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Zika Vaccines: Role for Controlled Human Infection

Anna P. Durbin[1] and Stephen S. Whitehead[2]

[1]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and [2]Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Zika virus (ZIKV), a previously little known arbovirus, caused an unprecedented outbreak in Latin America and the Caribbean throughout 2015 and 2016. The virus has been associated with the congenital Zika syndrome (CZS), which can occur with maternal ZIKV infection during any trimester and can result from asymptomatic infection. There is concern that even low levels of viremia can result in CZS, meaning an effective vaccine will need to induce very high levels of protection. Controlled human infection models (CHIMs), in which subjects are infected with a pathogen of interest, have been used to down-select vaccine candidates and have provided efficacy data in support of vaccine licensure.

A ZIKV CHIM could be instrumental in determining which of the many ZIKV vaccine candidates provides the highest degree of protection and should be advanced in clinical development. The development of a ZIKV CHIM is not without challenges. The ZIKV, unlike other flaviviruses, is sexually and mosquito-transmitted, and an increase in the incidence of Guillain-Barré syndrome was reported in some countries during the ZIKV outbreak. These obstacles can be overcome with thoughtful study design to ensure maximal risk mitigation. If successful, a ZIKV CHIM could de-risk and accelerate ZIKV vaccine development.

Keywords. controlled human infection model (CHIM); Zika vaccines; Zika virus.

Although Zika virus (ZIKV) was first isolated from a sentinel rhesus macaque in Uganda in 1947, it caused only sporadic infections in Africa and Asia until 2007 when the first major outbreak occurred on the island of Yap in Micronesia [1–3]. After the outbreak in Yap, ZIKV spread to French Polynesia in 2013 and subsequently caused an unprecedented outbreak throughout Brazil and Latin America in 2015 and 2016. Although ZIKV generally causes an asymptomatic or mildly symptomatic illness (low-grade fever, rash, myalgias) [3], the virus targets human trophoblasts and has an unusual tropism for developing fetal brain tissue [4–6]. These characteristics allow for vertical transmission of the virus if infection occurs during pregnancy and can result in severe birth defects, including microcephaly and/or fetal demise [7]. Although the congenital Zika syndrome occurs most commonly with infection during the first trimester, it can occur with infection during any trimester [8]. A recent analysis of pregnant women who traveled to ZIKV-endemic areas and had laboratory evidence of recent ZIKV infection reported that birth defects were found in 51 of 972 (5%) completed pregnancies [9]. Recognizing the catastrophic consequences of congenital ZIKV infection, the World Health Organization (WHO) declared the ZIKV epidemic in Latin America a Public Health Emergency of International Concern in February of 2016.

Correspondence: A. P. Durbin, MD, 624 N. Broadway, Room 251, Baltimore, MD 21205 (adurbin1@jhu.edu).

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CHALLENGES TO ZIKA VACCINE DEVELOPMENT

The WHO recently released its consultation report on the regulatory expectations for ZIKV vaccines for use during an emergency [10]. This report identifies women of child-bearing age, which may include pregnant women, as the major target population for vaccination during an outbreak, and it specifies the minimal and preferred characteristics for ZIKV vaccines. Researchers and vaccine manufacturers rapidly mobilized to begin developing potential vaccines for the prevention of Zika, and there are currently approximately 40 ZIKV candidate vaccines in preclinical development [11–15]; 3 of these candidates have entered Phase 1 clinical trial. However, there are still many obstacles to the development and licensure of an effective ZIKV vaccine. These include the most appropriate choice of efficacy endpoints, the cost of vaccine development, and the ability to perform a large-scale, Phase 3 efficacy trial.

Most ZIKV infections do not cause significant clinical illness, making them difficult to detect, even with active surveillance. In addition, because congenital Zika syndrome can result from asymptomatic Zika infection in the mother [9], there is concern that even low levels of viral replication in the mother could result in placental transfer to the fetus with devastating consequences. For this reason, the prevention of symptomatic illness in pregnant women and the general population may not be enough to prevent congenital Zika syndrome, but it may be sufficient to interrupt mosquito transmission. An effective vaccine may need to do more than prevent illness; it may need to prevent virus infection (induce sterilizing immunity). The prevention of infection as a vaccine efficacy endpoint cannot be measured in traditional Phase 3 clinical trials. To compound

this difficulty, using the prevention of microcephaly or congenital Zika syndrome as an efficacy endpoint would likely require an enormous sample size as well as years to complete, especially in the face of decreased disease incidence.

Development of a vaccine from preclinical discovery through Phase 1, 2, and 3 clinical trials is extremely expensive and must be de-risked. Eleven clinical trials of 5 different candidate vaccines have already been registered at www.clinicaltrials.gov (accessed August 29, 2017). Limited resources, both financial and human, are available to evaluate each of these vaccines through traditional efficacy studies. If an early determination of efficacy could be accomplished, only those vaccines that demonstrate the most favorable safety and efficacy profile (sterilizing or near-sterilizing immunity) would move forward to traditional larger Phase 2 and Phase 3 evaluation. More importantly, the ZIKV epidemic appears to be waning, and powering a Phase 3 trial to demonstrate efficacy may not be possible. If ZIKV transmission declines substantially such that it resembles that of West Nile virus or Chikungunya virus, the incidence of infection will not be high enough or predictable enough to conduct the traditional efficacy study required for licensure.

CONTROLLED HUMAN INFECTION MODELS AND VACCINE DEVELOPMENT

How can these obstacles to vaccine development be overcome? Controlled human infection models (CHIMs), in which normal healthy volunteers are infected with a known dose of a pathogen in a controlled setting, have been used to advance vaccine development in a more strategic manner. The CHIMs have evaluated the efficacy of candidate malaria, dengue, respiratory virus, and enteric vaccines and therapeutics [16–24]. The CHIMs can measure the efficacy of a candidate vaccine early in the development pathway, helping to identify inferior candidates before initiating large safety and efficacy trials. This allows valuable resources to be focused on those candidates that have the greatest potential for success. A malaria CHIM provided critical information for the development of the malaria vaccine RTS,S. Malaria CHIM studies were performed to first evaluate the efficacy of RTS,S and to then further refine the formulation and dosing regimen [18, 25–28] before initiating Phase 3 efficacy evaluations in Africa. The malaria CHIM has also been used to define the most effective route of administration and dosing regimen for the live-attenuated whole sporozoite vaccine PfSPZ (progress with Plasmodium falciparum sporozoite) [29, 30]. A dengue CHIM was used to determine which formulation of a live-attenuated tetravalent dengue vaccine should be chosen to move forward in a Phase 3 efficacy trial in Brazil [19]. In addition, most directly, evaluation of the efficacy of a live-attenuated cholera vaccine in a human infection model proved to be the pivotal efficacy trial to support US Food and Drug Administration (FDA) licensure of this vaccine [31]. Use of the cholera CHIM was critical for 2 reasons: (1) because of the low incidence of cholera infection in travelers, a traditional field efficacy study was not feasible; and (2) this trial established an immunologic correlate of protection that could be used as a regulatory criterion for immunologic bridging.

As demonstrated by the examples provided above, the development of a Zika CHIM could be instrumental in de-risking and accelerating the development of a safe and effective ZIKV vaccine. The ability of a vaccine to induce sterilizing immunity against ZIKV can easily be evaluated in a CHIM. Vaccine recipients and controls would be infected with a known inoculum of ZIKV at a prescribed time-point postvaccination (generally at least 3–6 months). Samples would be collected at frequent timepoints postchallenge and evaluated for the presence of ZIKV by both molecular detection (quantitative polymerase chain reaction [PCR]) and virus culture. The proportion of vaccine recipients who developed sterilizing immunity as evidenced by the inability to detect ZIKV postchallenge in any blood, urine, or other collected sample, as well as a lack of antibody boost (<4-fold rise in antibody titer) post-ZIKV challenge would be determined. An immune correlate of protection, such as titer of neutralizing antibody required for protection, could potentially be identified using this model by comparing those protected with those experiencing breakthrough infection. The specific correlate is likely to vary depending on the vaccine and the repertoire of immune responses that can be induced. Only those candidate vaccines that elicited the highest level of protection in this model would move forward for additional safety and efficacy testing in endemic areas. This strategic down-selection of candidate vaccines allows the limited financial and human resources required for large safety and efficacy trials to be focused only on those candidates with a demonstrated indication of success.

Current epidemiologic data indicate that the ZIKV outbreak is waning in Latin America and the Caribbean [32]. Should this trend continue, it may not be possible to identify clinical trial sites with a sufficient incidence of ZIKV infections to demonstrate vaccine efficacy. Promising vaccines could not be licensed without efficacy data and would therefore be unable to move forward. Similar to that of the recently licensed cholera vaccine, a ZIKV CHIM could provide needed efficacy data in the absence of ongoing ZIKV transmission. Although additional evaluation of the vaccine in pre- or postlicensing trials would be required in larger populations to ensure safety, these efficacy data could be used to support licensure.

CHALLENGES TO THE DEVELOPMENT OF A ZIKA VIRUS-CONTROLLED HUMAN INFECTION MODEL

Although experimental human infection with ZIKV has already been performed in a single individual [33], the development of a safe and reproducible ZIKV CHIM is not without difficulties. The ZIKV infection, if symptomatic, is generally mild in healthy, nonpregnant adults. However, unlike other flaviviruses, ZIKV is not limited to vectorborne transmission; it can be transmitted

sexually [34, 35]. In addition, ZIKV has been associated with an estimated 2.5-fold increased risk of Guillain-Barré syndrome (GBS) [36]. Unfortunately, despite the duration and severity of the ZIKV epidemic, the data related to sexual transmission of ZIKV and GBS are primarily observational and anecdotal. In additional, there are no data available evaluating the magnitude of ZIKV viremia and its effect on symptoms, shedding of the virus in other bodily fluids, or the occurrence of GBS. For these reasons, it is difficult to determine the absolute risk of sexual transmission or GBS, although both seem to be low. Of the approximately 5000 travel-associated cases of Zika in the United States since 2015, there have been 46 cases of reported sexual transmission in partners of those returning from travel (<1%) [37]. All reported cases of documented sexual transmission of ZIKV have occurred within 21 days of return from an area of ZIKV transmission, and all but 1 has been from symptomatic travelers [34, 38–41].

To date, there have been only 2 studies that evaluated the duration of shedding of ZIKV in human bodily fluids in a prospective, longitudinal clinical study [42, 43]. A third study evaluated the duration of ZIKV shedding in the semen of 12 symptomatic men from French Guiana. None of the studies included a control group. This study also attempted to determine to what extent infectious ZIKV was shed in these secretions rather than just focusing on detection of ZIKV genome by molecular means [42]. In the study, slightly more than half of the 55 men (53%) who were initially ZIKV-positive in either blood or urine by PCR and who provided at least 1 semen sample were shown to be positive for ZIKV genome in the semen sample by reverse-transcription (RT)-PCR. Only 6 of 20 (30%) RT-PCR positive semen samples that were tested by culture for infectious virus were positive. The authors determined that a RT-PCR threshold cycle (C_T) value of ≤27 in serum or semen correlated with infectious virus. All semen samples collected after day 45 postsymptom onset had a C_T value ≥27 (only 3 of those samples had a C_T value = 27). Although 132 of 150 participants had ZIKV detected in at least 1 serum sample by RT-PCR, all serum samples collected after day 8 postsymptom onset had a C_T > 27. These data suggest that infectious virus is cleared from blood relatively soon (within 8 days of symptom onset) and that shedding of infectious ZIKV in semen may occur much less frequently and for a shorter duration than presumed by RT-PCR testing. Biologically, this course of events is expected because the degradation and loss of infectious virus particles is followed by a more protracted degradation and processing of genomic ribonucleic acid fragments.

CHARACTERISTICS OF THE IDEAL ZIKA VIRUS-CONTROLLED HUMAN INFECTION MODELS

For a ZIKV CHIM to be most useful, it should induce objective endpoints with a sufficient frequency to power studies for statistical significance with relatively few subjects. Zika illness would not be a required endpoint for 2 reasons: (1) this is an infection model not a disease model, and (2) approximately 80% of ZIKV-infected individuals do not demonstrate symptomatic illness. Detection of infectious virus thus becomes the desired objective endpoint as used previously in our dengue virus CHIM [19, 44]. To minimize safety risk, a dose-escalation study first evaluating a low dose of a ZIKV challenge strain (eg, 100 plaque-forming units [PFU]) in a small numbers of subjects (5–10) could be performed to identify the lowest inoculum dose that results in viremia levels of 2–3 $\log_{10}$ PFU/mL in ≥80% of inoculated subjects. This level of viremia is low enough to reduce the risk of mosquito transmission (and possibly sexual transmission) but sufficient to allow the detection of variable levels of protection. Of course, an inoculation dose that induces recovery of infectious virus in ≥80% of exposed subjects and does not result in shedding of infectious virus in vaginal secretions or semen would be ideal because it would abrogate the risk of sexual transmission. When the specified criteria of the model have been met in the first few subjects, testing of that dose in an expanded number of subjects would be appropriate to confirm the reproducibility of the model. If clinical signs of infection such as rash, fever, or nonpurulent conjunctivitis are noted, the expected incidence of each could be added as characteristics of the model but may not be required as outcomes if the incidence is low. A ZIKV CHIM that induces infection, as evidenced by the recovery of infectious virus from ≥80% of inoculated flavivirus-naive subjects, with or without other clinical signs, can be used to assess the protective efficacy of experimental ZIKV vaccines and the duration of that protection in a relative small clinical trial. Should a vaccine induce only limited protection (reduced peak viremia or protection against viremia in only some subjects), that candidate could be modified or eliminated from further evaluation. In addition, the CHIM could be used to evaluate the kinetics of ZIKV replication in the blood and other fluids as well as any relationship between peak viremia in the blood and shedding of ZIKV in semen or vaginal fluids. This would contribute greatly to our understanding of ZIKV infection, sexual transmission, and their management.

RISK MITIGATION

As with any clinical trial, safety of the volunteers is the highest priority. For this reason, any ZIKV CHIM must have a plan to mitigate the risks associated with ZIKV infection, and protocols must be reviewed by the appropriate regulatory authorities including the FDA, the institutional review board, the institutional biosafety committee, and a data and safety monitoring committee. As described above, these risks consist primarily of risk to a fetus, risk of mosquito transmission, risk of sexual transmission, and risk of GBS. Because of the risk of Zika congenital syndrome, obviously only nonpregnant women would be eligible for enrollment. Additional eligibility criteria for women of childbearing potential should include the required use of

highly reliable birth control including oral contraceptives, hormonal patches or implants, and intrauterine devices, for at least 8 weeks after inoculation, in accordance with current Centers for Disease Control and Prevention guidelines. To mitigate the risk of vectorborne transmission, ZIKV CHIM studies should be conducted in mosquito-controlled environments such as an inpatient unit during the periods of viremia with the potential for mosquito transmission. Housing of subjects in an inpatient unit during the 10- to 14-day period of viremia would also minimize the risk of sexual transmission, although it is currently not known whether levels of viral replication in the blood correlate with shedding of virus in semen or vaginal secretions. All subjects should be required to use barrier contraception post-discharge from the inpatient unit to further reduce the risk of sexual transmission. In addition, because sexual transmission from infected males is much more common than that from infected females, limiting initial enrollment to females would further diminish the risk of sexual transmission. Persons who are older than 55 years of age and those with a history of GBS or other autoimmune disease are at highest risk of GBS [45–47]. For this reason, eligibility criteria should include age ≤50 and those without a history of GBS or autoimmune disease. In addition, appropriate diagnosis and management of GBS, should it occur, should be available at no cost to the subject. Other risk mitigation strategies may become apparent should additional data regarding the risk of ZIKV sexual transmission and GBS associated with ZIKV become available.

CONCLUSIONS

A ZIKV CHIM has the potential to de-risk ZIKV vaccine development and accelerate the pathway toward licensure. Demonstrated efficacy in a ZIKV CHIM would not necessarily guarantee the vaccine would be highly efficacious or proceed to licensure, but it would eliminate early those candidates that perform poorly and should not advance further in development. This would allow limited human and financial resources to be focused on those candidates with the best chance for success. Should the ZIKV outbreak wane in the next 2–3 years, as appears to be likely given current levels of incidence, traditional Phase 3 efficacy testing would no longer be possible. However, a ZIKV CHIM could be used to generate efficacy data that could support licensure of a ZIKV vaccine or therapeutic. In addition, the ZIKV CHIM has the potential to identify correlate(s) of protection for ZIKV, which could then be used to further refine vaccine development. From a clinical perspective, the ZIKV CHIM could determine the onset, magnitude, and duration of shedding of infectious ZIKV in blood, urine, semen, and other bodily fluids, something that is difficult or unfeasible in natural infection studies. These data are critical to a better understanding of ZIKV sexual transmission and the development of evidence-based guidance to prevent it. The development of a ZIKV CHIM is not without its challenges. The protection of volunteers is paramount, and mitigating the risk of fetal, vector-borne, and sexual transmission is of the utmost importance. Protocol development and risk management should be done in collaboration with the appropriate regulatory and ethical authorities.

Notes

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