typically only allow for compensation for time, travel, inconvenience/discomfort, as well as some level of risk, though no formal risk-related economic analyses are usually conducted. While it is currently unclear if, how much and through what procedures, compensation for risk should be quantified in medical research, some have already argued that research participants should be fully compensated for risk along the line of other risk professions such as deep sea diving or construction work (Savulescu, 2001).

In the absence of such adequate compensation for risk ex ante (before the trial commences), if participants do experience significant harm, they should be awarded levels of compensation commensurate with harm suffered. For example, compensation for risk might be in the range of hundreds to thousands of dollars; compensation for loss of limb or prolonged hospitalization with permanent disability in the range of hundreds of thousands of dollars. This should be the case even in the presence of full disclosure of risk and competent (non-negligent) conduct of the research.

**Upper Limit of Reasonable Risk?**

Is there an upper limit to the amount of risk that a capable adult can consent to in a challenge study (provided the above benefit–harm criteria are satisfied)? Guidance from the Academy of Medical Science suggests that in challenge studies, ‘however valuable the research, the degree of risk of harm can be no more than “minimal”’ (Academy of Medical Sciences, 2005). The Academy does not extrapolate as to why this may be so, though in other contexts ‘minimal risk’ is commonly invoked as a threshold for permissible risk in research involving children or adults incapable of providing informed consent, but it is commonly assumed that adults
can autonomously assume higher levels of risk. Whether a threshold for permissible risk is appropriate for consenting adults and, if so, what it should be is the subject of continuing debate. Candidate thresholds include minimal risk (Hope and McMillan, 2004), the risks assumed by volunteer firefighters (London, 2007), the risks assumed by kidney donors (Miller and Joffe, 2009) and greater than a 1 per cent chance of death, permanent disability or severe injury (Resnik, 2012).

Like the Academy of Medical Sciences, we contend that there is one major reason why risks should be limited for human challenge studies. As others have already warned, challenge models that may be perceived by the public as overly risky (whether or not such perceptions are ill-founded) and violating a principle of non-maleficence may jeopardize the future of this kind of research (Hope and McMillan, 2004). Development of vaccines that could save large numbers of lives might thus be delayed or prevented altogether, which is a grave consequence. However, whether studies should be limited to ‘minimal risk’ (which generally refers to the risks involved in daily life1) is another question entirely, and a limitation we believe too strict for challenge studies. Exposing volunteers to infections by *Vibrio cholerae* can cause diarrhoeal loss in excess of 5 litres (Cohen et al., 1999), while several days of fever, headache and myalgia are common symptoms for volunteers infected with *Plasmodium falciparum* (Church et al., 1997). Undoubtedly, the severity of these symptoms is above those encountered in daily life, though these studies may still be conducted safely for a range of infections. We propose the following risk threshold for challenge studies, namely that: under no circumstances the research exposes volunteers to risks of irreversible, incurable or possibly fatal infections. This standard protects volunteers from serious risk, but is more permissive than a minimal risk standard and allows important and ethical research to go forward.

In the case of a highly infectious, highly lethal pandemic, we also believe there may be good and acceptable reasons to conduct rapid challenge studies of highly promising vaccines in an experimental setting. In this way, challenge studies are different from non-therapeutic research—the threat to large numbers of currently unaffected people can be much higher than in, say, cancer or motor neuron disease. Since pandemics represent a continuing, if not increasing, threat to global welfare, the issue of which principles of evaluating risk in challenge studies increases in importance, as does the relevance of the discussions in this article.

What were the Risks and Benefits to Phipps?

For ethics committees or regulatory authorities to assess acceptable risk for proposed challenge studies, methods are required to weigh up the risks and benefits of the research for both the participants and society. For the risks involved in Jenner’s experiment to be accurately assessed and minimized as much as possible, it is clear that substantial scientific background would be required.

Though many would correctly deduce that if Jenner’s hypothesis was incorrect, Phipps would be in danger of dying, and, if it were correct, Phipps would benefit from acquiring lifelong immunity to smallpox, fewer would be able to appreciate the implications of these outcomes. For example, many would not know that at the time of Jenner’s experiment, smallpox was the leading cause of death in Europe, killing around 400,000 Europeans every year, and causing a third of all cases of blindness (Riedel, 2005). Fewer still would appreciate how contagious smallpox infection was, where coughed up aerosolized droplets or direct contact with the host could easily transmit the virus for many weeks during infectivity (Centers for Disease Control and Prevention, 2013).

As Phipps lived in an era where smallpox infection was both common and deadly, these factors would need to be fully appreciated when weighing up whether Jenner’s model involved an acceptable balance of risks and benefits. We suggest that this knowledge-dependent process may be too demanding for research ethics committees alone. The mistakes of research ethics committees in the governance of basic medical research has already been associated with the death of previously healthy volunteers (as the case of Ellen Roche illustrated). The avoidance of similar tragedies should be a vital priority for current regulatory protocol and may justify additional measures to safeguard volunteer safety and reassure the public in the case of challenge studies in particular.

In addition to requiring full systematic review of existing evidence, an appraisal from independent experts in the investigated field should be an additional ethical safeguard for future challenge studies. This may be justified because experts in the field of infectious diseases (e.g. infectious disease physicians) will best understand the risks and benefits posed by proposed challenge studies, more so than the constituents of research ethics committees, making them an ideal, accessible and underutilized resource in the regulation of such research.
We recommend that prior to full review by a research ethics committee, all new challenge studies be reviewed and approved by two independent infectious disease experts identified/selected by the ethics committee. The expert reviewers should ensure that (i) the use of a challenge study is justified; (ii) there is no reasonable alternative design; (iii) the study methods are appropriate; (iv) study participants will be selected appropriately; (v) steps have been taken to minimize risks to participants; (vi) overall study benefits (i.e. mainly to science/society) outweigh risks to participants; and (vii) risks to participants fall within reasonable limits. Recommendations from independent experts may lead to changes in the proposed study. The study may proceed to full review by a research ethics committee only when both independent experts are satisfied that the challenge study satisfies scientific and ethical requirements. Expert reviewer reports should be submitted independently to the study protocol to the research ethics committee.

By including an additional review of the risks, we may better ensure the safety of future volunteers, more ethical research practice, and greater accountability to public scrutiny. Given the backlash that resulted from Ellen Roche’s death in a non-microbial challenge study in June 2001, where important and unrelated studies were halted because of doubts about the effectiveness of medical research regulation, the need for more explicit and effective regulatory protocols for microbial challenge studies justifies an independent expert-based review.

What were the Benefits for Society?

Jenner’s challenge model lead to the advent of vaccination and, ultimately, the eradication of smallpox (WHO, 2013b). These are among the greatest achievements in medical history, and many hundreds of millions of lives have been saved as a result.

Though challenge models may have great benefits for humanity, we stress the imperative to ensure the research adequately protects those (research participants) who risk their own health to benefit others. Ensuring that volunteers are only exposed to risks that may be considered reasonable by contemporary standards entails that challenge studies should be limited to infections that are either self-limiting or easily treatable, which is not to say that this limitation detracts from the potential for social benefits from the research, as many diseases currently investigated with challenge studies (such as malaria and typhoid) already have effective treatments but continue to cause large global mortality without the availability of an effective vaccine.

Challenge studies should be limited to self-limiting or easily treatable infections because they fundamentally involve exposing volunteers to infections that carry inevitable health risks that may not otherwise have arisen. This may mean smallpox challenge studies, or any other study of an infectious disease that is not self-limiting or for which there is no curative treatment (e.g. HIV) may be considered unethical (whether or not there is accurate risk assessment and informed consent).

Alternatively, challenge studies conducted in endemic areas—where volunteers have a high chance of becoming infected with a particular disease in the wild regardless of their involvement in the research, and where the research is especially relevant to local community interests—should be considered more ethically justifiable in terms of volunteer risk-benefit analysis. This is because the comparative risks involved from participation in challenge studies in endemic areas are lessened, given the heightened chance of encountering such risks outside of the study, and the potential benefits to participants, given the optimal care that would be provided in the context of the study and the opportunity to gain immunity to subsequent wild-type infections (i.e. in the case of challenge studies testing vaccines), are increased. However, this has to be balanced against the fact that (in such contexts, often involving developing countries) there may be less general education, more fear and greater baseline willingness to participate. This requires special attention to the consent process and procedures for the equitable selection of study participants.

What then may be the ethical considerations pertinent to the proper conduct of human challenge studies in non-endemic areas? After all, many of our greatest infectious killers are now limited to (or most prevalent in) tropical or sub-tropical environments, such as parts of Africa, Asia and South America. Because contemporary challenge studies are usually conducted in industrialized nations—where greater resources are available, and where potential participants may often be less ‘vulnerable’—it is important to clarify what, if any, additional considerations should be made by investigators and regulatory bodies to safeguard ethical research practice in these situations.

Though human challenge studies conducted in non-endemic areas may be ethical, the conduct of such research may raise unique ethical dilemmas that analysis of Jenner’s smallpox challenge may not adequately illustrate. We present a contemporary malaria challenge model that
may more explicitly illustrate these considerations and further contextualize arguments presented thus far.

Case 2. A Contemporary Perspective—Malaria Challenge Studies

While Edward Jenner’s smallpox experiment may have paved the way for the development of many important vaccines, there is currently no licensed malaria vaccine available. Because malaria continues to be a major public health problem, with the World Health Organization estimating that malaria infected approximately 219 million people and caused around 660,000 deaths in 2010 (WHO, 2013a), continuing related biomedical research is vitally important.

Though the advent of artemisinin combination therapies (ACT) has provided a highly effective way of treating malaria in recent years, this medication has so far failed to reach many endemic areas, mainly because of its cost, poor public awareness about the concept of combination therapy and limited knowledge about the safety of ACT in specific demographics (e.g. pregnant women) (Mutabingwa, 2005). Moreover, worrying trends in the prevalence of artemisinin-resistant malaria are continuing to rise, making the need to develop alternative therapies particularly urgent.

As vaccines can most effectively decrease the prevalence of infectious disease and overcome the pressing issue of drug resistance, the development of a safe, efficacious vaccine against malaria could prove to be one of the greatest victories for medical science in the modern era (Wiwanitkit, 2010). Malaria challenge studies have played a pivotal role in fast tracking the development of malaria vaccine candidates for many years, where their routine use in the UK, USA and the Netherlands expedited the long and complicated process of vaccine development. Without optimization in malaria challenge studies, the most advanced malaria vaccine (RTS/S), currently in phase III clinical evaluation in Africa, would almost certainly never have been developed (Agnandji et al., 2011).

Healthy, adult volunteers are exposed to the bites of infectious mosquitoes (sporozoite challenge) or to an inoculum of blood-stage parasites (blood-stage challenge) in a highly controlled but artificial environment, where they are regularly monitored for signs of infection on an outpatient basis, and treated with a curative regime of antimalarials when malaria develops (Sauerwein et al., 2011). Though there are various types of malaria, research has focused on P. falciparum, which causes the most deadly form of the disease. When volunteers are challenged with malaria, researchers can assess (i) the ability of the vaccine to prevent malaria; (ii) the safety of the vaccine; (iii) the response of the human immune system to the vaccine (The Jenner Institute, 2013).

With the current lack of clearly identifiable correlates of immune protection against malaria in either animal models or ex vivo assays of human tissues, there is a justifiable and ongoing need to test malaria vaccine efficacy in human challenge studies (Sauerwein et al., 2011).

What are the Risks and Potential Benefits to Volunteers?

The main risk posed to participants involved in malaria challenge studies is the development of malaria. Other risks, such as allergic reactions and side affects caused by administration of candidate vaccines, though generally minor and uncommon, should also be accurately assessed and conveyed to volunteers.

Unpublished data show that, as of 2009, of the 526 volunteers who had taken part in malaria vaccine trials worldwide, 118 were protected against infection by the vaccine candidate, meaning the chances of a volunteer suffering malaria whilst participating in a malaria challenge study is roughly 80 per cent (Sauerwein et al., 2011). The classical symptom of infection for adults is paroxysm, a cyclical occurrence of rigors, fever and sweating. This is usually accompanied by headache, myalgia and joint pain, all of which may last for around 10–15 days (Nadjm and Behrens, 2012).

The risk of volunteers developing severe or life-threatening complications is very low due to the administration of curative treatment as soon as a diagnosis of malaria is made. Researchers test malaria strains prior to infection to ensure that only treatment-sensitive strains are used, ensuring effective intervention. No severe or life-threatening malaria has occurred in any of the 1343 volunteers challenged to date (Church et al., 1997, Epstein et al., 2007).

Unlike Phipps’s exposure to smallpox, which was a prevalent and deadly disease in England during the 18th century, participants challenged with malaria in the UK, USA and the Netherlands would not usually gain any medical benefit from participation in the research. Some may volunteer for altruistic reasons, whilst others may seek financial compensation for the time and inconvenience involved in their participation.

Like Jenner’s work, the discovery of an effective vaccine against malaria could prove to be one of the greatest
triumphs of modern medicine. Not only is this an important consideration when determining whether future malaria challenge studies are ethical and involve acceptable risks, but the very fact that the stakes for the research are so high should motivate more explicit guidance and regulation.

Selection of Participants

The equitable selection of study participants in challenge studies is an important issue for investigators and research ethics committees. Volunteers should be compensated fairly for the time and risks involved in their participation in the research. Additionally, challenge studies may involve members of vulnerable groups, such as the poor, those with low levels of education or the unemployed. Adequate protections for vulnerable participants must be in place in all challenge studies.

It is common practice for participants in challenge studies to be paid for their time and exposure to study risks to some degree. What payments to participants ought to be permitted? It is widely accepted that research participants may be reimbursed for expenses incurred as a result of study participation, including travel, meals and parking. Additionally, participants may be paid for their time and endurance of uncomfortable procedures and risk. Hourly rates may be set to be commensurate with unskilled jobs in the community associated with similar risks and may be augmented to take account of uncomfortable or burdensome study procedures (Dickert and Grady, 1999; Savulescu, 2001).

Much of the attention in the literature has focused on the potential impact of payment on the validity of informed consent. We believe that claims that payment may constitute coercion to participate in research rest on a conceptual error. Offers of payment are not threats of rights violations that reduce options available to potential participants; they are offers that may expand the scope of available options (Wertheimer and Miller, 2008). Further, it has been questioned whether offers of money actually undermine the rationality of informed consent (Savulescu, 2001; Richards, 2012).

Less appreciated is the potential impact of payments on equity and public trust. While too small a payment to subjects may exploit the poor and unemployed, too large a payment may result in the preferential recruitment of vulnerable participants into challenge studies, arguably exploiting them. As a result, members of these groups may bear an unfair share of the burdens of research. Further, large offers of payment may cause potential participants to withhold information (or lie) about medications, medical conditions or other factors making them ineligible for study participation and thereby exposing them to undue risk. Finally, payment practices that result in inequities or harm to participants may undermine public trust and confidence in the research enterprise (Grady, 2005).

For these reasons, rather than moving to full economic compensation for risk (ex ante), it would be preferable to put in place mechanisms for compensation for harm (ex poste). Compensating for disability or loss of life is hardly likely to be a significant attraction to participants, at least in the West.

Conclusion

The challenge model is one of our greatest weapons in our ongoing fight against infectious diseases and investigators; ethics committees and regulatory bodies are charged with the vital task of ensuring ethical research design and regulation in this important area. In this article, we have explored a set of generalizable ethical criteria that may aid these bodies in their decisions and ensure satisfactory evaluation of the risks involved in the research. This may encourage safer and more ethical research practice in future and help to safeguard the future of this vital research alternative.

We have argued that challenge studies pose novel challenges because of risk to the public of spread of challenge-induced infection and the requirement for compensation for harm. Such measures are necessary to protect public confidence. In many cases, the adequacy of the measures to protect participants from the pathogenic harm is sufficient to argue that researchers are not intentionally causing significant harm and there is no significant violation of the principle of non-maleficence. However, in other cases, it may be that challenge studies pose significant, though reasonable, risks to participants. In such cases, it is important that measures are in place to publicly justify the ethical necessity of such research.

Challenge studies should not be considered ethically unacceptable. To the contrary, in this article we argue that they may sometimes be ethically required. Because they are at least ethically problematic—e.g. because sometimes more risky than other kinds of non-therapeutic research involving health subjects—they should, however, be subject to especially rigorous oversight.
Acknowledgements

We acknowledge the Wellcome Trust, British Infection Society, Jenner Institute and the NIHR Oxford Biomedical Research Centre.

Funding

This work was supported by the Oxford Martin School, University of Oxford. C.W.’s research was supported by a Tier I Canada Research Chair and an operating grant from the Canadian Institutes of Health Research.

Conflict of Interests Declaration

This work was supported by the Oxford Martin School, University of Oxford and the NIHR Oxford Biomedical Research Centre. C.W.’s research was supported by a Tier I Canada Research Chair and an operating grant from the Canadian Institutes of Health Research.

Note


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