

# ETHICAL CONSIDERATIONS FOR ZIKA VIRUS HUMAN CHALLENGE TRIALS

REPORT & RECOMMENDATIONS

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## Executive Summary

1. The National Institute of Allergy and Infectious Diseases (NIAID) and the Walter Reed Army Institute of Research (WRAIR) convened a planning committee with members from relevant federal agencies, researchers, and ethicists to determine how best to address the ethical issues raised by a possible Zika virus human challenge study. This group planned an expert consultation meeting in Rockville, Maryland, on December 12, 2016 and formed an independent writing committee with cross-disciplinary expertise to develop recommendations. The writing committee was charged with answering the following questions:
  - Can a Zika virus human challenge trial be ethically justified?
  - If so, under what conditions?
2. Given the potentially devastating effects of Zika infection during pregnancy, the insidious nature of the disease, and the promise of what can be learned from human challenge trials, the writing committee concluded that a Zika virus human challenge trial could be ethically justified if certain conditions were met. However, at this point in time, based on what was heard at the consultation meeting and on our review of the latest scientific and ethics research, the writing committee has determined that these conditions preclude the conduct of a Zika virus human challenge trial, as detailed in the body of this report.
3. At some point in the future, if circumstances change or if a protocol is designed to address the recommendations in this report, members of this writing committee (or a similar body) should apply these recommendations to determine if a specific proposal for a Zika virus human challenge study is ethically sound.

## Introduction

Zika virus is an emerging infectious disease that was first identified in 1947, and that has more recently become a major public health threat around the world.<sup>1</sup> Zika virus has recently been shown to cause devastating neurological damage in infants and serious complications in adults in some cases, and may have other effects that have not yet been identified or definitively linked to the virus. There are no treatments or vaccines for this insidious virus.<sup>2</sup> While important, current measures for mosquito control are insufficient in most settings to prevent the spread of the virus.<sup>3</sup> Recommendations that women who live in or travel to endemic areas avoid pregnancy for long periods of time are unrealistic, particularly in contexts where access to reproductive services is limited,<sup>4</sup> and threaten to leave those most likely to suffer the devastating consequences of Zika without effective protection. There is therefore urgent need to develop biomedical interventions in parallel with ongoing public health efforts against Zika virus. While interventions are being developed and tested, a large number of infants will likely be born with intrauterine exposure to a virus with increased risks of adverse outcomes in regions of the world where the epidemic is ongoing. One powerful tool for developing treatments and vaccines for infectious diseases is human challenge research, in which volunteers are purposefully exposed to pathogens in order to answer research questions with enhanced rigor and efficiency.

Infection challenge studies have a long and storied history in medical research. As early as 1796, Edward Jenner used variolation (the deliberate infection of volunteers with cowpox and smallpox) to learn how to induce immunity, and his work ultimately led to the development of a smallpox vaccine.<sup>5</sup> Indeed, in 1956, a British researcher conducted an experimental human infection challenge with Zika on himself.<sup>6</sup> Notwithstanding some egregious examples of infection challenge research that did not have rigorous human subject protections, this research method has been used productively in recent decades without reports of major adverse effects on the volunteers involved. In at least two cases, infection challenge studies have been part of the data submitted to the U.S. Food and Drug Administration in support of successful licensing applications for vaccines.<sup>7</sup>

Because infection challenge research involves the deliberate infection of volunteers with pathogens, however, these studies are ethically complex. Despite the long history of infection challenge studies, formal analysis of the ethical issues they raise only began in 2001.<sup>8</sup> Existing ethical analyses generally focus on diseases that are unlikely to have lasting adverse consequences for volunteers or that can be effectively treated. As a result, there is little to guide research sponsors, institutional review board (IRB) members, researchers, community members, and other stakeholders regarding the use of infection challenge in the context of Zika virus research.

In 2016, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the Department of Defense Walter Reed Army Institute of Research (WRAIR) received a proposal to use a human challenge study to investigate a Zika virus vaccine. Recognizing the complexities and uncertainties inherent in such an endeavor, NIAID and WRAIR convened a planning committee with members from relevant federal agencies, researchers, members of research review boards, and ethicists to determine how best to address the ethical issues involved. This group planned an expert consultation in Rockville, Maryland, on December 12, 2016, and formed an independent writing committee with cross-disciplinary expertise to develop recommendations regarding the following questions:

**Can a Zika virus human challenge trial be ethically justified?**

**If so, under what conditions?**

With the help of NIH staff, the committee completed an exhaustive literature search on Zika virus and the ethics of human challenge trials (along with other relevant ethics literature) in advance of the meeting, reviewed the available literature, attended the December meeting with a series of presentations by experts in

relevant and diverse fields, engaged in discussion throughout the meeting, and began deliberating at the close of the meeting and for several weeks following its conclusion. (See Appendix A for meeting agenda & Appendix B for methodology.) In what follows, we offer our report and recommendations on Zika challenge research. In Part 1, we provide background information, surveying the landscape of infection challenge studies and concluding with a basic framework to evaluate the proposal of a Zika virus human challenge study. In Part 2, we elucidate and examine the components of this framework in light of the key issues for Zika virus human challenge trials—are the risks reasonable, to what extent can they be minimized, and are they justified by the potential social value of the knowledge to be gained from the research? We consider available evidence about the public health impact of Zika virus, challenge study risks, and the scientific opportunities presented by such studies. In Part 3, we address additional protections that should be standard for human challenge trials in general, and briefly discuss how they would apply to a Zika virus human challenge model. In Part 4, we synthesize our evaluation by providing all of the recommendations made at the conclusion of each section.

## Part 1: Background

### Prior literature on the ethics of infection challenge studies

Researchers have long recognized the ethical stakes in infection challenge studies. Walter Reed’s yellow fever experiments in Cuba in the early 1900s provided some protections for subjects, such as asking for informed consent, prospectively weighing the risks and benefits, and compensating participants (including providing payment to families in the event of a volunteer’s death).<sup>9</sup> However, these protections were not universally honored in subsequent studies. Researchers who conducted challenge studies with syphilis and gonorrhea in Guatemala in the late 1940s failed to obtain the informed consent of the research subjects, withheld established effective treatment, did not take measures to protect third parties from the spread of the infection, and inappropriately included subjects from vulnerable populations.<sup>10</sup>

In 2001, Frank Miller and Christine Grady offered the first systematic analysis of infection challenge experiments.<sup>11</sup> They argued that infection challenge studies are not a morally distinct category of research. Although infection challenge studies do involve intentional exposure of research participants to *pathogens*, many research procedures—like research biopsies and bronchoscopies, and drug administration in healthy volunteer studies—expose subjects to risk without any compensatory direct benefit (hereafter called “net risk”). This view—that there is no essential ethical

### Box 1: Ethical considerations for challenge studies

- (1) **Key question:** Are the risks reasonable, minimized, and justified by the potential social value of the trial?
- (2) Are vulnerable populations protected?\*
- (3) Is there a robust informed consent process?\*
- (4) Is the level of compensation adequate but not undue?\*
- (5) Is the right to withdraw respected (given constraints based on safety)?\*
- (6) Have independent expert reviews been conducted?\*\*\*
- (7) Is there a system of compensation for injury?\*\*\*
- (8) Is there a plan for community engagement?\*\*\*

\*Miller & Grady (2001)

\*\*Bamberg et al. (2015)

\*\*\*Zika Virus Human Challenge Research Writing Committee

distinction between infection challenge and other widely accepted nontherapeutic research activities—has not been contested. Later, this report will address the level of risk in infectious challenge studies and its comparability with other research activities. For now, it is sufficient to say that Miller and Grady argued that infection challenge studies can be ethical provided core ethical conditions are met (see Box 1).

Since that time, a handful of other commentators have offered additional analysis on infection challenge studies and made some conceptual additions to the Miller-Grady framework. In particular, Bamberg et al. argued that although challenge studies are not necessarily a morally distinct category of research, challenge studies should offer extra safeguards, in addition to standard research protections, for two reasons: (1) infections in challenge studies could spread to others in the community, and (2) challenge studies are so “alien” to the public’s understanding of research that they have the potential to spark negative reactions that could threaten other important research activities.<sup>12</sup> They proposed some additional safeguards (see Box 1). Although we will address each of these conditions below, it is worth noting one important and shared aspect of the existing ethical frameworks for human challenge studies. Within the existing ethics literature on human challenge trials, there is general agreement that the potential harms to participants in infection challenge studies should not be irreversible, lead to permanent disability, or be potentially fatal.

The writing committee reviewed this literature and found it informative and useful, but the committee identified numerous areas requiring further theoretical development. First, the prior literature on infection challenge has largely addressed infections that are relatively well understood scientifically. Zika infection and its effects are not currently well understood, and the literature provides limited guidance on the ethics of conducting challenge studies when the medical consequences of infection are more uncertain. Second, the ethics literature provides very little specificity on the reasonable limits on net risk to research volunteers. For example, prohibiting “potentially fatal” investigations offers limited guidance, since even relatively benign research activities (e.g., antibiotic administration leading to anaphylaxis) can entail nonzero risks of fatality. Third, the question of how to address risks to third parties is unsettled in prior literature. Finally, the prior literature does not articulate a requirement for community engagement, what it would entail (including who should be engaged), and what it is meant to accomplish.

Each of the above issues invites its own systematic investigation. However, the Zika public health crisis and research proposals cannot necessarily await a satisfactory resolution of the above questions. If Zika challenge studies *are* ethically acceptable, the opportunity costs associated with postponing their deployment until resolution of the above issues is morally relevant. The writing committee therefore resolved to build on a framework reflecting the existing published work on infection challenge research ethics and allowable risk, with the addition of community engagement. The writing committee also concluded that although all of the conditions we have put forth in this report are important, the first—ensuring that there is an acceptable level of risk and sufficient scientific and societal rationale to justify that risk—requires the most attention and analysis for present purposes. Accordingly, our analysis is structured by an evaluation of whether Zika challenge studies could currently meet the conditions laid out in Box 1, concentrating primarily on the risks and social value of Zika virus human challenge studies.

## **Prior experience with challenge models**

Challenge studies, models, or trials have also been referred to as infection challenge research or controlled human infection models (CHIMs). Whatever the terminology used, it is useful to note that volunteers are typically exposed to pathogens aimed ultimately at aiding in the development of effective vaccines or treatments in a controlled fashion:

- By using a specific strain, dose, and route of administration of the pathogen;
- By limiting the duration of infection and the spectrum of disease that develops, based on adequate understanding of the pathogen and disease and use of available treatment; and
- By containing the pathogen to minimize the risk of transmission to third parties.

Infection challenges have been used for studies of pathogenesis and natural immunity, and for the evaluation of candidate vaccines and drugs. On behalf of the Bill & Melinda Gates Foundation, PATH



conducted a literature review on CHIMs for 13 pathogens of public health importance and surveyed 42 experts who conduct CHIM research with these pathogens. Through a literature review and with input from PATH staff, PATH compiled a list of 69 experts on the available human challenge models for the diseases included in this review, and a few individuals with general knowledge of using human challenge models to support vaccine development. Forty-six experts were invited to respond to a survey, and two declined to participate. The results of this work are detailed in an unpublished 2015 report,<sup>13</sup> and relevant portions of this report are summarized below.

One major finding of this report is that challenge studies have been in widespread use for a number of years. More than 6,500 volunteers have participated in a CHIM study and nearly 60 different challenge strains have been used. CHIMs have been developed for pathogens that cause vector borne, respiratory, and enteric diseases. The most widely used CHIMs are those for the pathogens that cause influenza, typhoid, and malaria, with volunteer participation in the low thousands for each of these. Additionally, and consistent with the ethical framework outlined above, interviews of the experts who were surveyed revealed agreement on the following constraints on CHIM research:

- Volunteer safety should be maintained;
- The potential for transmission to third parties should be effectively minimized;
- The study should have clear potential for public health impact;
- There should not be alternative means to gather the same information; and
- The study should produce reliable, relevant data.

These conditions align with the focus in our report on determining whether risks are reasonable, minimized to an acceptable level, and justified by the social and scientific value of the Zika virus human challenge trial.

In the literature reviewed and among the experts interviewed, PATH could not find any reports of a serious adverse event in a human challenge study. Rarely, disease was more severe or persistent than anticipated. Of course, it is possible that challenge studies with severe adverse events have not been published, and some challenge studies, such as Walter Reed's yellow fever experiments in Cuba in 1900, were not included and are known to have resulted in the death of one volunteer.<sup>14</sup> As will be discussed later in the section on risks, this report is an important contribution to the goal of obtaining comprehensive information on the types of challenge studies that have been conducted and the risks involved; in the future, a more systematic review of the risks associated with challenge studies could be very useful.

The experts interviewed prioritized vaccine development, vaccine discovery, and determining correlates of protective immunity above drug discovery, studies of pathogenesis, antigen discovery, or hypothesis generation. Those interviewed also believed that CHIM studies are more justified when there is no relevant animal model that could be used to gather the pertinent data. There was broad agreement that data gathered in a CHIM study are more likely to be relevant when the model uses an epidemiologically relevant strain, is administered by the natural route of infection, and when disease symptoms closely mimic the mild end of the spectrum in natural infection. There was less agreement on the relevance of data from a CHIM study to vaccine development. Some were confident that evidence of protection in a CHIM could be used in part to support vaccine licensure, while others were reluctant to abandon a candidate vaccine that did not work in a challenge study.

There seems to be general agreement among the experts interviewed for the PATH report that the development of a CHIM can be considered for those pathogens of broad public health importance that can be relatively safely administered to healthy adults. Under this justification, CHIMs have already been developed for many of the pathogens that are significant contributors to morbidity and mortality in infants and young children in developing countries. It is equally important to realize that many pathogens have been considered unsuitable for the development of a CHIM. Two of the pathogens of greatest public health impact today, human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (the causative agent of TB in humans), are generally considered inappropriate for the development of a CHIM due to their capacity to establish persistent latent reservoirs that are difficult, if not impossible, to eradicate with drugs. Many other pathogens, like Ebola, that could grow into global public health threats should be excluded from CHIM

development on safety considerations alone. Regardless of social value, the risks to research participants would simply be too high.

## **Part 2: Ethical Evaluation of a Zika Human Challenge Trial**

### **Key issue: Are the risks of reasonable, minimized, and justified by the social value?**

All major ethical codes of human research protections state that research should not be pursued unless the risks to participants are reasonable, minimized, and justified by the benefits to subjects (if any) and others in society.<sup>15</sup> Applying these conditions to a potential Zika virus human challenge study is particularly difficult because of the uncertainty about how and for how long Zika virus can be transmitted to others, the risks associated with Zika virus, the future of the epidemic, and the practical and logistical complications that could arise for Zika vaccine research (including but not limited to human challenge studies). We therefore spend the bulk of our analysis on the evaluation and justification of risks in a Zika virus human challenge trial, beginning with an analysis of whether the risks are reasonable.

#### ***Are risks reasonable and minimized?***

One persistent challenge for research ethics has been determining what upper limit of risk should be allowed in research. Perhaps the first major code of research ethics to be developed, the Nuremberg Code, only rules out very high risk research as ethically unacceptable: “No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.”<sup>16</sup> Since that time, neither the U.S. federal regulations governing research nor most major codes of research ethics have placed explicit upper limits on net risk in research for volunteers who have the capacity to consent.<sup>17</sup> One exception to this general rule is the International Conference on Harmonization’s Good Clinical Practices, which do not allow the use of placebo controls when risks would be life-threatening or associated with permanent disability.<sup>18</sup> Another is reflected in FDA regulations, which indicate that if research poses significant and unreasonable risks to subjects, it can be placed on a clinical hold, but the terms “significant” and “unreasonable” are not defined.<sup>19</sup> For research with vulnerable populations who lack the capacity to consent (along with otherwise complex populations including pregnant women and prisoners), however, many guidelines permit no more than minimal, or a minor increase over minimal, net risk.<sup>20</sup>

Risk is generally understood as composed of three elements: (1) the probability of an adverse event or chance a harm will occur, (2) the amount of harm that could occur—which includes both the degree of harm and how long it lasts, and (3) a comparison to the baseline risk that volunteers would otherwise encounter if they did not enroll in research.<sup>21</sup> Regulations offer limited guidance about how to operationalize and apply these three elements to setting limits on net risk in research with consenting adults.

To concretely determine what probability of harm would be a reasonable ceiling on risk in research, commentators have looked to other activities that are morally similar to research. There is some debate about whether research should be treated as distinct from other activities in life, or whether it is on a par with mundane or risky activities of everyday life, ranging from driving a car to coal mining to firefighting to space exploration.<sup>22</sup> Although it may be difficult to justify treating research as exceptional,<sup>23</sup> there are many morally relevant differences between research and other risky activities. One important difference is that it is uniquely important to preserve the public’s trust in research. Another key difference is that research volunteers rarely receive social recognition or status for the risks they take on, unlike firefighters or astronauts, for instance.

Comparing challenge studies to other types of acceptable but risky research, such as phase I trials that enroll healthy volunteers, is therefore likely to be more fruitful for determining whether the risks involved are reasonable. As with infection challenge, phase I trials with healthy volunteers expose individuals to risk solely to produce generalizable knowledge that will help future patients. Published analyses of the risk

levels of phase I trials have shown that they have very low rates of serious adverse events but high rates of minimal and moderate harms and discomforts.<sup>24</sup> Nevertheless, in rare cases, volunteers have suffered serious morbidity or mortality.<sup>25</sup> According to officials at the European Medicines Agency, there have been only “two trials with very severe adverse events affecting several volunteers among the 14,700 studies (3100 first-in-human studies) involving 305,000 participants that have been conducted in the EU since 2005.”<sup>26</sup> In one of these trials, one subject died, and at least five were reported to suffer persistent neurological deficits.<sup>27</sup> In another, the TGN1412 trial, six volunteers experienced multiple cytokine-release syndrome and multi-organ failure but survived after intensive care.<sup>28</sup> To our knowledge, estimates of severe complication rates from FDA-regulated first-in-human trials are not available.

A better analogy to Zika virus human challenge trials in terms of study design would be other types of challenge trials that have been conducted after approval by institutional review boards, such as malaria, influenza, or Dengue virus. We are not aware of any systematic reviews describing rates of complications in malaria challenge studies. One 2007 report stated, on the basis of exposures to 532 volunteers, that malaria human challenge studies had no lasting adverse effects but high rates of minimal and moderate harms such as fever, muscle and joint pain, fatigue, headache, and chills.<sup>29</sup> The report also noted that although no volunteers developed complicated or severe malaria, 21% of volunteers experienced at least one symptom from the above list that was described as “severe.”<sup>30</sup> However, one key major difference between a Zika virus infection challenge and a malaria infection challenge is that there are effective treatments for malaria, which can prevent harm to research participants beyond symptomatic suffering and potential adverse reactions to malaria treatment.<sup>31</sup> No such treatments are available for Zika virus, though there are opportunities for symptom management and supportive care. A second major difference—noted in the introduction—is the relatively predictable disease course for malaria. In contrast, the disease course and consequences of Zika virus exposure are less well understood. Regarding influenza, one review of influenza challenge studies found a very low rate of severe events (0.04%) in published studies involving 2,462 subjects.<sup>32</sup> Studies reporting upper respiratory symptoms noted that over half of volunteers experienced symptoms such as runny nose, congestion, sore throat, and sneezing. Many of the published influenza challenge studies, however, did not indicate whether adverse events occurred.

Perhaps an even better, though still imperfect, analogy to a Zika virus human challenge model is a Dengue virus CHIM. Both Dengue and Zika viruses are flaviviruses with no proven effective treatments or vaccines. Like Zika virus, infection with Dengue virus is usually asymptomatic, but it can have serious consequences such as high fever, severe pain, and in rare cases, hemorrhagic fever (particularly without prompt medical attention when complications arise).<sup>33</sup> Dengue virus infection challenges have been in use since 1902.<sup>34</sup> Importantly, there is sufficient scientific knowledge about different strains of Dengue fever that mild strains can be selected for infection challenge studies. Key differences between Zika virus and Dengue viruses include: (1) Dengue viruses can only be transmitted through mosquitoes; (2) there is a long history of research on Dengue viruses, including infection challenges; (3) Dengue virus does not pose risks to fetuses; and (4) attenuated strains of Dengue have been developed. After identifying the risks associated with a Zika virus human challenge model, in Table 1 (below), we will compare these risks to the risks in phase I trials and malaria and Dengue human challenge trials.

### *Assessing risks in a Zika challenge study*

To assess the risks in a Zika virus human challenge study, we must consider risks to the volunteers and to third parties. For each of these types of risks, the first step is to identify the risks of Zika infection and the burdens that would be posed by participating in the study itself. Next, we have to identify ways to minimize these risks. Finally, we will need to compare these risks to the baseline that volunteers and third parties would otherwise experience as well as to other, similar activities (e.g., early phase research with healthy volunteers and other types of human challenge studies).

## *Risks to volunteers*

### Risk assessment

The vast majority of adults infected with Zika virus appear to be asymptomatic. However, adults with Zika virus infection can experience symptoms such as fever, rash, conjunctivitis (or “pink eye”), pain associated with eye movement, fatigue, joint and muscle pain, and headache.<sup>35</sup> These symptoms have a variable duration, typically from few days to a week, but they can be severe enough to interfere with daily activities.<sup>36</sup> Post-infectious symptoms such as headaches, fatigue, and other less specific symptoms may linger for several weeks. The major known and serious risks associated with Zika virus are Guillain Barré Syndrome (GBS) and other neurological complications in adults (including myelitis, encephalitis, and optic neuritis) and significant neurological complications in fetuses, including Zika congenital syndrome and Zika-associated microcephaly. We will first address the risk of GBS in considering risks to potential research participants, and then address the risk of microcephaly when we consider risks to third parties. There may also be other serious complications in adults that have not yet been fully characterized or identified.

There is considerable uncertainty about the incidence of Zika-associated GBS. Although the estimated incidence of GBS in the overall population ranges between 0.8-1.9 cases per 100,000 people per year,<sup>37</sup> there has been a remarkable rise in GBS cases in connection with Zika outbreaks, far above the normal incidence rate.<sup>38</sup> Data from the outbreak in French Polynesia suggest that the risk of GBS is 2.5 per 10,000 infected patients.<sup>39</sup> Perhaps the best estimate to date compiles data across different outbreaks: “Estimated GBS risk associated with Zika virus infection was assumed to be 1.1–2.3 cases/10,000 infections on the basis of a separate analysis of data aggregated from French Polynesia, Yap, Brazil, Colombia, El Salvador, Honduras, the Dominican Republic, and Puerto Rico.”<sup>40</sup> The risk of GBS appears also higher in older adults. Among different age groups in Colombia, the highest rate of GBS associated with Zika virus was 1.88 cases per 10,000 in males over 60 years of age.<sup>41</sup> Extrapolation of these estimates to healthy volunteers is greatly complicated by the difficulty of establishing a denominator of exposures in epidemiological studies.

Additionally, studies of Zika-related GBS in Colombia suggest that most of the patients with Zika-related GBS appeared to have a secondary flavivirus infection, as immune assays showed what appeared to be anamnestic response to Dengue.<sup>42</sup> The potential for interaction between Zika and other flavivirus infections and immune responses is still unclear, particularly in terms of the risk of developing GBS, and a cautious approach would be to exclude volunteers with previous exposure to flavivirus from a Zika virus CHIM until there is information suggesting that this risk is low or nonexistent.

Recent findings also suggest that the kidney may serve as a reservoir for Zika virus,<sup>43</sup> and that there is damage to the testes in mice infected with Zika, although it is unclear what relevance this has for humans.<sup>44</sup> Finally, even for participants who were asymptomatic, a Zika virus CHIM would also involve significant burdens, such as isolation and confinement of participants for 1-2 weeks (if not longer), as well as multiple blood draws and urine samples. Before assessing these risks in comparison to risks from similar types of research, we must consider what steps can be taken to minimize these risks.

### Risk minimization

Perhaps the most significant risk to minimize for individual participants themselves is the risk of GBS. GBS is a disease affecting the nerves outside of the spinal cord and brain; it can cause weakness, loss of sensation, and difficulty breathing, and can result in long-term disability. As mentioned above, there are variable estimates of the risk of GBS in individuals infected with Zika virus, with the best estimates ranging from 1.1-2.3/10,000. Being of older age, having had an auto-immune disorder in the past, and previous exposure to a flavivirus may elevate risk of complications such as GBS. The risk of death from GBS is also higher for elderly patients.<sup>45</sup> One way to minimize the probability of GBS-related complications would therefore be to exclude older individuals and people who previously had auto-immune disorders or flavivirus

infection from a Zika virus challenge study. Considered another way, however, consequences associated with Zika infection could be more significant for younger volunteers, since severe adverse events could be associated with more disability-adjusted life years lost in younger patients.

It should be noted that within a challenge study, subjects could be carefully monitored for development of motor or sensory symptoms, and if they were suspected of having GBS or diagnosed with GBS, they could be treated with intravenous immunoglobulin (ivIG) and/or plasma exchange to prevent further development of severe symptoms.<sup>46</sup> It is difficult to know how much this approach would mitigate the risks associated with GBS because the course of illness is variable—the serious complications of GBS can range from mild loss of sensation to a more complicated clinical picture including paralysis, respiratory failure, or cardiac failure; symptoms can develop within days or hours.<sup>47</sup> There is no proven way to predict the course of GBS for an individual patient, but an early diagnosis would lead to early treatment, which would minimize the severity of the disease. Although most of the clinical trials for GBS have tested treatment offered after 14 days, it is assumed that patients who progress rapidly should be treated very early. Some authors have summarized this clinical picture by noting that “Guillain-Barré syndrome is still a life-threatening disorder with frequent morbidities, even with the best treatment available.”<sup>48</sup> We therefore have assumed that, even within the confines of a carefully designed human challenge study, the risks of GBS with prompt treatment would be similar to treatment efficacy rates and long-term effects currently documented in the literature. One case-controlled study with long-term follow up of 70 patients afflicted with GBS found that 33% of patients had such serious long-term complications that they had “to make substantial changes in their job, hobbies or social activities” three to five years after their illness.<sup>49</sup>

There may also be future risks of GBS for volunteers who were exposed to Zika virus in a challenge study and then were later exposed to another flavivirus or arbovirus, such as Dengue or West Nile viruses. Theoretically, previous exposure to Zika and subsequent exposure to another flavivirus could lead to development of antibody-dependent enhancement of infection and lead to possible immune reactions, which may include neurological complications like GBS. One possible reassuring point regarding this risk is that although there has been a resurgence of Dengue virus in parts of Colombia and Brazil where Zika virus outbreaks recently occurred, there has not been a corresponding increase in GBS. This might be explained by the fact that Dengue virus has limited neurotropic effects and has only very rarely been associated with GBS,<sup>50</sup> so being infected with Dengue virus after having Zika virus may not increase the risk of neurological complications like GBS.

Careful strain selection could potentially limit the effect on study volunteers to viremia, rather than disease symptoms, and such a strain could enable screening of candidate vaccines for those that provide the most viremic control. If the ultimate goal is to protect the developing fetus from infection, this kind of model could be appropriate. A small pilot study in a handful of volunteers to better determine the kinetics of viremia in blood and other body fluids could provide a wealth of information that would inform Zika virus vaccine development generally, as well as shed light on the feasibility of a CHIM for this virus.

There may be other unknown risks that cannot easily be minimized. Ways to prevent unknown complications from causing significant harm could include close and prolonged monitoring of participants and prompt treatment and compensation for injury. Notably, however, longer periods of confinement and frequent study visits would increase the length of time to conduct a Zika virus CHIM and may make the trial more burdensome to participants, which could compromise its efficiency and compliance. Given that efficiency is usually a reason to prefer CHIMs over other research designs and compliance critical for risk management, this approach to minimizing risks might undercut the justification for a Zika virus human CHIM.

Another potential way to minimize risk is to conduct a Zika virus CHIM in an endemic region where participants are already at a baseline level of risk from Zika virus. Comparing the risk of being closely monitored in research and having some probability of infection with Zika virus to the alternative of being infected with Zika virus without this monitoring, the risks of research participation might be lower than the risks of daily life and therefore potentially more justifiable than conducting the study in a non-endemic area. There are five main disadvantages of such an approach, however. First, volunteers might be exposed to the virus in the course of their daily lives, and this would make it difficult to collect reliable data about the effects of the intentional exposure or how effective a vaccine was at preventing exposure after the initial period of

confinement. Second, if a challenge study were conducted in an area with the proper conditions for an outbreak, it could pose risks to the community of reintroducing the virus or introducing a new strain after the previous outbreak waned. Third, prior infection with a flavivirus, which would be more common in Zika-endemic areas, could put volunteers at a higher risk of unknown immune interactions that might increase the risk of serious complications, including GBS. Flaviviruses like West Nile do occur in many regions of the world where Zika is not endemic, but flaviviruses like Dengue are more prevalent in regions where Zika is endemic, and if such prior infections are not detected during screening, this could raise the risks of the trials. Fourth, treatment for complications such as GBS may be less readily available in regions with less healthcare infrastructure in place where Zika virus is endemic, again complicating the ability to minimize risk. Fifth, sophisticated research infrastructure is needed to conduct human controlled infection platforms, and this may not be present in many countries with ongoing Zika virus epidemics, although it may exist in some.<sup>51</sup> Thus, although this suggestion for minimizing risk is initially appealing, it may be too difficult to put into practice in a manner that would effectively lower risk, and it might carry risks of its own to the integrity of the data and in terms of causing a new outbreak in the community.

As illustrated in Table 1 below, in terms of the degree of harm to adult participants in a Zika virus human CHIM, the known risks of symptomatic discomfort during the study appear to be in line with the risks seen in healthy volunteers in phase I trials and malaria challenge studies. Using the best estimates currently available about known risks, the risks of symptomatic discomfort and serious harms for adult volunteers in a Zika virus human CHIM appear to be roughly equivalent to the risks seen in phase I trials with healthy volunteers. Nevertheless, there is substantial uncertainty about the risks that healthy volunteers would face in a Zika virus human CHIM, and it is also unclear whether the data about the risks to volunteers in human challenge studies are comprehensive. In particular, the level of risk associated with GBS, the severity of complications associated with Zika virus, and the full spectrum of disease involved with Zika virus are not fully known. With respect to the duration of symptoms and the uncertainty about what harms could occur, the risks may be greater than the risks posed by phase I trials and other challenge studies.

**Table 1: Comparing risks for volunteers in a Zika virus challenge study to risks in other research**

	<b>Risks in phase I trials with healthy volunteers</b>	<b>Risks in Malaria human challenge trials</b>	<b>Risks in Dengue virus human challenge trials<sup>52</sup></b>	<b>Risks in Zika virus human challenge trials</b>
Low-to-moderate harms/symptoms	Gastric ulcer, fever, vomiting, anemia, headache, croup, injection site pain, diarrhea, nausea, acute bronchitis	Fever, muscle pain, joint pain, chills, headache, fatigue (some “severe”)	Headache, pain, joint pain, rash, mild bleeding	Rash, conjunctivitis, muscle pain, joint pain
Serious harms	Birth defects, miscarriage, multi-organ failure, severe neurological complications, death	None described	Dengue fever, neutropenia, elevated liver enzymes	Potential risks include GBS, miscarriage, microcephaly, kidney damage, unknown risks
Duration of symptoms	Not reported	1-10 days	0-12 days	Highly uncertain with wide range (rash: 3-7 days; joint pain: 2-21 days; <sup>53</sup> eye pain: 44.2 days; fatigue: mean: 28 days, max: 166 days) <sup>54</sup>
Probability of minimal-to-moderate harms	6.9-12.2% (n=3017)	61-79% of participants	Approx. 10% of people infected symptomatic; rates in CHIMs: 0-100%	Approx. 20% of people symptomatic
Probability of serious harms	0.31% serious adverse events, .003% life-threatening events/deaths	None reported out of 532 volunteers; likely low	None reported in 28 volunteers	GBS risk: .01%-.023%, Long-term disability from GBS: .003%-.008%, Mortality from GBS: .0003%

**Recommendation 1A:** There is substantial uncertainty about the risks to potential volunteers in a Zika virus human challenge study. Although the known risks of a Zika virus human challenge trial appear comparable to the risks of phase I research with healthy volunteers, without greater knowledge about outcomes from Zika exposure, these risks would require high social benefit to be justified. Strategies to minimize risks include careful selection of inclusion and exclusion criteria, close medical monitoring, relatively long periods of confinement, and prompt medical attention for volunteers who become ill.

upper limit of risk allowable in research.

### *Risks to third parties*

Zika virus can be transmitted to humans in several ways. Zika virus can be transmitted by a mosquito that bites an infected person and then an uninfected one; from a pregnant woman to her fetus during pregnancy and delivery; through male-to-female, female-to-male, and male-to-male<sup>55</sup> sexual contact; and through blood transfusions. Zika virus is present in breastmilk and could theoretically spread through breastfeeding, though this has not yet been demonstrated. In addition, there may be other modes of transmission that have not yet been identified, as illustrated by an unexplained case of infection between a father and son in Utah.<sup>56</sup> Evaluating the ethics of a Zika virus human challenge trial requires assessing and minimizing risks of transmission to a range of third parties.

Many types of research present third-party risk, including xenotransplantation studies, trials involving caregiver participation, trials testing radiotherapies, research on contraception, HIV cure research requiring structured treatment interruptions, and (depending on who is understood to be the subject of research) research involving pregnant women. Despite this, current research regulations have little to say about protecting third parties.<sup>57</sup> Still, there are compelling ethical reasons to confer especially strong protections for third parties exposed to research risk. First, third parties usually have not provided informed consent for being exposed to risk, may not be known to the research staff in advance, and may not be aware that they have been exposed to risk in the first place. Second, some third parties, like children, are limited in their ability to provide voluntary informed consent and protect their own interests. Third, transmission to third parties without their prior consent seems much more likely to invite public concern and threaten trust. Many studies of risk perception indicate that involuntary risk exposures generally result in especially strong public backlash.<sup>58</sup> As discussed below, the imperative to maintain public trust is especially high in a realm like vaccine development, since field trials will ultimately require engaging large and diverse healthy populations.

### **Risk assessment**

Zika virus infection during pregnancy has been linked to a number of potential abnormalities in infants, the most well-known of which is microcephaly.<sup>59</sup> A causal relationship between prenatal Zika virus infection and microcephaly and other serious brain anomalies has been documented.<sup>60</sup> Prior to the Zika epidemic, the reported rate of microcephaly in the United States varied from 1 to 6 cases per 10,000 births.<sup>61</sup> The rate of first trimester exposure Zika-related microcephaly was initially estimated to be 1% (data from the French Polynesia epidemic) and later up to 13% (based on estimates from the Brazilian epidemic).<sup>62</sup> One complication in interpreting these numbers is that there may be other factors affecting the rate of microcephaly in these contexts, such as environmental contaminants and nutrition. A report of the outcomes of more than 400 pregnancies from a registry of Zika-exposed pregnant women and their infants in the United States and its territories is helpful in this regard. The incidence of infants with birth defects among pregnant women infected with Zika virus was 6% for those presenting with or without symptoms. In addition, the rate of birth defects among women exposed during the first trimester was 11%.<sup>63</sup> More recent data from Brazil suggest a more significant risk, reporting a rate of congenital abnormalities associated with infection during pregnancy as high as 55% when infection occurs in the first trimester (and 42% across trimesters).<sup>64</sup> This study found overall adverse outcomes of 46% for the offspring of women who tested positive for Zika virus, as compared with 11.5% of the offspring of Zika-negative women.<sup>65</sup> Postnatal development of microcephaly has also been documented; at least 13 Zika-exposed infants who were born with normal head circumference have been diagnosed with microcephaly in the first year of life.<sup>66</sup> These findings both challenge our ability to quantify the likelihood of harm resulting from infection during pregnancy and suggest that even infants who appear normal at birth are still at risk for development of serious disability and brain dysfunction.

Although it is important to reiterate that the impact of Zika virus infection is still not fully known, congenital Zika syndrome (CZS) has now been characterized. Congenital Zika syndrome has distinctive features that are not limited to abnormalities in brain development (such as severe microcephaly and brain



calcifications) but also include ocular damage on the retina and defects on extremities such as congenital contractures and hypertonia.<sup>67</sup> Zika infection during pregnancy is also associated with other adverse outcomes including growth restriction, miscarriage, intrauterine fetal deaths; the long-term impact on children exposed before birth is unclear.<sup>68</sup> Fetal loss (miscarriage) and intrauterine fetal demise (IUFD) have been described with more frequency in some cohorts, but not in all.

Preliminary findings from Puerto Rico suggest other troubling possibilities. Findings from ultrasounds of women with Zika virus during pregnancy show temporal decrease in head circumference associated with Zika infection with catch-up growth afterward.<sup>69</sup> The head circumference falls within the normal range for the majority of the fetuses, but we do not know the significance of these findings. Since Zika virus is neurotropic, potential neurologic damage might be seen after birth, as was the case of the 13 infants reported from Brazil. Alternatively, Zika virus may have both short-term and long-term effects on infants and children, such as neurodevelopmental abnormalities, learning disabilities, psychiatric disorders, and other unknown but yet to be described disabilities that could affect a much higher percentage of infants who are exposed but do not develop CZS.

One challenge in interpreting how likely these risks are to materialize in a Zika virus human challenge trial is that the period of transmission for Zika virus is not known. Individual case reports have demonstrated that Zika DNA can persist in semen for approximately six months after an individual is symptomatic,<sup>70</sup> Zika virus can be found in semen for up to 93 days after infection,<sup>71</sup> one woman appears to have been infected by a sexual partner who had previously had a vasectomy,<sup>72</sup> and one woman was infected through sexual transmission from her partner at some point between 34 and 41 days after he was infected.<sup>73</sup> For women, the period of perinatal infectivity is similarly unclear. Based on the limited information currently available, the CDC now recommends that women wait eight weeks after symptoms start or after a potential exposure to Zika virus to become pregnant, and that men wait at least six months after symptoms start or after they could have been exposed to Zika virus to try to conceive a child.<sup>74</sup>

#### Risk minimization

In theory, the risks associated with spreading Zika virus in the context of a Zika CHIM could be minimized through careful selection of inclusion and exclusion criteria, a period of isolation in a research facility with close medical monitoring of volunteers, and a rigorous informed consent process in which participants commit to taking precautions to avoid transmission through mosquito bites, sexual activity, and pregnancy. To minimize the risk of infection to women who are pregnant and their fetuses, a Zika virus CHIM could enroll only men who have sex with men, men who are celibate, and women who have had hysterectomies or are otherwise unable to conceive a child and who have no intention of doing so and are either post-menopausal (but not above the age at which the risk of GBS increases), sterilized, or using effective long-acting reversible contraception, which could reduce the risk of unintended pregnancy to less than one percent.<sup>75</sup> A CHIM should also provide and attempt to ensure the use of adequate and effective contraception by volunteers, preferably long-acting reversible contraception, such as injections, intrauterine devices (IUDs), and subdermal contraceptive implants, as well as barrier contraception.

The risk that a Zika CHIM study could pose to the community via introduction of infected mosquitoes is not well defined at present. Keeping volunteers confined in the hospital until they no longer test positive for Zika virus is one way to reduce the risk that they would transmit Zika virus to others in the community. Conducting research in regions where there are no mosquitoes that transmit Zika virus is another way to reduce this risk. If a challenge study were conducted in an endemic region, use of insect repellent and other forms of mosquito control could reduce the risk of Zika virus spreading to others in the community from a CHIM.

One approach to manage risks to fetuses would be, perhaps counterintuitively, to select only women as volunteers. This would ensure that the most significant risk—the risk of transmitting Zika virus to a fetus—is prevented more directly (by screening, counseling, and obtaining voluntary informed consent from a woman) and reduces the likelihood that this risk would be borne by third parties (female sexual partners of male participants) who have not given their consent and may not know they are at risk. Moreover, since the

risk of transmission of most sexually transmitted infections (STIs) is greater by male-to-female transmission, enrolling female volunteers could reduce the risk of sexual transmission to third parties. It appears that transmission from semen is epidemiologically important for Zika virus as well, because so far, the great majority of documented sexual transmission cases are male to female or male to male. This approach would also make it easier to carefully follow volunteers and identify inadvertent pregnancies in the unlikely circumstance that they were to occur. Finally, another advantage to conducting a Zika virus human challenge study only with female participants is that such an approach could yield more robust data on preventing viremia in women—a key goal of such research.

These approaches to risk minimization are not foolproof, however, and they would rely on participants to be honest about their sexual practices, to be compliant with study participation, and presumably to have confidence in their partners' sexual practices as well. The committee was also uncertain how compatible these risk minimization strategies are with designing a challenge study that can rigorously answer the relevant and important scientific questions. The period of transmission of Zika virus through semen could be as long as 24 days (if not longer), but this estimate is highly uncertain. Most challenge studies do not confine participants for more than 10 days, however, given that long periods of confinement are a significant hardship for most people and might limit recruitment for challenge studies. More work to develop strategies to reduce the risk of transmission to fetuses would be very valuable.

In Table 2, we compare the risks to third parties posed by a Zika virus CHIM to other types of studies. The risks to fetuses are likely very low in phase I trials, risks to others in the community are not generally present in phase I trials, and both risks to fetuses and others in the community are relatively low and able to be reduced to near-zero for malaria and Dengue CHIMs. This suggests that, in order for a Zika virus human challenge study to proceed, the risks to third parties from a Zika virus human challenge study should be reduced to near-zero.

The third-party risks associated with a Zika virus human challenge trial, however, are associated with a high degree of uncertainty in terms of how the virus might be transmitted and for how long. Without this information, it may be difficult to fully assess whether the risk involved in a Zika virus human CHIM is reasonable. This suggests that Zika infection challenge studies would require greater certainty about modes of transmission and duration of infectiousness. More research using virus culture, which detects infectious virus rather than virus genetic material, will be needed to clarify the period of infectiousness and the relative risk of exposure to different body fluids, and it is an important unmet condition for the present pursuit of a CHIM for Zika virus.

**Table 2: Comparing risks to third parties from a Zika CHIM to other types of studies**

	<b>Phase I healthy volunteer studies</b>	<b>Malaria human challenge trials</b>	<b>Dengue human challenge trials</b>	<b>Zika human challenge trials</b>
Who might be at risk	Fetuses	Very low probability of local transmission of malaria to community through mosquitoes	Very low probability of local transmission of Dengue fever to community through mosquitoes	Potential risks of transmission to fetuses, low chance of transmission to third parties by mosquitoes, sexual transmission, transmission through bodily fluids
Type of risk	Miscarriage, stillbirth, birth defects	Risks associated with malaria (see Table 1)	Risks associated with Dengue (see Table 1)	Microcephaly, miscarriage, stillbirth, risks associated with Zika virus for community (see Table 1)
Can risk to third parties be reduced to near-zero?	Depends on use of contraceptive measures	Yes, can isolate volunteers until malaria tests are negative	Yes, can isolate volunteers until Dengue tests are negative	For fetuses: depends on use of contraception & sexual activity; For communities: not clear, given uncertainty about modes of transmission and period of infectiousness

**Recommendation 1B:** The committee was particularly concerned about possible risks to third parties, i.e., that Zika virus might be transmitted from study volunteers to others, such as fetuses and members of the community. Because these third parties generally cannot know about, protect themselves from, or consent to risks, risks to them are only reasonable if they can be reduced to near-zero. However, the mechanisms of transmission of Zika virus and how long individuals with Zika virus can infect others are not fully understood. Before proceeding with a Zika virus challenge study, researchers should therefore demonstrate that the risks to third parties are not likely to be realized. This could be done through developing risk management strategies and obtaining relevant data. Approaches to minimizing risk would rely upon either relatively long periods of isolation, the use of effective long-acting reversible contraception, careful inclusion and exclusion criteria (including potentially enrolling only women), and/or individual participants' self-report about their own sexual practices as well as the practices of their partners, though the committee was not certain to what extent these strategies would be compatible with appropriate scientific design. Additional information could be gathered through modeling based on rates of transmission and pregnancy in similar studies and research to characterize the modes of infection and transmissibility of Zika virus. More research using virus culture, which detects infectious virus rather than virus genetic material, could clarify the period of infectiousness and the relative risk of exposure to different body fluids, and is an important priority for the development of a Zika virus human challenge study.

### ***Would Zika human challenge trials have sufficient social value?***

Social value is a foundational ethical requirement for research.<sup>76</sup> Although there are many different types of justifications for a social value requirement, when research volunteers are not expected to benefit from their research participation, social value is the primary benefit that can justify exposing volunteers to net risk.<sup>77</sup> In general, higher social value is understood to justify higher risk to research volunteers, as long as other protections are in place (including informed consent), and there is widespread agreement that risk still cannot exceed a threshold of what should be allowed in research with human subjects.<sup>78</sup> Social value is not well defined in the ethics literature, but it is generally understood in terms of a study's potential to answer scientific questions that are relevant to addressing unmet medical or public health needs that will benefit society.<sup>79</sup> Whether a research study has social value therefore depends on a variety of factors, including (1) whether the study seeks to answer an unresolved scientific question; (2) whether the study is designed, conducted, and reported in a manner that resolves or advances knowledge relating to that scientific question; (3) whether resolving the scientific question is likely to have an impact on medicine or public health; (4) what would occur if research were not conducted (i.e., the counterfactual); and (5) whether there are other, less risky or burdensome approaches for obtaining the same knowledge. Applying these considerations to a Zika virus human challenge trial reveals that the condition that may be most difficult to meet is the last—establishing that a Zika virus human challenge trial is the best and least risky or burdensome approach to obtaining valuable knowledge.

With respect to the first condition, a key consideration is whether an investigation is prompted by sufficiently robust prior evidence. Where prior evidence is insufficiently compelling, trials become risky gambles that may produce very little in terms of advancing a translation trajectory. This past decade has uncovered numerous problems with the way preclinical research is designed and reported.<sup>80</sup> The conduct of Zika challenge studies would necessarily depend on there being high-quality preclinical evidence and data from animal models to support launching human challenge research. The committee did not have enough information to determine whether this criterion has been met, but it did learn that Zika virus studies have been conducted in mouse models and rhesus macaque monkeys<sup>81</sup> and are being planned in baboon models because the placental structure in baboons closely resembles that in humans.<sup>82</sup> To the extent that critical information can be gleaned from relevant animal models and conducting this research would not take an inordinate amount of time, we recommend waiting to conduct a human challenge study until after this information is gathered.

The second key feature of social value noted above concerns whether studies are designed and reported in ways that support valid and meaningful clinical inferences. For the purposes of this report, we assume that study design and statistical considerations for challenge studies are no more complicated than other types of research, and may in fact be easier to resolve than other types of research (though with some questions about generalizability). Data gathered in a human challenge study are more likely to be relevant when the model uses an epidemiologically relevant strain and is administered by the natural route of infection. It is also advisable to study a strain when disease symptoms closely mimic the mild end of the spectrum in natural infection, both to protect volunteers and to allow for relevance to the vast majority of people who have Zika infection and might conceive a fetus at risk of congenital Zika infection. One important limitation on Zika virus human challenge trials is that it will take a great deal of time to develop a model in which volunteers would be infected with Zika virus by mosquitoes (as in malaria challenge studies), and other forms of transmission (i.e., sexual and vertical transmission) could not be used ethically in a challenge study. The route of administration will have to be through injection, which will have some limitations, but this criterion does not present major complications for a Zika virus human challenge trial.

A third element for social value is the potential impact of a study in terms of addressing unmet health needs and whether the experimental intervention or information to be learned from the study is promising and timely. Rarely would a single study lead to approval of a safe and effective vaccine or treatment. However, if a Zika virus CHIM could advance the goal of obtaining approval of an intervention that could protect against Zika infection, it seems straightforward to suggest that such a study could address an important scientific question with critical public health implications. There are no proven effective medical interventions to prevent or treat Zika virus, and its effects on fetuses and older adults can be devastating.

There are still unknown and emerging potential complications and it is even possible that there are currently unidentified modes of transmission. Although the potential impact of a Zika virus human CHIM is clear in relation to addressing unmet health needs, the impact of a study also depends on the base rates of successful clinical translation. Drug development programs that have a greater record of delivering actual health benefits can make a stronger claim to value than those that rarely deliver benefits, or that deliver benefits only after substantial delay. Thus, an important consideration in evaluating Zika challenge studies is projected success rates and timelines for developing vaccines against similar diseases—in this case, flavivirus infections. As noted in Figure 2 below, there has been substantial progress made in developing a vaccine for Dengue virus, with some evidence that challenge studies have helped accelerate the process.

Fourth, to be socially valuable, trials should be coordinated with each other such that each trial adds something important to the body of scientific knowledge. Thus, an additional consideration for evaluating challenge studies concerns whether there is sufficient investment and resolve among public and private sponsors to use data from a challenge study in ways that would significantly alter their vaccine development plans. There are several Zika virus vaccine studies currently underway, and it appears likely that these studies will go forward whether or not a Zika virus CHIM is conducted. To the extent that research sponsors and product developers determine that they would have good reason to plan their trials around the results from a planned human challenge model, however, this would strengthen the case for conducting a challenge study. Additionally, as we will discuss further below, if field trials become impossible to conduct because the epidemic changes, this might be a compelling justification for conducting a Zika virus human challenge study.

Finally, and most importantly for our purposes, studies involving high or uncertain net risk must be evaluated carefully against the possibility of obtaining similar knowledge using other, less risky or burdensome research methods. In the committee's view, a Zika virus human challenge study will have a more compelling justification where it is believed—on the basis of expert opinion—to be the *best* way to answer a valuable scientific question that is likely to have a major public health impact, as compared with ethically acceptable alternatives.<sup>83</sup> This approach strikes a balance between the urgency of the threat posed by Zika virus and the need for ensuring that a human challenge study is not conducted when another approach would be roughly equivalent. Some might argue that approaches like Zika CHIMs should be conditioned on their being the *only* way to address a valuable scientific question, given the ethical concerns around this design. Such a standard seems excessively demanding, given the urgency of developing interventions against Zika and that there is often uncertainty at the outset of investigations regarding which approach is most likely to be most productive with regard to a longer-term goal. Others might simply demand that Zika CHIMs be a *rational* way to answer a valuable scientific question. However, given the uncertainties involved, the chance that participants or others could be harmed as the result of deliberate infection or transmission to others, and the potential consequences of adverse events in the burgeoning field of infection challenge research (as will be discussed further below), such a threshold may be too permissive.

In order to determine if a Zika CHIM is the best way to answer a valuable scientific question with a major public health impact, we need to consider what the different rationales for conducting a CHIM might be. At the consultation meeting, we discussed three types of reasons for a Zika virus human CHIM:

Possible types of rationales for a Zika virus human challenge trial

1. Learning about Zika virus: To learn about pathogenesis or modes of transmission.
2. Accelerating vaccine development: To speed up the path to licensure for a particular vaccine.
3. Preserving ability to combat Zika virus: To test vaccines and treatments if the current Zika epidemic temporarily wanes and field trials are prohibitively difficult to conduct.

We will now turn to examining these three different rationales for conducting a Zika virus human challenge study, as compared with the alternative ways of learning the same information. As we will argue below, we conclude that the first does not compare favorably against the alternatives, the second could justify a study if preceded by good evidence of clear coordination between research sponsors to use the results from a Zika virus human CHIM to accelerate vaccine development (about which the committee had insufficient evidence to make a judgment), and the third is the strongest justification for doing a Zika virus human challenge study but has not yet come to pass.

### *Rationale 1: Learning about Zika virus*

The first reason to conduct a Zika virus human challenge trial that we will consider is to learn more about Zika virus, including pathogenesis, modes of transmission of Zika virus, and what happens when volunteers are co-infected with Zika virus and other flaviviruses. It is possible that a Zika virus human challenge trial could provide unique insights into the early stages of infection. Patients typically come to their doctors for tests for Zika virus after they develop symptoms. The ways that patients with Zika virus are usually followed by their doctors fails to capture early infection before symptoms appear, because patients are typically detected based on having clinical symptoms in the first place. Zika infections that are asymptomatic are rarely detected or detected very late—sometimes after a fetus is born with complications. Even for those who experience symptoms, there is a delay between infection and symptoms, called the incubation period, when important disease mechanisms occur but are not noticed and cannot be studied in usual clinical care or research.

CHIM studies could provide a unique opportunity to address those early events that occur during the incubation period and could reveal information about how the disease affects the body and spreads through it, along with the ways that the immune system can respond effectively. Studying the incubation period can provide clues of ways the immune system can attack the disease effectively and to find a biomarker associated with being protected against the virus (i.e., a correlate of protection). Such results might be useful to tailor products in development in order to shift immune response in the most effective way. This approach could also help avoid some adverse reactions or ineffective aspects of a vaccine candidate by changing different parts of the vaccine (e.g., the adjuvant or route of administration).

Nevertheless, such potential advantages might not occur, and they may not be critical for vaccine development. Vaccines have long been successfully developed with limited information on immunogenic mechanisms, by proving that they work in large-scale immunization programs.<sup>84</sup> Given the amount that has already been discovered about Zika virus in terms of complications and modes of transmission in the last six months alone, there appear to be alternative ways to develop vaccines with a reasonable probability of being protective. Since volunteers would be isolated and advised to take considerable precautions to prevent transmission to others, the only information that could be learned about modes of transmission would be to identify different compartments where Zika virus resides in the body. Moreover, there are important ethical limits on what can be learned about viral reservoirs in humans, given the risk and discomfort associated with invasive procedures, which limits what can be learned from a CHIM as compared to animal research. For instance, brain biopsies for research purposes only could not be done in humans, but they may be permissible in animals. There are also ethical concerns with studying what happens to people who are co-infected with Zika virus and other types of flaviviruses, such as Dengue or West Nile, because there is the possibility that this will increase risks by activating the volunteers' immune systems or causing them to have complications like GBS. There is enough evidence about this risk that studying Zika virus in order to learn about the risks of co-infection through a challenge model would contradict researchers' ethical obligations to minimize risks.

Therefore, this justification for doing a Zika virus human challenge trial is a weak stand-alone reason to support CHIM use. It seems more effective to learn about modes of transmission by closely examining unusual case studies or by conducting animal research (including studies with pregnant non-human primates, particularly given that such research with human volunteers would not be ethically acceptable) where it is more ethically acceptable to examine whether the virus is present in different compartments of the body through biopsies or autopsies.

Although a Zika virus human CHIM is *not* the best way to learn more about the virus in terms of its effects on the body or the ways that it can be transmitted to others, learning about pathogenesis or early immune response might be an additional benefit if there is another, stronger reason to conduct Zika virus human challenge trials. Additionally, this conclusion could change if animal models prove to be poor predictors of what vaccines might work in humans, but at present it seems reasonable to presume that animal models, observational studies, registries, and surveillance can teach us a great deal about pathophysiology and transmission, and a Zika human CHIM is not critical for this purpose.

### *Rationale 2: Accelerating development of a vaccine that could protect fetuses*

Challenge studies could speed up the development of a Zika virus vaccine in several possible ways. One way is to select the best candidate vaccines faster and more accurately. In the development of a pharmaceutical product, several go/no-go decision points occur. Those points are critical to avoid unnecessarily exposing participants in clinical trials to an experimental vaccine that is unlikely to work and to save resources and time that might be better used to study other vaccine candidates. Narrowing down the field of candidates can be very valuable because studying a vaccine in the field is often costly, difficult, and requires exposing larger numbers of patients to a new intervention.

Another, related justification for conducting a Zika virus human challenge study would be to identify a correlate of protection or immune marker that would protect against congenital Zika infection. In other words, a Zika virus CHIM could identify a biomarker that would reliably indicate when a woman who had received the vaccine would be protected from Zika virus such that she would not have to worry about infecting a future fetus. For instance, identifying the level of neutralizing antibodies that is sufficient to protect against virtually any virus replicating in the body might be the best way to determine whether a fetus will be protected from the virus. This immune correlate of protection could then be used by different stakeholders in different ways, including as a way to prioritize among different vaccine candidates.

Finding a correlate of protection could be important because there is currently no way to estimate a safe viremia level to avoid Zika virus intrauterine infection. Pregnant women who have no or few symptoms, and presumably only low viremia levels, have had their offspring affected by Zika virus-associated conditions.<sup>85</sup> Complete, or sterilizing, immunity is not only a very hard target to achieve for any vaccine candidate, but demonstrating this high level of immunity in a field trial would pose logistical challenges that would be hard to overcome, such as requiring thousands of participants to reliably come to study sites for very frequent testing. Although a WHO expert consultation suggested that clinical Zika virus disease should initially be the primary efficacy parameter for Zika vaccine trials,<sup>86</sup> this would not work for a Zika CHIM. Relying on disease as the primary outcome of a Zika CHIM would require developing strains that are more pathogenic than those isolated in recent outbreaks, since somewhere between 50-80% of people infected with Zika virus have no major symptoms.<sup>87</sup> This suggests that a challenge study could be uniquely able to develop a correlate of protection that could indicate when an individual is protected against Zika virus, and when a woman who might become pregnant is protected against the negative consequences of Zika virus for a future fetus. Of course, obtaining this correlate of protection from a human challenge study in healthy, non-pregnant volunteers will require some degree of inference to apply to women who are pregnant or who become pregnant. Studies in pregnant, non-human primates may be needed that support this inference in advance of a challenge study designed to identify a correlate of protection against congenital Zika infection.

Relatedly, some experts have suggested that the use of a Zika virus challenge study might be a pivotal study for vaccine approval.<sup>88</sup> Although the use of a challenge model as a stand-alone study to demonstrate efficacy has never supported a vaccine being licensed, a Zika virus challenge study would be conducted along with safety studies (including studies involving hundreds of volunteers to build a robust safety database on a particular vaccine candidate). The potential use of a CHIM as a pivotal study to show efficacy would require that several conditions be met. The most important condition is a basis for believing that challenge study outcomes would be predictive of outcomes if vaccines were given to people in the field. Unlike in a challenge study, vaccine recipients in the real world might be diverse in terms of sex, health status, or other exposures. The strains that infect people might have important differences from the strain that was chosen for use in a

challenge study, thereby limiting the value of what is learned in a CHIM. Most people might also not be as adherent to vaccination regimens as clinical trial volunteers who are motivated to participate and given incentives to do so. Finally, one of the most important objectives in developing a vaccine is to prevent the transmission of infection to fetuses, and this could not directly be studied in a challenge study. Given these potential differences between a Zika virus human challenge study and the Zika virus epidemic, it will be important to ensure that the results from a challenge study can in fact help advance the goal of developing a vaccine that actually protects infants from congenital Zika infection.

Other conditions for using a challenge study as a pivotal study to establish efficacy of a Zika vaccine include having limited genetic diversity of the virus and well-characterized parameters to assess efficacy. Fortunately, Zika virus strains linked to intrauterine infection are well-identified and have low genetic variability, which suggests that setting up a CHIM seems feasible. On the other hand, parameters to assess efficacy are still under debate. There is consensus that testing whether a vaccine protects women against intrauterine infection and complications for the fetus would be difficult, because the rate of complications for fetuses is low enough that such a trial would take several years to complete and would require large numbers of volunteers, and it is important to reiterate that sterilizing immunity is very difficult to achieve (and prove).

In summary, although obtaining an effective Zika virus vaccine without using a CHIM seems possible, a key question is whether a CHIM can accelerate the process to obtain and/or provide access to a Zika virus vaccine. In this case, months saved in development could make a difference in terms of preventing significant morbidity from Zika virus. It is also important to note, however, that field trials conducted on Zika virus can only be conducted during ongoing outbreaks, which in turn vary based on location and time of year. This suggests that answering questions about vaccine efficacy quickly may not hasten the process of vaccine development unless the timing is right. The rationale of conducting a Zika CHIM to accelerate vaccine development is also dependent on the decisions of people other than researchers and sponsors. For instance, if it is very difficult to obtain ethical and regulatory approval for a Zika virus CHIM, or if community consultation takes time and reveals multiple concerns that need to be addressed, or if a Zika virus CHIM has trouble recruiting that field trials would not, any or all of these outcomes being realized could mean that very little time would be saved by conducting a Zika virus CHIM.

Critically, the viability of the rationale to use a CHIM to choose between different vaccine candidates depends on whether funders, both public and private, might use a challenge study as a strategy to prioritize vaccine candidates and wait to conduct field trials until the results were available. One problem with this justification is that the consultation process did not uncover any indication that the NIH, pharmaceutical companies, or the Food and Drug Administration would wait on the development of this type of information to proceed with vaccine trials or make key decisions. Another important issue is that a correlate of protection for healthy, non-pregnant adults might not be sufficient to determine what level of immune activation is needed in pregnant women to protect a developing fetus, so further animal studies in pregnant non-human primates (including challenge studies) and field trials of vaccines in pregnant women might be needed to ensure the same correlate is in fact protective and durable throughout pregnancy and delivery.

The committee had difficulty evaluating this type of rationale in the compressed schedule we had for decision-making. We heard evidence at the meeting that animal models and results in early phase trials could be sufficient to pick the best vaccine candidate. We also gathered some evidence on whether challenge studies have sped up vaccine approvals, based on other disease models, and we concluded that the evidence is mixed (see Figure 2).<sup>89 90 91 92 93 94</sup> Nevertheless, we recognized that it is possible that the NIH, CDC, or other U.S. government agencies could use an immune correlate of protection to determine which vaccine research to prioritize, which vaccines to purchase for the military or for aid in Zika-affected areas, and/or which vaccines to include in the general schedule of vaccination. There was no clear indication or evidence of such a commitment at the consultation, and at least some information that this could also be addressed through alternative means. However, if evidence from a Zika virus human challenge study would be used in decision-making about Zika virus vaccines or interventions, this justification might be a way to support a conclusion that the risks of Zika virus CHIM are ethically justifiable.



Figure 2: Evidence that challenge studies can help speed up vaccine development



### *Rationale 3: Preserving the ability to combat Zika virus*

Finally, the committee concluded that preserving the ability to study vaccines and/or treatments for Zika virus in light of changing conditions that rule out other ways to test these vaccines and treatments is the most compelling justification for conducting a Zika virus CHIM. If field trials are prohibitively difficult to conduct or if there are very limited resources to do research in terms of sites or volunteers, there could be few viable alternatives to conducting a Zika virus CHIM to develop interventions to fight the epidemic.

Epidemiological information from areas with recent documented outbreaks indicates that after an initial, skyrocketing number of cases, new infections tend to disappear in the following months. It is difficult to predict where outbreaks will occur. Although the Zika virus epidemic appears to be waning in some parts of the world,<sup>95 96</sup> it is not yet clear whether this is due to better control of vectors and more precautions being taken, or if it is because Zika virus infection is seasonal. Additionally, vaccine phase III clinical trials usually require significant time and resources to prepare staff, infrastructure, and logistics to enroll hundreds of volunteers at each clinical site. In the recent Ebola outbreak, an unprecedented collaborative effort was required merely to conduct clinical trials during an ongoing outbreak, but the results were ultimately inconclusive due to the small number of cases in the waning days of the outbreak.<sup>97</sup> This raises the worrisome possibility that Zika virus vaccine developers may find it difficult to select clinical sites with sufficient incidence of Zika virus to demonstrate efficacy in a clinical trial, and the inability to test efficacy of a vaccine in a large phase III trial could become a bottleneck that delays the availability of a vaccine.

At present, however, it seems premature to conclude that this reason has been met because there are ongoing efforts and collaborations to conduct phase II and III trials of Zika virus vaccines,<sup>98</sup> and not enough reason to think these efforts will be unsuccessful. Nevertheless, this is potentially a robust justification for conducting Zika virus human challenge trials in the future. A critical component of this justification is that Zika virus would have to be declining sufficiently to make field testing difficult, but is still likely to reemerge as a continued public health threat in the future.

#### *Summary of social value: Would a Zika virus CHIM have adequate social value?*

In sum, because a Zika virus CHIM would not offer direct benefit for individuals, particularly if it were conducted in a non-endemic region, the risks involved must be reasonable, minimized, and justified by the benefits to society. Given the potential for risks to third parties who will likely not be able to be approached for their consent, and the high degree of uncertainty about the risks posed by a Zika virus human challenge trial more generally, considerable social value is needed to justify the risks involved. The above analysis suggests that, if field trials were prohibitively difficult to conduct, or if there was a commitment from research sponsors and other stakeholders to use a human challenge trial to accelerate development of a vaccine to protect against congenital Zika infection, a Zika virus human CHIM would have high social value that arguably could justify research at the upper limit of what is acceptable in research with healthy volunteers who have the capacity to give their own informed consent. A human challenge trial conducted solely to learn more about Zika virus, however, does not appear to be justifiable.

In light of the current unknowns about the risks associated with a Zika virus human CHIM and in the absence of (1) a strong argument and evidence that a challenge study will accelerate vaccine development or (2) an indication that field trials will be prohibitively difficult to conduct, the committee concluded that it is premature to proceed with a Zika virus human challenge trial. It is also worth noting that although a Zika virus human challenge trial may be difficult to justify at present, it may become much more ethically acceptable in the future if conditions change or if more information is provided that changes the calculus. For instance, if antivirals become available for Zika virus that will make it a treatable illness, and the period of infectivity is within the range of a reasonable amount of time to isolate individual research participants, the risks and uncertainty associated with a Zika virus CHIM may be reduced to a level that is possible to justify with a lower amount of social value. Or if the epidemic becomes uncontrolled in many more regions throughout the world, the public health threat may be high enough to justify extraordinary risks in research. The committee merely notes these examples to suggest that our analysis is not exhaustive and should be revisited if conditions change from what is known at present.

**Recommendation 2:** Whether a Zika virus human challenge trial has sufficient social value to proceed depends on the reasons for doing it and whether there are alternative ways to obtain the information. The most compelling rationale for conducting a Zika virus human challenge trial, given the risks and uncertainty, would be if field trials were prohibitively difficult to conduct in light of a waning epidemic. This rationale is not currently met, but it could come to pass in the future. Another valuable reason to conduct a challenge trial would be to accelerate the development of a vaccine that could prevent congenital Zika infection. This rationale must be accompanied with strong evidence that results from a Zika virus human challenge trial would be used by stakeholders (e.g., indication from regulatory agencies that finding a correlate would speed up the licensing of a vaccine). The committee did not hear sufficient evidence that this rationale is currently met. Finally, using a challenge trial solely to learn about the pathogenesis and natural history of Zika infection is unlikely to justify the risk involved given the alternative ways to obtain similar information.

### Part 3: Additional Safeguards That Should Be in Place

Although we have concluded that a Zika virus human challenge trial would not be justified as present, we recognize that the facts on which we based this analysis may be incomplete, or the conditions may change or be met in the future. For the sake of completeness and to ensure that there is no unnecessary delay in conducting a Zika virus CHIM if it is ethically justifiable to do so, this section lays out additional considerations that should be satisfied before a Zika virus human challenge trial could be launched, assuming the risks have been judged to be reasonable, minimized, and justified by the social value. Unlike the conclusions reached in Part 2, our analysis suggests that these safeguards could be put into place at the present time.

#### Protection of vulnerable populations

Vulnerability in research has been defined as having a higher risk of being wronged or harmed by the research as compared to a typical research participant.<sup>99</sup> To protect vulnerable populations, research subjects should be selected based on scientific reasons for enrolling particular populations, not for ease or convenience. Historically, scandals arose when researchers experimented upon participants who lacked the capacity to provide informed consent or were simply not given adequate respect or moral consideration. This led to a wave of protectionism in research ethics, which inadvertently excluded certain populations (not all of which in fact meet the criteria for vulnerability) from not only the risks of research but also the benefits.<sup>100</sup> After recognizing the paucity of research with children, women, and pregnant women, many commentators argued for the responsible inclusion of these populations in research.<sup>101</sup> Nevertheless, there may be good reason not to conduct early phase, risky research on populations for whom risks would be increased, or with individuals unable to give their own consent since they may not understand the extent of risk involved or how to take precautions to protect themselves and others.

A Zika virus human challenge trial should not enroll individuals who lack the capacity to give their own consent or pregnant women, whose fetuses would be at high risk for complications. A more challenging question is how to ensure that populations that are vulnerable but not enrolled in the research directly are still protected from the risks. As discussed above, several protections for third parties, particularly those from vulnerable populations, should be in place for a Zika virus CHIM to be ethically acceptable.

**Recommendation 3:** A Zika virus human challenge trial should only enroll individuals with capacity to provide their voluntary informed consent. Such a trial should also take steps to reduce the risks to fetuses to as close to zero as possible.

#### Robust informed consent process

Informed consent is a key component of ethical research that has been studied extensively, the practical reality falls far short of the theoretical ideal.<sup>102</sup> The existing data on informed consent suggest that there is no clear difference in understanding in populations in different parts of the world, but that volunteers of lower education and older age may have less comprehension of research, and concepts like randomization and the right to withdraw from research at any time may be more difficult for many participants to understand.<sup>103</sup> Research on ways to improve informed consent has demonstrated that commonsense approaches can improve understanding and satisfaction—namely, giving volunteers more time and one-on-one discussion about the research and testing their understanding with feedback for incorrect answers, and enhancing informed consent forms with graphics, multimedia, or increased font size in some cases for some populations.<sup>104</sup> These and other approaches have been used in other types of challenge trials. For instance, some challenge study researchers attempt to ensure that participants are very motivated and likely to comply

with study restrictions by only enrolling participants who contact the study staff multiple times to set up initial appointments for obtaining information about the study and then signing informed consent documents.<sup>105</sup>

In a Zika virus human challenge trial with uncertain risks and a strong need to minimize risk, it may be important to test individual understanding of the risks and uncertainties involved. Approaches that have been used for other human challenge trials could easily be employed for a Zika virus human challenge trial. In the context of a Zika virus human challenge trial, elements that will be especially important to emphasize and test volunteers on to make sure they understand them include the highly uncertain nature of the risks involved, the need to take precautions to avoid transmission to others in the community and to fetuses, and restrictions on the right to withdraw to preserve safety.

**Recommendation 4:** Researchers and sponsors of a Zika virus human challenge trial should use a robust informed consent process. For example, researchers and sponsors could require multiple voluntary steps for individuals to take to enroll, adequate time for discussion, and evaluation of and feedback given to enhance participant understanding about critical issues (e.g., the uncertainty involved, the risks to third parties and fetuses, precautions that should be taken, and restrictions on the right to withdraw).

### **Adequate but not undue level of compensation**

Compensation for time and effort spent in research is ethically important. Volunteers should not have to spend their own money to contribute to research findings (e.g., expenditures on transportation costs, medical care, etc., should be paid for or reimbursed by researchers). Yet many are concerned about the potential for coercion or undue inducement.<sup>106</sup> In our view, the best definition of coercion is that it occurs when individuals are threatened with losing something to which they are otherwise entitled.<sup>107</sup> As a result, offering someone payment (that she is not otherwise entitled to) cannot constitute coercion.<sup>108</sup> By contrast, undue inducement is the concern that volunteers might be so enticed by the offer of money for research participation that they do not adequately weigh the risks or may not be honest about their eligibility for a research study, and this could, in theory, occur in a Zika virus human challenge trial.<sup>109</sup>

As long as risks are carefully assessed and minimized before a study is approved to begin recruitment, some argue that undue inducement should not be a concern because research participation will be a reasonable choice.<sup>110</sup> Some empirical studies have also suggested that volunteers who are motivated by money are more likely to understand the risks, and that payment may serve as a useful signal of a study's risk.<sup>111</sup> Yet others have pointed out that there are legitimate concerns that high payments may lead participants not to reveal facts that would disqualify them from the research or to fabricate information but not comply with research requirements.<sup>112</sup>

When assessing acceptable payment amounts, participants should be compensated for out-of-pocket costs, and further payment should account for the burdens they are asked to undertake, such as the discomfort of infection symptoms and confinement to protect others.<sup>113</sup> There is less agreement about compensation for risk, although it is worth noting, as we have previously, that in other arenas individuals are paid higher amounts for taking on increased risks (e.g., deep sea fishing, working on an oil rig, and logging).<sup>114</sup> At the very least, payment should be set in a manner that seeks to balance concerns about high payment with concerns about low payment, including fair compensation for contribution and impact on ability to adequately recruit.

In a Zika virus human challenge trial, even assuming that payment will be provided for time, inconvenience, and out-of-pocket expenses rather than for risk, the amount of compensation offered to participants could be relatively high given the anticipated lengthy period of confinement. It is advisable to find objective ways to verify that volunteers meet the inclusion and exclusion criteria and are compliant with study requirements, rather than relying on self-reporting, wherever possible.

**Recommendation 5:** Volunteers should be paid fairly for their time and inconvenience, but they should demonstrate understanding of the risks and uncertainties involved and be evaluated with objective evidence of their eligibility and compliance wherever possible.

## Respect for the right to withdraw

By regulation, volunteers in research “may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.”<sup>115</sup> In a Zika virus human challenge trial (and other types of challenge studies), however, it may not be possible to allow volunteers to leave isolation or stop taking precautions that prevent them from infecting others at any time, suggesting that volunteers would not have an unfettered right to withdraw.<sup>116</sup>

In general, rights have limits when exercising them could cause harm to others, and the right to withdraw from research can be and has been respected in some senses even in cases where the safety of others is a concern. For instance, in bone marrow transplantation research, participants may not be able to leave the research site safely immediately after receiving ablative chemotherapy that kills off their white blood cells and leaves them without a functioning immune system. Such participants could still immediately stop contributing data to a research study even if they could not leave the research site right away. Notably, it would also be in volunteers’ interests to remain confined to have their own safety monitored for at least some period of time. This suggests that Zika virus human challenge trial participants could have their right to withdraw from research respected even while maintaining the protections necessary to prevent transmission to others.

Still, there may be important limits on whether, how, and for how long volunteers can be kept in isolation after they have withdrawn from research. One helpful analogy is to the use of quarantine in pandemic situations. Although isolating infectious individuals from others can be ethically justified if there is significant potential harm to others, it must be established that the confinement is necessary and applied fairly, is the least restrictive means to achieving the end of protecting the public, and that there are due process protections so people who are confined can appeal the decision to restrict their movement.<sup>117</sup> Thus, such a protection may require establishing prior conditions for confinement that are reviewed and approved by others (such as the IRB), demonstrating that confinement as opposed to other measures of infection control is the least restrictive approach to protecting others, and providing volunteers with information about someone to contact at the institution if they think their confinement is unjustified. Finally, the possible need for confinement even after a participant withdraws from research is an important element of a Zika virus human challenge trial that should be made very clear to potential participants during the informed consent process.

**Recommendation 6:** The right to withdraw should be respected in challenge trials by halting the collection of data for volunteers who want to withdraw even if they will have to remain confined to protect themselves or others.

## Independent expert review

This protection suggests that independent infectious disease or other experts assess the risks of a human challenge trial, outside of the IRB review process.<sup>118</sup> Within this particular consultation regarding the ethical acceptability of a Zika virus human challenge trial, a neurologist, obstetrician/gynecologist, and infectious disease specialist have contributed to this report and assessed the risks involved. Given the rapidly evolving state of the science on Zika virus, it may be advisable to have contemporaneous external evaluation of the risk by experts if a future Zika virus human challenge study does go forward.

Such a step is not without precedent. For instance, for higher risk protocols in pediatric research, regulatory mechanisms have been developed to have an external committee evaluate risk.<sup>119</sup> For a Zika virus

human challenge trial, convening experts across relevant disciplines to review a protocol closer in time to its launch may be a more effective approach.

**Recommendation 7:** Contemporaneous external evaluation of risk by relevant experts is advisable before a Zika virus human challenge trial proceeds.

## System for compensation for research-related injury

Research participants may be injured as a result of their study participation, with injuries manifesting during the study or potentially thereafter. U.S. federal regulations do not mandate compensation for research injuries and instead leave the issue of care and compensation for participant injury to the discretion of individual investigators, research sites, and sponsors. Yet every federal bioethics commission to examine the question of research-related injury, the Institute of Medicine, various regulations from other countries, and numerous scholars have questioned this regulatory approach and argued that there is an ethical duty to provide compensation for research-related injury.<sup>120</sup>

The reasons for providing care and compensation for research-related injury are based on the duty to minimize risks and the principle of justice.<sup>121</sup> Providing adequate care and compensation to injured participants is one way to minimize the risks they face, and minimizing risk is both a regulatory requirement and an ethical responsibility. For example, should an injured participant be unable to access or afford adequate care, the potential for harm from research participation is greater than if adequate care had been provided or paid for by the study. With regard to justice, participants have taken risks for the benefit of others, even if they have done so consensually and recognizing the possibility of serious risk, and even if (in certain types of research) some benefits may redound to them. While physical costs cannot be shifted, financial costs can be shared.

There are, however, certain details to be worked out in each case. First is the question of what qualifies as a research-related injury. Once it has been established that an injury is research-related, the next question is what it will take to render the injured participant “whole.” Providing free care (or reimbursing medical expenses related to treating the injury that are not covered by insurance) is the most basic ethical responsibility, as this protects injured participants from costs that would otherwise have to be borne out-of-pocket. Injured participants ought to be compensated for all “but for” costs of their research participation. This suggests that CHIM study volunteers should be assured of free medical care as needed for as long as needed for any health concerns that would not have been experienced but for Zika infection (and/or exposure to any investigational product), both for the duration of a trial and thereafter. Volunteers might also need to be compensated for lost wages and earning capacity, child care expenses, and travel costs that result from research-related injury.

To satisfy this responsibility, researchers should obtain, and study funders should fund, insurance to cover research-related injury. Researchers should also ensure that insurance policies that are purchased have adequate processes in place to efficiently and fairly evaluate and resolve claims. There is precedent for this as some multinational NIH grant-funded studies have obtained insurance to cover research-related injury.<sup>122</sup> Given the specialized nature of treatment for Zika complications, as well as the potential to infect others, it seems most appropriate for researchers to provide any necessary care within a study itself, rather than reimbursing participants for care obtained elsewhere, unless necessary care is beyond researchers’ expertise or capacity. Importantly, care and compensation for research-related injury in a Zika virus CHIM trial is unlikely to demand substantial resources, as risks will already be minimized to the extent possible, and healthy individuals are typically only mildly affected by the virus.

More challenging questions arise around the possibility that non-participant third parties may also be put at risk due to a Zika virus CHIM study. Numerous protections would need to be put in place to avoid transmission to third parties before a CHIM could ethically proceed, as discussed above, but in the event

such transmission occurred (and was causally linked to the CHIM, rather than some other mechanism of exposure), infected third parties should also be provided with free care and compensation of financial losses.

Finally, the most challenging issue, in theory, would be possible fetal exposure in a research participant or a participant's sexual partner. Again, avoiding such exposure is one of the most foundational prerequisites for a Zika virus CHIM study, so this sort of research-related injury should not occur. If it did, however, there would be significant questions related to whether termination of pregnancy constitutes "care" that ought to be provided or paid for, should a volunteer desire it, and whether it even could be in a federally funded research study.<sup>123</sup> Should a pregnancy exposed to Zika virus as a result of a CHIM trial proceed and the child be negatively affected, there would also be questions of whether the child and/or parents should be compensated for harm, for which harms, and for how long; these questions would mirror those that arise in cases of wrongful birth and wrongful life litigation for reproductive malpractice. At the very least, Zika virus human challenge study participants should be made aware of the relevant risks related to fetal exposure and informed of which costs would be covered should it occur.

**Recommendation 8:** In the event a Zika virus CHIM trial proceeds, study sponsors should ensure that sites are adequately insured to cover the costs of care and compensation for research-related injury, to both study participants and third parties, and that insurance policies that are purchased have adequate processes in place to efficiently and fairly evaluate and resolve claims.

## Community engagement

Community engagement is a final requirement that the members of the writing committee considered important. Though community engagement has not been addressed in the literature on the ethics of human challenge studies, it is considered to be an important benchmark for ethical research in general.<sup>124</sup> Community engagement would be critically important for a Zika virus human challenge trial. A Zika virus human challenge trial could introduce Zika virus to a new community if the risks were not managed appropriately and could pose risks of harm to members of the community who did not give their own consent. This suggests that community engagement would be important to help obtain buy-in for the research, ensure that the research is consistent with the community's values, show respect for the members of the community, and enhance transparency.<sup>125</sup> With such goals in mind, this community engagement should occur before the launch of a Zika virus human challenge trial and with clear information and ability to incorporate the community's feedback into the design of such a trial as appropriate. These goals also suggest that a community in this case would be the geographical community that might be exposed to risk of Zika infection by hosting a Zika virus human challenge trial.

**Recommendation 9:** Community engagement with the geographical community surrounding the site(s) of a Zika virus human challenge trial should be conducted in advance of the research to show respect for the community and its values, obtain community buy-in to the goals of the research, and proceed with transparency.



## **Part 4: Summary of Recommendations and Answers to the Charge of the Consultation**

The Zika virus human challenge research writing committee has the following findings and recommendations regarding the charge of the consultation:

**1A:** There is substantial uncertainty about the risks to potential volunteers in a Zika virus human challenge study. Although the known risks of a Zika virus human challenge trial appear comparable to the risks of phase I research with healthy volunteers, without greater knowledge about outcomes from Zika exposure, these risks would require high social benefit to be justified. Strategies to minimize risks include careful selection of inclusion and exclusion criteria, close medical monitoring, relatively long periods of confinement, and prompt medical attention for volunteers who become ill.

**1B:** The committee was particularly concerned about possible risks to third parties, i.e., that Zika virus might be transmitted from study volunteers to others, such as fetuses and members of the community. Because these third parties generally cannot know about, protect themselves from, or consent to risks, risks to them are only reasonable if they can be reduced to near-zero. However, the mechanisms of transmission of Zika virus and how long individuals with Zika virus can infect others are not fully understood. Before proceeding with a Zika virus challenge study, researchers should therefore demonstrate that the risks to third parties are not likely to be realized. This could be done through developing risk management strategies and obtaining relevant data. Approaches to minimizing risk would rely upon either relatively long periods of isolation, the use of effective long-acting reversible contraception, careful inclusion and exclusion criteria (including potentially enrolling only women), and/or individual participants' self-report about their own sexual practices as well as the practices of their partners, though the committee was not certain to what extent these strategies would be compatible with appropriate scientific design. Additional information could be gathered through modeling based on rates of transmission and pregnancy in similar studies and research to characterize the modes of infection and transmissibility of Zika virus. More research using virus culture, which detects infectious virus rather than virus genetic material, could clarify the period of infectiousness and the relative risk of exposure to different body fluids, and is an important priority for the development of a Zika virus human challenge study.

**2:** Whether a Zika virus human challenge trial has sufficient social value to proceed depends on the reasons for doing it and whether there are alternative ways to obtain the information. The most compelling rationale for conducting a Zika virus human challenge trial, given the risks and uncertainty, would be if field trials were prohibitively difficult to conduct in light of a waning epidemic. This rationale is not currently met, but it could come to pass in the future. Another valuable reason to conduct a challenge trial would be to accelerate the development of a vaccine that could prevent congenital Zika infection. This rationale must be accompanied with strong evidence that results from a Zika virus human challenge trial would be used by stakeholders (e.g., indication from regulatory agencies that finding a correlate would speed up the licensing of a vaccine). The committee did not hear sufficient evidence that this rationale is currently met. Finally, using a challenge trial solely to learn about the pathogenesis and natural history of Zika infection is unlikely to justify the risk involved given the alternative ways to obtain similar information.

**3:** A Zika virus human challenge trial should only enroll individuals with capacity to provide their voluntary informed consent. Such a trial should also take steps to minimize the risks to fetuses to as close to zero as possible.

**4:** Researchers and sponsors of a Zika virus human challenge trial should use a robust informed consent process. For example, researchers and sponsors could require multiple voluntary steps for individuals to take to enroll, adequate time for discussion, and evaluation of and feedback given to enhance participant

understanding about critical issues (e.g., the uncertainty involved, the risks to third parties and fetuses, precautions that should be taken, and restrictions on the right to withdraw).

**5:** Volunteers should be paid fairly for their time and inconvenience, but they should demonstrate understanding of the risks and uncertainties involved and be evaluated with objective evidence of their eligibility and compliance wherever possible.

**6:** The right to withdraw should be respected in challenge trials by halting the collection of data for volunteers who want to withdraw even if they will have to remain confined to protect themselves or others.

**7:** Contemporaneous external evaluation of risk by relevant experts is advisable before a Zika virus human challenge trial proceeds.

**8:** In the event a Zika virus CHIM trial proceeds, study sponsors should ensure that sites are adequately insured to cover the costs of care and compensation for research-related injury, to both study participants and third parties, and that insurance policies that are purchased have adequate processes in place to efficiently and fairly evaluate and resolve claims.

**9:** Community engagement with the geographical community surrounding the site(s) of a Zika virus human challenge trial should be conducted in advance of the research to show respect for the community and its values, obtain community buy-in to the goals of the research, and proceed with transparency.

# Appendix A: Agenda for Zika Virus Human Challenge Trials Ethical Consultation

<b>Consultation on the Ethics of ZIKV Human Challenge Trials</b> December 12, 2016 5601 Fishers Lane Conference Center Rockville, Maryland	
This workshop is co-sponsored by the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIAID) and the Walter Reed Army Institute of Research (WRAIR).	
<u>Agenda</u>	
<b>Monday, December 12, 2016</b>	
8:45 – 9:00 a.m.	Welcome and introduction Cliff Lane, National Institute of Allergy and Infectious Diseases Nelson Michael, Walter Reed Army Institute of Research Seema Shah, Consultation Chair, University of Washington and Seattle Children's Research Institute
9:00 – 9:10 a.m.	Round the room introductions
9:10 – 9:40 a.m.	State-of-the-Science on Zika Virus Hilary Marston, National Institute of Allergy and Infectious Diseases, Office of the Director
9:40 – 9:50 a.m.	Q&A
9:50 – 10:10 a.m.	Global Epidemiological Perspective on Zika Virus, Modes of Transmission, Public Health Responses, and Magnitude of the Public Health Impact Marc Fischer, Centers for Disease Control and Prevention
10:10 – 10:20 a.m.	Q&A
10:20 – 10:40 a.m.	Break
10:40 – 11:20 a.m.	Clinical Perspectives Panel - (10 minutes each) Adult: Mark Mulligan, Emory University Neurology: Carlos Pardo, Johns Hopkins University OB/Gyn: Carmen Zorrilla, University of Puerto Rico School of Medicine Peds: Bill Kapogiannis, National Institute of Child Health and Human Development
11:20 – 11:35 a.m.	Q&A
11:35 – 11:55 a.m.	Exploration of a Zika Virus Human Challenge Model Barney Graham, National Institute of Allergy and Infectious Diseases, Vaccine Research Center
<hr/> 1   Page	11:55 – 12:05 p.m. Q&A  12:05 – 12:20 p.m. Zika Vaccine Candidates Gerald R. Kovacs, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority  12:20 – 12:30 p.m. Q&A  12:30 – 1:15 p.m. Break for Lunch  1:15 – 1:35 p.m. Extrapolating from Animal Models about Zika Virus Cristina Cassetti, National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases  1:35 – 1:45 p.m. Q&A  1:45 – 2:05 p.m. The Potential Role of Human Challenge Trials in the Zika Virus Vaccine Development Pathway, Alternative Approaches to Answering Similar Questions Wellington Sun, U.S. Food and Drug Administration  2:05 – 2:15 p.m. Q&A  2:15 – 3:15 p.m. Lessons Learned from Infectious Disease Challenge Research Stephen Thomas, SUNY Upstate Medical University Anna Durbin, Johns Hopkins University Francine McCutchan, PATH MaryAnne Garner, Research Participant  3:15 – 3:40 p.m. Q&A  3:40 – 4:00 p.m. Break  4:00 – 4:30 p.m. Presentation and Moderated Discussion on Ethical Framework for Challenge Studies Seema Shah, University of Washington and Seattle Children's Research Institute  4:30 – 5:30 p.m. Discussion on Critical Issues Moderated by Seema Shah  5:30 p.m. Adjournment
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## Appendix B: Methodology

To address the ethical issues raised by the possibility of conducting a Zika virus human challenge trial, a planning committee was formed with representatives from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the Walter Reed Army Institute of Research (WRAIR), the Department of Defense (DOD), and Biomedical Advanced Research and Development Authority (BARDA), along with two ethicists who had previously worked at the Department of Bioethics at the NIH Clinical Center. The planning committee held several teleconferences and decided to convene an independent writing committee and organize a one day expert consultation meeting in Rockville, Maryland on December 12, 2016. The planning committee identified the relevant expertise for members of the writing committee and speakers for the meeting by consulting with colleagues and reviewing the literature.

The writing committee was designed to be independent, so it did not include any employees of federal agencies who might sponsor or review a Zika virus human challenge trial or researchers who might conduct a Zika virus human challenge trial. The writing committee was composed of experts across relevant disciplines and included ethicists with expertise in several subfields of research ethics (i.e., the ethics of human challenge trials, study design, translational and early phase research, and research with pregnant women), a neurologist, two obstetrician/gynecologists, and an infectious disease physician. Two members of the planning committee who met the criteria for inclusion into the writing committee were included in the writing committee, and seven other individuals joined them, for a total of nine members. The final members of the writing committee are all listed as authors on this report. The planning committee and NIH staff conducted a comprehensive review of the relevant scientific and ethics literature and made this available to the writing committee in advance of the meeting.

At the meeting on December 12, 2016, cross-disciplinary experts were invited to present on the state of the science of Zika virus, the epidemiology of Zika virus, the clinical aspects of Zika virus, Zika virus vaccine candidates, what can be learned from animal models, how a Zika virus human challenge study might fit into the vaccine development pathway, lessons from other human challenge models, and ethical considerations for human challenge studies. The first day of the meeting involved presentations from relevant experts and discussion across all invited participants, panelists, and speakers. There were fifty-nine participants in the meeting, with one member of the writing committee participating by teleconference. The second day of the meeting involved executive sessions to clarify issues with the planning committee and the writing committee, and then to allow the writing committee time for independent deliberation.

The writing committee's deliberations began with an airing of each individual's views and then moderated discussion by the chair to identify areas of consensus and disagreement. Individual members of the writing committee were tasked with writing sections of the report depending on their expertise, and the chair composed a document consolidating these recommendations and placing them into a larger ethical framework. All members of the writing committee were active participants in the discussion and commented on the entire report. The writing committee had two conference calls to discuss the report and remaining disagreements, and several email exchanges to clarify individual views and achieve consensus.

At the end of January, the writing committee solicited feedback on a draft of the report from a small group at NIH (Bob Eisinger, Catharine Paules, and Hilary Marsten) for any factual corrections, to ensure the report fully addressed the issues raised by the consultation, and to resolve any ambiguities. Anthony S. Fauci reviewed the executive summary to improve clarity. The committee took care to ensure the independence of their deliberations, however, and the substance of the report and recommendations was not altered by NIH staff in any way. After revising the document for clarity and accuracy, the document was shared with the planning committee. A final version of the report was posted on NIAID's website in February 2017.

## Endnotes

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22.pdf. Note that this guideline may be revised soon:

[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/GCP\\_Renovation/ICH\\_Reflection\\_paper\\_GCP\\_Renovation\\_Jan\\_2017\\_Final.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/GCP_Renovation/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf).

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