



**World Health Organization and
National Institute of Allergy and Infectious Diseases, National Institutes of Health**

Scientific Consultation on Zika Virus Vaccine Development

**10–11 January 2017
5601 Fishers Lane
Rockville, Maryland**

Meeting Summary

Tuesday, 10 January 2017

INTRODUCTION

Anthony S. Fauci, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), United States

The National Institute of Allergy and Infectious Diseases (NIAID) and the World Health Organization (WHO) convened the Scientific Consultation on Zika Virus Vaccine Development to discuss challenges and recent advances in the development of Zika virus (ZIKV) vaccines. The NIAID Director opened the meeting by stating that the recent spread of ZIKV mirrors that of other emerging arboviruses in the Americas in the past several years, including chikungunya, West Nile, and dengue. The NIAID research response to Zika builds on those experiences. A primary goal of this research is to develop medical countermeasures including diagnostics, therapeutics, and vaccines. Challenges specific to the development of a Zika vaccine include: the lack of adequate animal models; uncertainties in the epidemiology, which affect clinical trial site selection; the likelihood that the vaccine will need to induce sterilizing immunity to prevent congenital Zika syndrome (CZS); preexisting immunity to other flaviviruses in some regions; and potential specific risks such as Guillain-Barré syndrome (GBS) and the administration of live vaccines to pregnant women. Several Zika vaccine candidates are being developed with different development timelines and likely target populations. The planned timelines include large, well-controlled clinical trials to evaluate safety and efficacy, and if successful, subsequent licensure; should public health need and available safety and efficacy data justify deployment of vaccine before licensure, access through appropriate regulatory mechanisms could be considered. Several vaccine candidates are currently in development by NIH and its partners, with initial results of Phase 1 testing of the VRC DNA and WRAIR/NIAID Zika purified inactivated virus (ZPIV) vaccine candidates expected in mid-2017. Emerging infectious diseases are a perpetual challenge, and the lessons learned from Zika will be applicable to other unexpected emerging infectious diseases.

Marie-Paule Kieny, World Health Organization (WHO), Switzerland

The WHO Assistant Director-General remarked that Zika is a disease hitherto considered of limited public health relevance that has recently become a global concern. WHO rapidly developed a comprehensive plan to monitor and better understand Zika infection and its consequences. WHO's interest in countermeasure development goes beyond vaccines, and includes diagnostics, therapeutics, and public health and systems research. A Public Health Emergency of International Concern (PHEIC) was declared on 1st February 2016 following the unusual clustering of microcephaly cases observed in Brazil and their possible association with Zika virus. While Zika is no longer designated a PHEIC, sustained effort will be required to contain the disease over the long term. One significant challenge is the limited understanding of the epidemiology of the disease and how it will evolve in the years to come. The development of a Zika vaccine has similarities to the development of an Ebola vaccine; however, a major difference is that Ebola vaccine candidates were already in development when the Ebola outbreak struck. Although the WHO played an implementation role in the Ebola vaccine effort, for future vaccine development, the WHO is developing a [WHO R&D Blueprint](#) for action and establishing a research-enabling environment to minimize uncertainty for product development in the context of a public health emergency. Zika has become an important test case of the R&D Blueprint. In support of the objectives of the R&D Blueprint, the coalition of partners in support of product development has been established (Coalition for Epidemic Preparedness Innovations, or CEPI).

SESSION 1: ZIKA EPIDEMIOLOGY AND VACCINE EFFORTS

Dynamics of Zika

Zika Epidemiology for Vaccine Efforts: Data from Yap, French Polynesia, Pernambuco and Brazil

Laura Rodrigues, London School of Hygiene & Tropical Medicine, United Kingdom

The course of an epidemic is measured using data on incidence of infection, incidence of complications, and seroprevalence. Differences in the speed of progression of Zika outbreaks can be attributed to differences in vectors, and human and geographical factors. The outbreak in 2007 that occurred in Yap, a small group of Micronesian islands with a total population just over 7,000, lasted 3 months and presented no cases of microcephaly; the seroprevalence after the outbreak was 73 percent. The French Polynesia outbreak in 2013-2014 lasted 4 months with approximately two cases of microcephaly per 1,000 live births (detected retrospectively) and a post-outbreak seroprevalence of 66 percent. Pernambuco, a state in Brazil, experienced a sporadic outbreak over 8 to 10 months in 2015-2016; the prevalence of microcephaly was 2.8 per 1,000 live births, similar to that of French Polynesia, and the seroprevalence in the city of Recife at the end of the outbreak was 56 percent. The distribution of cases in Pernambuco is not homogenous, suggesting that many outbreaks are happening.

The geographical variation of households with *Aedes aegypti* larvae in breeding sites indicates that many areas are at high risk but have not yet had an epidemic. The pattern of microcephaly cases shows sporadic outbreaks and fluctuating incidence; the causes of this variability could include co-factors and/or mosquito density. Notifications of cases of microcephaly indicate that

transmission of the virus is still ongoing as sporadic or epidemic throughout Brazil. Very little is known about the rate of the spread of Zika in Brazil, and the interpretation of the microcephaly data is difficult. To be able to understand and predict the course of the epidemic, and endemic transmission, we need more ongoing age-stratified research, which could include seroprevalence surveys and repetition of seroprevalence studies in areas already surveyed. These data would be best interpreted in conjunction with microcephaly notifications to understand the spread of Zika.

Zika Dynamics in the Americas

Sylvain Aldighieri, Pan American Health Organization/WHO, United States

Several arboviruses were of public health importance in the Americas in 2015: dengue virus (DENV) has been endemic in the Americas since the 1980s; 13 countries and territories were at risk for yellow fever sylvatic transmission; and the chikungunya virus, introduced to the Americas in 2013, had spread to all subregions by early 2015. The rapid spread of chikungunya was facilitated by the widespread populations of *Aedes aegypti* and the introduction of the virus into areas with health systems already burdened with dengue response.

In early 2014, a Zika outbreak was detected on Easter Island, off the coast of Chile; populations of the region were immunologically naïve for Zika. In late 2015 and early 2016, Brazil and several other countries in the region started to report cases. Incidence rates have varied across the region, even in areas with similar climates. Some countries have shown differences in incidence rate by gender. Factors that can affect incidence include the availability of health clinics and seasonality. During more than 18 months of Zika transmission in the Americas, 707,000 cases were reported, 25 percent of which were laboratory confirmed. Incidence was high from 2015 to mid-2016; the decrease seen at the end of 2016 could have been caused by a reduced number of susceptible persons or by seasonal changes. The epidemic is still ongoing, however, and the virus may continue to spread to all areas with *A. aegypti*. The outlook of the epidemic is uncertain given that more than 500 million people live in areas at risk for *A. aegypti*-borne arboviruses.

Zika in Singapore

Yee-Sin Leo, Institute of Infectious Diseases and Epidemiology, Singapore

Zika has been in Southeast Asia for many years. A paper published in 1954 references its identification in long-term residents of Malaya (in close proximity to Singapore), and recent studies from many Southeast Asian countries confirm its presence. The first case of local Zika virus transmission in Singapore was detected in August 2016, with subsequent cases reported thereafter. The outbreak was quickly contained, most likely due to enhanced vector control. The virus isolated during the outbreak in Singapore is closely related to the strain from Thailand reported in 2014. Subsequent discovery of two viruses of different clades in Singapore suggest multiple introductions of the virus have occurred. Many questions have yet to be answered about Zika in Singapore. Few data exist on asymptomatic infection or seroprevalence, and it is unknown whether Zika will follow seasonal patterns similar to dengue. A longitudinal outbreak cohort study to characterize the clinical progression is in progress, and an ongoing population-based cohort study ends in December 2017.

Congenital Zika Syndrome and Guillain-Barré Syndrome

Congenital Zika Syndrome as Relevant for Vaccine Efforts

Demócrito de Barros Miranda-Filho, University of Pernambuco, Brazil

Microcephaly is a symptom of disease in the brain rather than a disease itself. With regard to CZS, a spectrum of manifestations of microcephaly exists, and others are yet to be described. Approximately 18 percent of reported microcephaly cases do not meet the WHO definition of microcephaly. The Microcephaly Epidemic Research Group, which studied microcephalic infants born in Pernambuco State in Brazil during 2015, found neuronal migration disorders, calcifications on imaging, and abnormalities in vision and hearing. The computed tomographic findings were consistent with those described in other CZS cases. The challenge now is to follow these children and monitor their development.

Studies have shown that women with Zika-related rash have a 46 percent rate of adverse pregnancy outcomes (including congenital anomalies and spontaneous abortions/late fetal losses) and a 42 percent rate of live births with grossly abnormal clinical or brain imaging findings. Clinical epidemiological studies are needed because microcephaly is only one abnormality manifested in CZS, and most cases of CZS do not develop symptoms of microcephaly. CZS is detected in almost half of the babies infected with Zika virus at birth. The proportion of infants who are asymptomatic at birth but become symptomatic later is unknown. Researchers recommend following newborns with CZS at least until they attempt to learn to read and write in case there are developmental defects or delays even in those who are asymptomatic at birth.

Zika Infection and Guillain-Barré Syndrome: Neurological Problems as Relevant Adverse Effects in Vaccination

Carlos A. Pardo, Johns Hopkins University School of Medicine, United States

Zika is associated with neurological disease in two different contexts: (1) direct viral pathogenic effects, such as microcephaly and encephalitis in infants; and (2) immune-mediated pathogenic effects, such as GBS in adult populations. Historically, etiologies that have been associated with GBS include viral and bacterial infections—such as HIV, influenza, and *Campylobacter jejuni*—and reactions to vaccines for such diseases as rabies, yellow fever, and influenza. One of the most aggressive forms of GBS occurs when the immune process targets the axon itself. In a more common form, the antibodies target the Schwann cell myelin structure. A marked increase in the incidence of GBS was seen during the outbreak of Zika, with rates far higher than those associated with other viral etiologies.

Virologists are working with neurologists and neuroscientists to characterize the clinical syndrome in the Zika context. The temporal profile of neurological problems in Zika is variable, but almost 50 percent of patients present with a para-infectious profile. GBS classically presents 2 to 3 weeks post-infection, but in the case of Zika, GBS symptoms become apparent a few days after or even simultaneous with Zika symptoms. Anti-flavivirus antibodies suggest the presence of an anamnestic response and a history of a prior flavivirus infection. As of 2016, only one study has calculated the risk of GBS in the context of Zika infection. That study showed a risk of

one case of GBS per 4,000 Zika-infected patients. Incidence of Zika-related GBS follows a temporal relationship with cases of Zika infection, and risk of GBS increases with age. Many patients with Zika-associated GBS recover from this condition. It is possible that Zika infection of specific organs, such as the kidney, may serve as a potential viral reservoir and trigger for hyperactive antibody responses and secondary neurological complications, such as GBS. This hypothesis would need further study to confirm or refute.

Sero-Epidemiology and Modeling

The Interplay Between Immunology and Epidemiology

Eva Harris, University of California, Berkeley, United States

Studies of pediatric ZIKV infection and disease are beginning to produce data that could help answer some pressing immunology and epidemiology questions, such as how to serologically distinguish between anti-ZIKV and anti-DENV antibodies, and how prior DENV or other flavivirus immunity might affect ZIKV infection. A pediatric dengue cohort ongoing since 2004 in Managua, Nicaragua, has recently added studies of chikungunya and Zika. Studies indicate that low levels of anti-DENV antibodies increase the risk of severe dengue disease, and high levels of anti-DENV antibodies protect against severe and symptomatic dengue. Data also indicate that the probability of symptomatic ZIKV infection in children increases with age and is greater in females. Researchers have not yet seen an association between pre-existing anti-DENV antibody titers and a greater incidence of symptomatic Zika. Studies in mice have suggested a possibility that certain cross-reactive human monoclonal antibodies to ZIKV could enhance dengue, but so far this has been observed only in animal models, and these studies were of monoclonal rather than polyclonal antibodies.

Studies of the level of cross-neutralization between anti-DENV antibodies and ZIKV have shown serotype-specific differences and a decay to a stable level over time; further research is underway. It is important to consider DENV and ZIKV together, as the cross-neutralizing antibody titer of anti-DENV neutralizing antibodies against ZIKV, although measurable and relatively stable, is much lower than the titer of anti-DENV antibodies against DENV, or anti-ZIKV antibodies against ZIKV. It remains to be seen how dengue and Zika immunity will affect subsequent epidemics. The spread and severity of disease associated with Zika may be modulated by the extent of cross-protective and cross-enhancing immunity between Zika and dengue.

Trajectory of the Zika Epidemic: Implications for Vaccine Development

Neil Ferguson, Imperial College London, United Kingdom

The timing of the global Zika epidemic may have been due to a genetic change in the virus, climate-related enhancement of transmission—which might suggest a lower transmissibility in future years—or random chance. The speed of transmission depends on such elements as population connectivity and seasonality; mathematical modelling suggests that the initial wave of transmission likely will be over within 1 to 2 years at a single location, and 3 to 4 years in Latin America. After that time, herd immunity is likely to result in up to 20 years of low incidence, before epidemics reoccur. While data issues make it challenging to estimate the reproduction

number and generation time for Zika, current analysis shows reproduction number estimates consistent with those of dengue. Sensitivity analyses of the models were performed, but the results were fairly insensitive to parameters related to transmissibility, seasonality, and human-to-human transmission. Reliable serological data still are lacking for many countries.

Data through December 2016 indicate that the epidemic is in rapid decline in most Latin American countries. To detect a substantial impact on incident infection or disease, interventions need to be introduced before substantial transmission has occurred in an area. It is therefore too late for vaccines to have an effect on the current wave of the epidemic in most locations, so trial design will be challenging. Sites with recent transmission are unlikely to see much more during the next 10-20 years, and it is difficult to predict which sites will be affected next. Sites could be chosen in areas where Zika incidence rates have been smaller than expected, but this expectation relies on the correlation between historical rates of dengue transmission and current Zika incidence. Tests of the potential of *Wolbachia* for sustained control of flavivirus transmission also are being conducted in Colombia and Brazil as this may affect Zika incidence in these areas.

Vaccine Efforts

Public Health Performance Characteristics for Vaccines

David C. Kaslow, PATH, United States

The WHO's Product Development for Vaccines Advisory Committee (PDVAC) oversees activities related to global vaccine research and development, including WHO target product profiles (TPPs). TPPs are developed to allow stakeholders to factor the WHO's preferences into development decision-making. A Zika vaccine TPP for emergency use was initially developed in April 2016. It was the subject of a consultation on regulatory expectations for licensure or accelerated approval in June 2016; a report of the meeting has been published. The TPP is a living document, so it will continue to be updated as new information about Zika becomes available.

Zika vaccine development remains an urgent priority, primarily for use in women of childbearing age to prevent CZS. The TPP proposes an indication for prevention of Zika-associated clinical illness in subjects 9 years of age or older, without contraindication for use during pregnancy or in lactating women. The desired vaccine would offer at least 1 year of protection in a single dose, and it is preferred that the product be a liquid formulation with a shelf life of at least 12 months at -20 °C. The next steps for this process are to finalize the updated TPP for emergency use and, in the future, consider the need for a routine-use TPP focusing on disease burden in low- and middle-income countries.

Zika Vaccine Opportunities and Challenges: A Vaccine Developer's Perspective

Thomas Monath, NewLink Genetics, United States

The epidemiology of Zika is changing, and unknown clinical factors, such as the best type of vaccine to match the desired indications and the immune mechanisms of protection, remain key questions. Development questions also must be considered, such as the relationship between supply and total market size, the regulatory pathway(s), and funding sources. As Zika has a

single serotype with high homology among sequences, and commercial vaccines against other flaviviruses have been successful, vaccine strategies applicable to other flaviviruses can likely be used. Challenges include the incidence of severe congenital infection, persistent infections, and autoimmune reactions. Safety also is an important consideration as the vaccine needs to be usable during pregnancy, particularly in the setting of an epidemic.

Development of a Zika vaccine likely is achievable using multiple technologies. However, novel technologies may have longer timelines and more regulatory hurdles. In addition, there is much complexity in characterizing the immune response. It is critical to understand how the immune response to Zika is affected by natural immunity to other flaviviruses and by other flavivirus vaccines. According to some analyses, the Zika vaccine market could be as large as ~\$10 billion per year in the Americas, Latin America, and the European Union. Manufacturing is an easily forgotten but critical component; manufacturing and affordability should be considered early in development. Early trials should evaluate immunogenicity and safety, bridge the nonclinical and clinical data, and determine immunological endpoints in patients with varying immunity to other flaviviruses. Vaccine development usually is time-intensive and costly, but there are opportunities to shorten timelines for Zika.

U.S. Government Zika Vaccine Pipeline

Armen Donabedian, Biomedical Advanced Research and Development Authority (BARDA), United States

The long-term goal of U.S. Government Zika vaccine development efforts is to prevent CZS through the use of safe and effective vaccines. At the time that Zika was declared a Public Health Emergency of International Concern by WHO in February 2016, the Zika vaccine landscape was sparse. As of January 2017, the landscape includes more than 40 vaccine candidates at various stages of development. To determine which candidate to support, the U.S. government considers funding mechanisms and correlation with its three aims: to evaluate, deploy under expanded access or EUA, and commercialize a Zika vaccine(s). Two nucleic acid vaccine candidates and one inactivated vaccine candidate are in Phase 1 trials. A second inactivated vaccine is scheduled for Phase 1 clinical study in early 2018. A live-attenuated dengue/Zika vaccine developed at NIAID also is under development, with Phase 1 trials planned for the spring of 2017. The current goal is that by the end of 2018, a vaccine that could support expanded access or emergency use will be available, and data to support licensure is targeted for availability by the end of 2020.

SESSION 2: DETECTING ZIKA VIRUS INFECTION AND IMMUNOLOGICAL RESPONSES

The Human Immune Response to Zika Infection

Human Antibody Responses in Zika/Dengue

Gavin Screaton, Imperial College London, United Kingdom

The generation of human monoclonal antibodies (mAbs) from cells taken from people infected with flaviviruses was first introduced in 2003, and nearly half of these antibodies have been shown to react to conformational epitopes. Experts generated more than 150 DENV-specific mAbs using these methodologies. Epitope mapping of the DENV-specific mAbs revealed a new

conformational epitope, the envelope dimer epitope (EDE), which was cross-reactive between the four DENV serotypes. The EDE mAb was shown to fully neutralize the virus in human and insect cells. Generally, flaviviruses differ in sequence homology by 30 to 35 percent. DENV differs from ZIKV by 41 to 46 percent in amino acid sequence in the envelope region.

Retrospective analyses of samples collected from 2002 to 2004 from DENV-infected patients enrolled in a study to investigate DENV infection in children in Khon Kaen, Thailand, demonstrated in an *in vitro* study that anti-dengue serum binds to ZIKV and enhances rather than neutralizes the Zika infection. In addition, recent studies revealed very high conservation of the EDE binding site between DENV and ZIKV, which also is the site for precursor membrane protein (prM) binding. Some EDE mAbs from dengue patients also cross-neutralize ZIKV. ZIKV vaccine developers may need to consider the following: complex epitopes could be the target for the best mAb, the potential for preexisting DENV immunity to promote antibody-dependent enhancement (ADE) versus neutralization, and preexisting dengue immunity could modify the immunological or protective effects of Zika vaccines.

T Cell Immunity to Zika

Alessandro Sette, La Jolla Institute for Allergy and Immunology, United States

Efforts that need to be addressed when investigating T lymphocyte (T-cell) immunity to Zika include determining whether DENV T-cell responses cross-react with ZIKV, whether ZIKV-specific responses are influenced by previous DENV exposure, and the antigenic targets of ZIKV T-cell responses in exposed individuals. Retrospective analysis of pre-Zika epidemic peripheral blood mononuclear cells (PBMCs) from donors in Sri Lanka and Nicaragua who were DENV-seropositive, with appreciable *ex vivo* response to the DENV CD4/CD8 epitopes, showed substantial cross-reactivity to ZIKV peptides. Individual epitopes also were mapped in representative cases, and in five of the six cases the reactivity was directed to identical or nearly identical sequences.

Investigations of PBMCs from six donor groups with differing Zika status (i.e., acute, convalescent, negative) and DENV status (i.e., seropositive or negative) assessed T-cell reactivity with overlapping Zika peptides. *Ex vivo* CD4/CD8 reactivity in the six cohorts were studied, and those results led researchers to the following conclusions: *ex vivo* ZIKV T-cell responses displayed more weakly or were delayed in DENV seronegative donors; results from ZIKV negative/DENV seropositive donors confirmed DENV-ZIKV cross-reactivity at the level of the T cell; DENV pre-exposure influences ZIKV responses; and the main protein targets of ZIKV-specific CD4 and CD8 responses appear to differ from the DENV-specific responses. In addition, epitope mapping suggested that DENV-seropositive donors recognize DENV/ZIKV highly conserved epitopes, and DENV-seronegative donors may recognize more divergent targets.

It is unclear from these data alone whether the CD8 response could be used as a diagnostic tool. Conducting studies on out-of-frame peptides would require support from others in the community.

The Status of PCR and Serology Assay Development

The Status of PCR Assays as Infection Endpoints

Uwe Scherf, Food and Drug Administration (FDA), United States

The FDA's EUA program is designed to authorize diagnostics for marketing in special circumstances and requires a declaration from the Secretary of the Department of Health and Human Services (HHS) that circumstances justify the issuance. Analytical and clinical evaluation requirements are less extensive, but the EUA is temporary and remains in effect only for the duration of the declaration. Several EUAs are currently active for nucleic acid amplification tests (NAATs) and two EUAs for serological assays. Eleven authorized NAAT designs are PCR-based assays, and developers of NAAT assays are required to use the FDA Zika Virus Reference Materials for nucleic acid test-based *in vitro* diagnostic devices. To date, the FDA has issued 14 EUAs. Zika virus EUA information is available on the FDA website <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika>.

The Status of ELISA Development for Vaccine Development

Jane Basile, Centers for Disease Control and Prevention (CDC), United States

Rapid serological assays for clinical trials are necessary to (1) prescreen for baseline antibodies from previous flavivirus natural infections or flavivirus vaccines, (2) distinguish baseline antibodies that are due to natural infections from vaccine-induced antibodies, (3) measure Zika vaccine-induced responses in flavivirus-naïve populations, and (4) measure Zika vaccine-induced responses in populations with high rates of flavivirus exposure and vaccine use. Assay targets for Zika include the whole virus, envelope (E) protein and premembrane (prM), E domain III plus virus-specific epitopes, and nonstructural protein 1 (NS1).

The CDC uses standard serologic screening assays for flaviviruses: immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (ELISA), or MAC-ELISA; immunoglobulin G (IgG) ELISA, which is not currently being used for Zika; and microsphere assays, which are not currently optimized for Zika. In confirmed diagnosis, cross-reactivity has been demonstrated between flaviviruses—in particular, DENV and ZIKV—when using MAC-ELISA, as well as in the IgG ELISA assay. The IgM and IgG ELISAs are 2-day tests that use either E/prM or whole virus antigen. They are sensitive and qualitative, but lack specificity among the flaviviruses. ELISAs are used in conjunction with the plaque-reduction neutralization test (PRNT) in the United States to provide confirmation and specificity for primary infections. More than 60 U.S. Department of State and Department of Defense laboratories are using the CDC Zika MAC-ELISA, which is available for use under the FDA's EUA. A commercially produced Zika ELISA is also available under EUA. Assays using NS1 antigen are commercially available, and although further characterization of their utility is needed, these may have some use in vaccine clinical trials because of their enhanced specificity over E-based assays.

NS1 Serological Assays

Eva Harris, University of California, Berkeley, United States

The NS1 blockade-of-binding (BOB) assay is based on an ELISA format, but it can be optimized for lateral flow formats. The NS1 BOB assay detects the presence of plasma antibodies specific for ZIKV NS1 and has minimal background interference, including low cross-reactivity with anti-DENV antibodies. Using samples collected from prior and ongoing studies in Nicaragua and Brazil and from returned travelers in Italy and the U.K., the Zika NS1 BOB assay showed that anti-NS1 inhibiting antibodies were developed within 2 weeks of ZIKV infection and were maintained through the last timepoint tested at 240 days post-infection. One hundred and forty-five of 158 samples from ZIKV RT-PCR-positive individuals from multiple sample sets scored positive (i.e., sensitivity of 91.8%), and 231 of 255 samples from DENV-immune individuals scored negative in the NS1 BOB assay (i.e., specificity of 90.6%). Of the 644 controls, which included individuals with other flavivirus infections, 618 scored negative (i.e., specificity of 96.0%). These results suggest that the NS1 BOB assay can be used for serological detection of symptomatic and asymptomatic ZIKV infections and in epidemiological studies to investigate age-stratified seroprevalence, the risk of Zika disease enhancement and the incidence rate of ZIKV congenital infection in areas where other flaviviruses are endemic.

Another group of researchers developed an anti-NS1 IgG3 assay to detect recent ZIKV infection. The assay was developed to ensure high sensitivity and reproducibility, and a panel of reference samples was used to characterize the inter-assay variance. This assay was specifically designed with IgG3, which has a serum half-life three times shorter than the other IgG subclasses. To date, NS1 IgG3 assays have been developed for ZIKV and DENV. Recent infection samples and retrospective analysis of samples from a community-based cohort in Salvador, Brazil, were used to test the utility of the assay. The DENV and ZIKV infections elicited anti-NS1 IgG3 antibodies, which remained positive for 4 to 6 months. Overall, the anti-ZIKV NS1 IgG3 antibodies elicited by ZIKV were recognized at much higher levels in the ZIKV NS1 IgG3 assay than in the DENV NS1 IgG3 assay, and vice versa. Other efforts to develop Zika NS1 assays include mutating potential cross-reactive epitope regions in ZIKV NS1 to develop a more specific antigen.

Neutralizing Assay Development for ZIKV

Ted Pierson, NIAID, NIH, United States

Flaviviruses have a complex serology because natural infection and vaccination elicits antibodies with the potential to cross-react among distantly related viruses. Assays that measure antibody-mediated neutralization of infection are typically more specific than biochemical (ELISA) approaches; neutralization titers are a correlate of protection for some flavivirus vaccines. Three types of neutralizing assays are currently in use to evaluate humoral immunity to flavivirus infection or vaccination. Flow cytometry-based ZIKV neutralization assays measure the ability of antibodies to block entry of the virus into cells. This assay format may be performed using infectious virions, infectious virions engineered to express reporter genes, or flavivirus reporter virus particles (RVPs). With these approaches, infection is measured by detecting viral or reporter gene expression in just a single round of the viral replication cycle.

RVPs are generated by complementation of a West Nile virus (WNV) replicon with the structural genes of homologous (WNV) or heterologous (ZIKV, DENV) viruses. The ability to exchange structural gene plasmids in RVP production protocols allows the analysis of multiple strain/variants, or cross-reactivity of antibodies among heterologous viruses. The ZIKV microneutralization (MN) assay format also evaluates the ability of antibody to block infection. In contrast to flow-based methods, this technique measures inhibition of viral antigen production in cells infected in the presence of antibody. Since the MN assay involves viral replication and spread, this assay requires ~4 days (as compared to 24 hours for flow cytometry-based assays). Finally, the focus reduction neutralization test (FRNT) and PRNT are relatively straightforward and commonly used assays that measure antibody neutralization as a function of a reduction in the number of plaques (or clusters of infected cells revealed by immunohistochemistry). Microneutralization and RVP assays are being used in Phase 1 clinical trials of candidate DNA and Zika purified inactive virus vaccine candidate samples.

Development of Reference Reagents and Considerations for Assay Validation

Development of an International Reference Antibody Standard for ZIKV Vaccine Development

Mark Page, National Institute for Biological Standards and Control (NIBSC), United Kingdom

NIBSC is working to establish an international Zika antibody reference standard endorsed by the WHO. International biological reference standards are the highest order standard with a formal status and are developed through multicentre collaborative studies. Assays should be calibrated against the international standard in International Units to permit comparability of results. It is important to note that assays will change over time even though they use standardized protocols. Therefore, reference to a physical standard is preferred to ensure data can be compared over many years (the life of the standard is usually greater than 5 years). The Zika NAAT standard has been developed and was endorsed in October 2016 by the WHO Expert Committee for Biological Standardization (ECBS). This was prepared from inactivated virus preparations of Polynesian/African lineages; a high dilution preparation, calibrated against the International Standard has potential use as an in-run control. The antibody standard is in development now, with the goals of submitting it to the ECBS in June 2017 and receiving endorsement in October 2017.

Antibody standards may be used for vaccine evaluation, serosurveillance, and diagnosis. The current effort is attempting to source antibody from recently infected individuals. The goal is to develop one standard for all three uses, but different needs may dictate what materials are suitable or available for a given purpose. Human samples are desired for commutability because the standard should behave as closely as possible to a human sample. Current assays used for serology standard characterization have issues (e.g., DENV cross-reactivity); the planned collaborative study will assess the suitability of candidate materials and assays. The use of a common positive control for current usage that can be calibrated to the international standard once it is endorsed in October is advised.

Reference Materials for Zika Vaccine Development

Cristina Cassetti, NIAID, NIH, United States

The two major repositories supported by NIAID that collect reagents for all relevant infectious diseases are the Biodefense and Emerging Infections Research Resources Repository and the World Reference Center for Emerging Viruses and Arboviruses. These repositories received at least 1,635 Zika reagent requests in 2016. NIAID has developed Zika reference materials for serological and molecular assays. To measure IgM in pregnant women, NIAID developed clinical sample reference panels validated with InBios MAC-ELISA. A second project developed quantitative PCR reference standards using heat-inactivated ZIKV diluted into serum, to support the evaluation of a PCR-based diagnostic currently under consideration for EUA.

NIAID is funding a Zika natural history study in the United States. Three universities will enroll up to 200 returned U.S. travelers and persons infected in the United States to study clinical presentation, immune responses, and viral persistence. Their samples will be made available to NIAID repositories. NIAID also is focusing on developing standardized Zika vaccine assays for research through a contract to Battelle. The assays will be available, on a case-by case basis, for transfer to vaccine developers or can be performed by Battelle for a fee. NIAID is consulting with other federal agencies to select specific assays for development.

Perspectives from Industry

Hansi Dean, Takeda Vaccines, United States

Assay selection for Zika vaccine development should address several questions: Is there a strong rationale to stay with the same immunogenicity platform as DENV virus assays for comparison purposes, or is this an opportunity to pursue potentially more sensitive and precise assay formats? What sample matrix is optimal for molecular assays to detect ZIKV infection? What practical sampling strategy can be used for infection endpoints in clinical trials? What scientifically sound approach can be used to streamline assay qualification and validation to meet accelerated clinical timelines? What is the contribution of flavivirus pre-exposure status to ZIKV vaccine immunogenicity and efficacy? What assays are best to understand the exposure history of clinical trial participants (especially in an area where there is flavivirus vaccination)? How do ZIKV and DENV interact in pathogenesis and immunity?

The desired endpoints for clinical assays for ZIKV vaccine development have many challenges. For example, the challenges associated with the endpoint of screening for prior flavivirus exposure include specificity, the identification of the correct panel (not only dengue), and the ability to enroll flavivirus-uninfected subjects in endemic areas. The challenges of vaccine immunogenicity include the contribution of cross-reactive antibodies and the validation of potential new assays. Immune correlates for fetal protection may be different than those for prevention of disease. For vaccine efficacy, regular sampling may be needed for the prevention of infection endpoint (to capture asymptomatic infection). A matrix suitable for subject self-sampling would be an advantage. It is important to develop clinical endpoint assays early, as potential vaccine development acceleration scenarios would require acceleration of assay qualification and validation. Insufficient experience with an assay before validation could lead to use of a suboptimal assay or failure of validation.

Important reference standards include the anti-Zika neutralizing antibody reference standard and the Zika antigen reference standard. Collaborative studies are critical to qualify reference standards and Zika-specific and flavivirus cross-reactive mAbs.

Development of Reference Reagents and Considerations for Assay Validation from the Regulatory Perspective

Yuansheng Sun, Paul-Ehrlich Institute, Germany

Evidence should be convincing to demonstrate vaccine efficacy. Assays used in pivotal efficacy trials should characterize the product in a reliable and reproducible manner. It also is important to consider using international standards, when available and appropriate, and to acknowledge that using different reagents and/or assay procedures makes it difficult to compare assay results. When developing and selecting assays, the critical parameters that affect assay performance should be identified and validated. It also is important to consider the flexibility of a particular vaccine platform or approach. Potential challenges specific to Zika vaccine evaluation include the differences in platform technologies and their intended use; a lack of knowledge about an immune correlate of protection for any candidate or vaccine platform; the lack of adequate animal models to infer vaccine efficacy against clinical disease; and the feasibility of obtaining clinical disease or infection endpoint data. Different assays need to be developed for different endpoints. Establishing reference materials and standards is critical for assay validation, as is addressing critical parameters (e.g., virus strain, cell line, incubation time, virus input, for neutralizing antibody assay validation). Clinical samples should be used when possible. Developing and selecting reliable and reproducible assays is indispensable to vaccine evaluation, as is ensuring that the evidence available to support suitable use is acceptable to relevant regulatory authorities. The regulatory decision on assay selection is science-based, allowing flexibility and case-by-case consideration. It is advisable to communicate early with relevant regulatory authorities and solicit their input.

SESSION 3: ANIMAL MODELS

Overview of Animal Models for Zika Pathogenesis

Overview of Mouse Models of Zika Virus Pathogenesis

Michael S. Diamond, Washington University School of Medicine, United States

Mouse models can be useful for studying Zika virus pathogenesis. Few animal studies of ZIKV existed before 2016, aside from the seminal 1947 study that first identified the virus in a sentinel NHP in Uganda. Subsequent studies led to the identification of ZIKV African strain MR 766 (ZIKV MR 766) in mice in 1952, and studies in 1976 demonstrated virus lethality in infected newborn and young mice. Investigators are generating and characterizing mouse models of ZIKV infection using various strains of the virus (African, Asian, or American) to model human disease. Initial efforts to generate models of different ZIKV strains using wild-type (WT) mice did not result in disease manifestations. Current tractable models include interferon (IFN) alpha and beta receptor subunit 1 (IFNAR1)^{-/-} B6 mice, IFNAR1^{-/-} 129 Sv mice, and AG129 (IFNAR^{-/-} + IFNGR^{-/-}). Immunocompromised mouse models of ZIKV infection can test the effects of virus strain variation on pathogenesis, be used in virus challenge studies where lethality is the outcome, and help study neuroinvasive disease. Although promising, these models have limitations: the vaccine responses are not likely to be normal in the absence of IFN immunity and this model does not entirely replicate human disease. To address these limitations, experts have developed other mouse models of ZIKV, including the mouse-adapted ZIKV-Dakar in WT mice (adapted strains), which can be used in the setting of low doses of anti-IFNAR1. Current ZIKV mouse models are used to study *in utero* and sexual transmission of ZIKV, gestational stage effects of ZIKV infection on disease pathogenesis, ZIKV persistence in the male reproductive tract, the consequences of ZIKV in the testes, potential therapeutics, and the window of protection. A review article summarizing the progress of the mouse models of ZIKV infection and pathogenesis will be published in early February.

Experimental Infection of NHPs With Zika Virus

David O'Connor, University of Wisconsin, Madison, United States

Several NHP species susceptible to experimental ZIKV infection experience some clinical manifestations seen in humans. The virus is detected in the same fluids with the same degree of persistence, and pregnancy outcomes appear similar. An advantage of NHP models is their flexibility, including multiple routes of virus exposure and various potential target subpopulations (e.g., nonpregnant adults, pregnant females, infants). Although sample sizes are limited, NHP model species are valuable for studying viral persistence in tissues and virus effects in newborns; evaluating the basis for protective immunity and providing insight for antigen design (protective immunity elicited by vaccination); demonstrating the effects of prior flavivirus exposure; identifying the mechanisms of the viral effects in pregnancy and fetal outcomes; defining maternal ZIKV reservoirs; and improving the understanding of prolonged maternal viremia.

Improving the NHP model would entail expanding studies to other species of Old World monkeys, as well as New World monkeys, and developing updated models for the different modes of transmission (i.e., sexual, oral, vector). To ensure compatible results between studies, the Puerto Rican ZIKV stock (ZIKV-PR) was standardized as a challenge virus and is available by Material Transfer Agreements to NHP researchers from Dr. O'Connor.

Opportunities for Efficacy and Correlates of Protection Using Animal Models

Preclinical ZIKV Vaccine Efficacy Studies

Dan Barouch, Harvard Medical School, United States

ZIKV vaccine development in mouse models and NHPs began in response to the expanding epidemic and public health concerns. Virus challenge stocks, immunologic assays, virologic assays, and animal models were developed rapidly. Three ZIKV vaccine platforms have been evaluated to date: purified inactivated virus (PIV) vaccine; DNA-based vaccines expressing ZIKV prM and E; and adenovirus (Ad) vector-based vaccines expressing prME. Preclinical vaccine efficacy studies in animal models began with the development of large-scale challenge stocks of ZIKV-PR and Brazilian ZIKV (ZIKV-BR) strains. Proof-of-concept studies showed that the DNA prM-E vaccine protected mice against ZIKV-BR and ZIKV-PR strains and, likewise, purified IgG from DNA prM-E vaccinated mice provided passive protection to recipient mice after adoptive transfer. This protection was not abrogated by T-cell depletion. The evaluation of PIV, DNA, and Ad vector-based vaccines in NHPs challenged with ZIKV-BR and ZIKV-PR showed complete protection (e.g., plasma, urine, cerebrospinal fluid) from ZIKV compared with animals exposed to conventional adjuvant alone. As seen in vaccinated mice, adoptive transfer studies in vaccinated NHPs showed that vaccine-induced antibodies afford protection to naïve hosts.

Ongoing studies focus on comparing neutralizing antibody assays, testing the durability of immunity following ZIKV vaccination, improving the understanding of the flavivirus cross-reactivity of ZIKV-elicited antibodies, and evaluating the impact of other flavivirus (e.g., DENV) immunity on ZIKV vaccination. These data raise optimism that the development of a ZIKV vaccine for humans is possible.

Correlates of Protection

Alan Barrett, University of Texas Medical Branch, United States

Correlates of protection are markers of immune function that statistically correlate with protection following vaccination, and generally have been inferred from either animal and/or human studies. (Plotkin and Gilbert CID 2012). Most often a surrogate of protection is used, which is an immune marker that can substitute for the clinical endpoint to predict vaccine efficacy. The mechanism of protective immunity of flavivirus vaccines in humans is not well understood, but available data for currently licensed flavivirus vaccines indicates that neutralizing antibodies is the surrogate for protection. Indeed, passive protection studies in animal models have shown that ex vivo neutralizing

antibody titers of 10 or more fully protected mice from virus challenge for Japanese encephalitis and tick-borne encephalitis vaccines.

The question remains whether neutralizing antibody is an immune correlate of protection for ZIKV. A clear methodology for comparing neutralization titer data is needed. A standardized, validated assay would be critical to quantitate neutralizing antibodies preferably in international units. Reference reagents would facilitate this work, or at least permit comparative studies between laboratories. Data from ZIKV vaccine studies in mice and NHPs show that the results are qualitatively like those of licensed flavivirus vaccines. Neutralizing antibodies appear to be protective, and immunity does not appear to be sterilizing based on the existence of an anamnestic response. Although current ZIKV animal models (e.g., NHPs, immunocompetent and immunocompromised mice) share some but not all of the characteristics of human disease, they likely will be useful in defining a correlate of protection as human vaccine data become available.

Studies to Understand the Role of Preexisting Flavivirus Immunity/Disease Enhancement

Antibody Enhancement of Flaviviruses: Poorly Understood and Often Misconstrued

Aravinda de Silva, University of North Carolina, Chapel Hill School of Medicine, United States

Most flavivirus researchers believe the presence of preexisting dengue-specific antibodies from a primary infection enhances the severity of secondary DENV infection and disease. However, most secondary infections are mild. Some researchers outside of this research field believe that secondary DENV infections almost certainly lead to severe disease. These conflicting viewpoints stem largely from improper interpretations of the *in vitro* assays that measure antibody-dependent enhancement (ADE) of flavivirus infections. A major challenge with the current ADE assays is antibody binding promiscuity. Cross-reactive antibody binding of various DENV serotypes or other flaviviruses hampers the specificity to DENV. Several recent *in vitro* studies demonstrate ADE of ZIKV infection by DENV antibodies, suggesting a potential role for DENV antibodies in ZIKV pathogenesis; however, there are many limitations in the interpretation and clinical relevance of these *in vitro* studies. Studies that link assay results to previous epidemiological research findings are necessary to understand and predict disease severity. Additional research priorities include novel assay development based on more relevant Fc receptor-bearing cells (i.e., primary human cell lines) and animal models using humanized mice and NHPs.

“Enhanced” Zika Virus Infections: Plausibility and the Data

Stephen J. Thomas, State University of New York Upstate Medical University, United States

No consensus definition of what constitutes “enhancement” exists. The conflicting perspectives among researchers are based largely on the different epidemiological observations and results from *in vitro*, *in vivo*, and clinical studies.

This inconsistency has affected our understanding of the relationship between enhancement and ZIKV disease, which creates challenges for studying the effect of preexisting immunity on the immunological and clinical response to ZIKV infection. When assessing the baseline plausibility of DENV-mediated enhancement of ZIKV, the similarities of other flaviviruses (e.g., Japanese encephalitis, West Nile virus) to ZIKV must be considered. Understanding the link between ADE and ZIKV has focused mainly on in vitro approaches. Several laboratory findings show that DENV serologic cross-reactivity drives enhanced ZIKV replication in vitro, and ADE has been proposed as the mechanism. Based on these results, it is plausible that vaccination against DENV might promote ADE of ZIKV infection. Conversely, vaccination of DENV-naïve subjects with ZIKV vaccine may promote ADE of DENV infection. In vivo studies demonstrated that cross-reactive mAbs to ZIKV can induce lethal DENV infection in small animal models. Studies in NHPs demonstrate that prior DENV immunity does not enhance ZIKV infection. It was concluded that little correlation exists between DENV-mediated ADE of ZIKV in vitro and enhancement of ZIKV disease in vivo, analogous to our understanding of other non-dengue flaviviruses. Therefore, DENV-associated immune enhancement is likely unique to the four dengue serotypes. Nevertheless, further clinical studies are important to rule out enhancement and corresponding immunology and clinical pathology. Prospective studies aligning preexisting immune profiles with infection and associated clinical outcomes will provide greater insight into ZIKV pathogenesis and any possible role of enhancement.

Regulatory Considerations

Clinical Development and Pathways for Licensure, Emergency Use Authorization, and Expanded Access

Marion Gruber, FDA, United States

The clinical development to support licensure of a Zika vaccine candidate will be influenced by several factors including the characteristics of the vaccine, available nonclinical and clinical data, the proposed indication, the target population and the availability of an immune correlate of protection or a surrogate endpoint reasonably likely to predict clinical benefit. For the U.S. Food and Drug Administration, licensure pathways for Zika vaccines include “traditional approval,” accelerated approval, and “animal rule” approval, and the choice of pathway may differ for each vaccine candidate. The requirements for Chemistry, Manufacturing, and Controls (CMC) information and safety data do not differ among the licensure pathways; however, there are different approaches to demonstrate effectiveness. Under FDA’s “traditional approval” pathway, demonstration of vaccine effectiveness is based on a clinical disease endpoint or a well-established correlate of protection. In the case of ZIKV disease, there is no scientifically well-established correlate of protection. Thus, currently, if the traditional approval pathway is considered for a Zika vaccine candidate, demonstration of effectiveness would be based on either a clinical disease and/or prevention of infection endpoint(s). Products for serious or life-threatening illnesses providing meaningful benefit over existing treatments can be approved under the accelerated approval provisions ([21 CFR 601.40/41](#)).

For a Zika vaccine, approval under these provisions would be based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immune response, prevention of infection) that is reasonably likely to predict clinical benefit. The surrogate endpoint could be derived from human studies or be an immune marker identified in vaccinated non-human primates that correlates with protection from Zika challenge. Approval under the “animal rule” ([21 CFR 601.90/91/92](#)) may be considered for products for certain serious or life-threatening conditions when human efficacy studies are not ethical or feasible. This pathway is appropriate only when traditional approval or the accelerated approval provisions cannot be used. Licensure of vaccines using this provision would be based on adequate and well-controlled animal studies establishing that the vaccine is reasonably likely to produce clinical benefit in humans. Both accelerated approval and “animal rule” approval would require post-licensure studies to verify and describe the clinical benefit of the vaccine.

In a public health emergency, individuals at high risk may be given access to investigational Zika vaccines under an investigational new drug (IND) clinical study ([21 CFR part 312](#)). Investigational Zika vaccines may also be made available under FDA’s “expanded access” provisions under an IND with informed consent provided certain regulatory requirements are met ([21 CFR 312 Subpart I](#)). Emergency Use Access (EUA) can also potentially be used to make an investigational Zika vaccine available in the case of certain public health emergencies, provided certain criteria are met.

Regulatory Aspects of the Nonclinical Safety Assessment of Preventive Vaccines

Kirk Prutzman, FDA, United States

The FDA Center for Biologics Evaluation and Research’s (CBER) primary objectives when reviewing an IND submission are the safety and rights of trial volunteers during all development phases and during Phase 2 and Phase 3 clinical trials to help ensure the study design will permit an adequate evaluation of effectiveness and safety. Under the IND regulations, sufficient CMC information describing the vaccine formulation to be evaluated in clinical trials must be provided. In addition, adequate information about pharmacological and toxicological studies of the drug, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations, must be provided before initiating the first study participant in a clinical trial. Potential safety concerns exist for certain ZIKV vaccines: neurotoxicity, prolonged infection (live-attenuated virus vaccine), risks during pregnancy, and disease enhancement of other flavivirus infections. Immunologically responsive animal models should be used for toxicology studies; one small animal species is typically sufficient. Toxicology study designs should consider the vaccine dose, frequency and route of administration, delivery device (if necessary and feasible), appropriate control groups, and in-life and terminal procedures. A sponsor should demonstrate vaccine safety in a developmental toxicology study before conducting a clinical trial of a ZIKV vaccine in pregnant women and prior to licensure of a ZIKV vaccine that is indicated for use in women of childbearing potential. CBER recommends that sponsors request a Pre-IND meeting with CBER prior to submitting their IND to obtain early regulatory advice to facilitate product development.

Panel Discussion With Regulators

Regulatory agency representatives from Germany's Paul Ehrlich Institute, Colombia's Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), Brazil's Agência Nacional de Vigilância Sanitária (ANVISA), and the U.S. FDA discussed the regulatory guidelines for ZIKV and DENV vaccine development. In Colombia's regulatory system, vaccines are included in the National Immunization Program only after WHO's recommendation. Germany's system of licensure is within the European Union regulatory framework and allows the licensure and use of a vaccine through different pathways and processes. Regarding the development of ZIKV vaccine, ANVISA has concerns about better understanding ADE and cross-reactivity, especially considering the co-circulation of dengue and yellow fever in Brazil. ANVISA and FDA co-signed a specific protocol to support and expedite the regulatory processes for Zika (Development of Vaccine and Therapeutics to Zika: Development of Diagnostic Tests).

SESSION 4: EFFICACY EVALUATION

Tailoring Trial Designs to Zika Clinical and Epidemiological Characteristics

A Research and Development Blueprint for Action to Prevent Epidemics

Ana Maria Henao-Restrepo, WHO, Switzerland

The [WHO R&D Blueprint](#) is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. Its aim is to fast-track the availability of effective diagnostic tests, vaccines and medicines that can be used to save lives and avert a large-scale public health crisis. WHO member states welcomed the development of the Blueprint at the World Health Assembly in May 2016. The R&D Blueprint builds on the efforts of international partners and communities. The first exploratory meeting co-hosted by Chatham House, the Wellcome Trust and WHO brought together key stakeholders in global R&D in November 2016. The participants reached consensus on the need to establish a Global Coordination Mechanism (GCM) and that WHO – through the Blueprint – should take the lead on creating this mechanism. In December 2016, the Blueprint team joined with subject matter experts to refine its original pathogen prioritization methodology. It published the methodology and updated the priority list in January 2017. An R&D roadmap for MERS-CoV has already been completed and published. Efforts are currently underway to develop roadmaps for Crimean-Congo hemorrhagic fever and Lassa fever.

TPPs have been finalized for the following: Ebola vaccines (outbreak response and long-term protection), Zika vaccine (for emergencies), Ebola diagnostics, Zika diagnostics, and MERS-CoV vaccine. TPPs are under development for Lassa fever vaccines and Nipah vaccines. Work has begun to define regulatory pathways for clinical trial approval and emergency use, including an update of the Emergency Use Assessment and Listing (EUAL) procedure.

WHO held a consultation to advance the development of data sharing norms in the context of public health emergencies, and the International Committee of Medical Journal Editors changed its guidelines to start publishing in real time new research and development data and evidence during public health emergencies to facilitate collaboration. A web-based tool is being developed to facilitate the use of Material Transfer Agreements for sample sharing. Work is underway with three expert groups on methodological issues, a decision-making tool and annotated protocols for Phase 3 vaccine trials for the Blueprint priority diseases. A future phase of this work will focus on efficacy trial protocols for therapeutics. The current lack of R&D preparedness is a problem that can be solved through effective collaborations. Working together with international entities will improve the current actions to prevent epidemics.

R&D Blueprint for Action to Prevent Epidemics: Case Study on ZIKV Vaccine Clinical Trial Design

Momodou Jasseh, Medical Research Council, Gambia

The general scope of the WHO R&D Blueprint involves nine WHO priority pathogens (including ZIKV) with potential to create epidemics (currently no effective and licensed therapeutics or vaccines). Since developing a work plan to facilitate design, implementation, and analysis of Phase 3 vaccine efficacy trials for all nine diseases proved challenging, four workgroups were formed to address particular aspects of the Blueprint: 1) major study designs, 2) a decision tree to guide trial design, 3) a trial simulator, and 4) generic protocols. This work is in progress, and future consultation meetings are planned.

Steven Bellan, University of Georgia, United States

For the purpose of designing vaccine efficacy trials, a decision-tree user interface was developed under the Blueprint. A decision tree provides a “bird’s eye” view of different trial designs to facilitate structured dialogue for stakeholders. A user-friendly web-based interface allows note taking, discussion, trial planning, and training. The decision tree consists of four sub-trees—target population, endpoint, randomization, and comparator. The purpose of these decision trees is to provide a pathway of decisions for vaccine clinical trials. Future work will improve the user interface design and refine the user survey/guidance content.

Ira Longini, University of Florida, United States

One of the four workgroups aims to assess Phase 2b and Phase 3 ZIKV vaccine clinical trial design options. The NIH, CDC, and WHO have ongoing efforts to predict where clinical trial sites should be located to capture sufficient Zika transmission. The selection of sites for ZIKV clinical trials emphasizes areas likely to have ZIKV transmission in 2017–2018. The goal is to establish multiple sites, find subpopulations for randomized vaccination within these sites, and assess predefined versus responsive vaccination.

Zika Vaccine Development Considering Endpoints

Stephen J. Thomas, State University of New York Upstate Medical University, United States

The goals for ZIKV vaccine development include reducing the burden of clinical outcomes (i.e., GBS, CZS), generating herd immunity, interrupting ZIKV transmission, and restoring normalcy to communities. In the context of vaccine clinical trials, efficacy is calculated from the relative risk of an endpoint among the vaccinated group compared with the unvaccinated control group. Efficacy endpoints to consider include infection, mild disease, severe disease, or a known correlate of protection. Secondary or supplemental endpoints could involve measuring reduction of viremia or RNAemia, attenuation of disease, or the performance of a vaccine against an established correlate of protection.

Understanding the occurrence and frequency of the various clinical outcomes is essential to developing an informed sample size. With regard to ZIKV and GBS, measuring rare outcomes will require large sample sizes and may be diagnostically complex and resource intensive. The selected clinical trial endpoints will affect all aspects of clinical trial planning, execution, data collection, and analyses, as well as the likelihood of being able to determine vaccine efficacy. Early vaccine clinical trials should be designed to extract maximum scientific value, allowing for detailed forensic analysis of positive or negative outcomes.

Current Experiences and Future Plans: Human Challenge Trials

Opportunities and Challenges for ZIKV Controlled Human Infection Model (CHIM)

Anna Durbin, Johns Hopkins Bloomberg School of Public Health, United States

The controlled human infection model (CHIM) can be used to down-select candidate vaccines or therapies, evaluate the ability of a vaccine to induce sterilizing immunity, and assess durability and efficacy. In addition, CHIM may be useful to characterize infection in humans, provide data for the development of public health guidelines, and characterize the effect of preexisting flavivirus antibody on ZIKV pathogenesis. Designing a CHIM requires a thorough risk-to-benefit ratio assessment. The risks of ZIKV infection are the illness itself, CZS, GBS, and the transmission of the virus. *Aedes aegypti* mosquitos are the primary species involved in vector transmission. To date, 38 cases of sexual transmission in the continental United States have been reported by the CDC.

A retrospective case-controlled study of a ZIKV outbreak in 2014 in French Polynesia was the first study linking GBS to ZIKV, but it was heavily critiqued for inconsistencies in the case and control groups. In February 2016, the Puerto Rico Department of Health and the CDC implemented the Guillain-Barré Syndrome Passive Surveillance System. Thus far, the number of reports of persons with suspected GBS and evidence of ZIKV has been more than twice the number reported with GBS and no evidence of ZIKV infection. Risk mitigation in ZIKV CHIM will be addressed at the participant level where pregnancy would be exclusionary, education of subjects will be a requirement, and age restriction will limit the risk of GBS occurrences. This as well as other risk mitigation strategies would allow the study to proceed in a safe and ethical manner.

Ethical Considerations on Human Challenge Studies: Report From a Consultation

Seema Shah, University of Washington and Seattle Children's Research Institute, United States

The serious public health threat from ZIKV resulted in NIAID receiving a proposal to develop a human challenge model for ZIKV. Although human challenge models expose healthy volunteers to an infectious disease, conducting safe infection challenge research is a powerful tool for testing various therapeutic and vaccine candidates for infectious diseases rapidly, rigorously, and effectively. Recognizing the inherent uncertainty in conducting a ZIKV human challenge study and the ethical issues it presents, NIAID and the Walter Reed Army Institute of Research (WRAIR) convened a 1-day consultation. The charge to the consultation was to discuss the ethical issues associated with conducting a ZIKV human challenge trial and the conditions that would potentially warrant this type of study. Topics discussed included the state-of-the-science on ZIKV, clinical perspectives, global epidemiological perspectives, ZIKV vaccine candidates, extrapolation from animal models, and the development of an ethical framework for human challenge studies. After reviewing the ethics literature on previous challenge studies, and hearing presentations on the latest science on ZIKV, an independent writing group is preparing a report and recommendations. The report will be made available to the public in late [January/early February 2017](#).

Zika Virus Vaccine Development: (Some) Ethical Considerations

Abha Saxena, WHO, Switzerland

The ethical principles are the same for development of all vaccines and include social value, beneficence and nonmaleficence, respect for persons, and justice. The Council for International Organizations of Medical Sciences has had a significant role in establishing ethical guidelines, and its updated *International Ethical Guidelines for Health-Related Research Involving Humans* will soon be released. The ethical considerations regarding the ZIKV infection preventative measures undoubtedly involve vaccine development, but also disease surveillance and laboratory evaluation, vector control, resource allocation, and studies involving pregnant women and children. Reaching beyond research participation, there also is a strong need to agree on priority research questions and TPPs. Rapid data sharing and the availability of reference materials to the community will be essential. Efforts should focus on identifying which vaccine candidates to accelerate in the validation process, developing an international database and tissue biorepository, engaging host country researchers as equal partners, and strengthening the internal capacities of prospective countries.

Ethics review teams can assist in the timely initiation of research studies by fast-tracking the review of research protocols, which may require establishing a special review or advisory committee under the WHO. Human challenge studies are not necessarily different from Phase 1 studies with regard to risk, but by design they contrast with the traditional role of the health system to improve the health of the sick. Mitigating risk when conducting these studies extends beyond informed consent and Institutional Review Board approvals. This points to the necessity to establish an upper limit of acceptable risk, and affected populations should be included in defining that upper limit.

Current Experiences and Future Plans: Phase 2b/Phase 3 Clinical Trials

Vaccine Research Center (VRC) Zika Vaccine Clinical Development

Julie Ledgerwood, NIAID, NIH, United States

The NIAID Vaccine Research Center (VRC) began work on a ZIKV DNA vaccine in 2015 and leveraged the design of a West Nile virus vaccine candidate made previously to guide its efforts. Two DNA vaccine candidates expressing the prM and E proteins were developed and were shown to be immunogenic in challenge studies conducted in mice and NHPs; both candidates protect NHPs from ZIKV challenge. Phase 1 clinical trial testing of the first candidate, VRC5288, opened in August 2016 and enrolled patients at three sites: NIH, the University of Maryland at Baltimore, and Emory University. A Phase 1 clinical trial of the second candidate, VRC5283, opened to accrual in December 2016 at the NIH. The goals of the VRC efficacy trial is to evaluate a safe and potentially protective vaccine candidate for efficacy against the current outbreak, demonstrate the safety and immunogenicity in endemic populations, show evidence of efficacy against virologically confirmed clinical Zika infection, and define the immunological correlates of protection. A Phase 2/2b randomized trial to evaluate the safety and efficacy of the Zika DNA vaccine candidate VRC 5283, is being planned. The study population will consist of healthy, nonpregnant volunteers ages 15–35 with no history of Zika infection, and the study will be designed to detect a vaccine efficacy of 50 percent or greater. Using traditional surveillance procedures and different modeling approaches, researchers hope to identify areas with substantial ZIKV transmission for this study. The trial activities and responsibilities are led by VRC and are shared between several divisions within NIAID, other governmental agencies, and contract research organization partners.

Update on the Sanofi Pasteur Zika Vaccine Program

Fernando Noriega, Sanofi Pasteur, United States

In February 2016, Sanofi Pasteur announced that it would commence activities to develop a ZIKV vaccine. In September 2016, Sanofi Pasteur established agreements with WRAIR to evaluate its Zika purified inactivated vaccine (ZPIV) candidate with funding from BARDA. Anticipating favorable results from the completion of WRAIR Phase 1 trials, Sanofi Pasteur will embark on a clinical development plan for the ZPIV to include a seamless Phase 2/3 adaptive design trial. Stage A/B aims to reduce the time to ZPIV registration. Stage A is an age de-escalation safety and immunological study that will be conducted in one to two countries/territories in Latin America with Zika endemic activity. Stage B is a case-driven efficacy assessment that will incorporate the remaining countries where Sanofi Pasteur has sites testing a dengue vaccine. Trial assumptions include an incidence of 0.65 percent and 1 percent seroprevalence of Zika infection. The advantages of a seamless, adaptive trial design for a Zika vaccine candidate include less downtime from tandem regulatory cycles by adopting a timeline optimization of the first protocol approval regulatory cycle.

Efficacy Evaluation of ZIKV mRNA Vaccine Candidate

Mike Watson, Valera, United States

A Phase 1 study investigating the ZIKV mRNA vaccine candidate began enrollment in December 2016. Preparation and planning for Phase 2/3 clinical trials of vaccine safety and efficacy have embedded overarching assumptions that innovation will be infused in the product and processes and that regulatory authorities will be flexible with multi-party dialogue. Matching study locations with outbreaks, predictive modeling, pre-established trial sites, ethics and regulatory approvals, and flexible/agile capabilities are key requirements. The study populations are of two types: non-endemic/non-epidemic (e.g., United States) and endemic/epidemic (e.g., Latin America). The challenge lies in establishing study endpoints that are representative of the population. In designing Phase 2/3 clinical trials, it is important to understand what immunological correlates of efficacy can be leveraged from prior flavivirus challenge studies. Additionally, it is important to consider how well the clinical outcome (e.g., pregnancy outcome) correlates to symptoms of ZIKV, whether reduction/prevention of viremia is an achievable goal, and to define clear clinical endpoints. A surrogate endpoint (e.g., neutralizing antibody titers) that is likely to predict clinical benefit is one type of endpoint that can be used for an accelerated approval. Study sizes will range from the hundreds for immunogenicity studies where there is no incidence of ZIKV, to thousands for efficacy studies with an assumed 1 percent to 6 percent ZIKV incidence. As the research community advances in establishing high neutralizing antibody titers and preventing viruria and virospemia, the ethics for continuing to conduct placebo-controlled studies of CZS endpoints will need to be addressed.

Roundtable of Vaccine Developers

Panelists were asked to provide an update of promising candidate vaccines from their respective companies, data, current clinical trials, and planned studies.

Takeda Pharmaceutical Company, in collaboration with BARDA, is developing a whole virus inactivated vaccine candidate, which is in preclinical development with clinical trials expected to begin in 2017. Subjects will be screened for antibody status. The overall vaccine development plan is still in draft form. Issues to be addressed include the choice of endpoints, location of clinical trial sites, developing surrogate markers of protection, and developing ZIKV-specific immune assays to discriminate ZIKV from cross-reactive responses.

Inovio Pharmaceuticals has partnered with GeneOne Life Sciences to co-develop a prM-Env synthetic DNA Zika vaccine, GLS-5700. A single immunization of GS-5700 vaccination protected mice from death, lowered viral load, and preserved brain and testicular tissue. Additionally, a single intradermal dose of GS-5700 protected against viremia in NHPs. Preliminary data from the Phase 1 clinical trial reveal a dose-related serologic response that was observable at 4 weeks.

Instituto Butantan in Brazil, in collaboration with BARDA, is developing a live-attenuated Zika vaccine. The clinical development plan is being formulated. It is challenging to test vaccine candidates in an endemic region such as Brazil. Plans include discussions with the NIH on the feasibility of developing a live-attenuated Zika-dengue chimeric pentavalent virus vaccine. Future plans use current infrastructure and leverage existing dengue epidemiological data to accelerate clinical evaluations of Zika vaccine candidates.

WHO tracks the Zika vaccine pipeline here:

http://www.who.int/immunization/research/clinicaltrials_newvaccinepipeline/en/

WRAP-UP AND CLOSING

Report-Backs from Session Chairs

The session chairs reported on the highlights of the 2-day meeting. During Session 1, participants engaged in discussions on Zika epidemiology and vaccine efforts in small and large populations. Experts concluded that ZIKV transmission is heterogeneous within regions. The technology also may not be sufficient to determine the state and rate of transmission worldwide, nor is the technology available to precisely predict new outbreaks. This information is important for selecting potential sites for future clinical trials.

Discussants presented two views on the future of Zika epidemics: (1) per modeling, the current epidemic will run its course in 3-4 years and will see long intervals (e.g., 10-20 years) before the next large outbreaks occur in the same areas; and (2) small, granular, and sporadic outbreaks are likely to continue in the interim. Some key conclusions and areas for future research include:

- extend and expand on prior DENV studies and leverage existing cohort data to improve our understanding on ZIKV;
- the severity of CZS and GBS warrants vaccine development;
- the ability to differentiate between vaccine-induced and natural infection immune responses;
- the need to generate data using validated tests; and
- coordinate vaccine development and testing sites.

During Session 2, discussions focused on detecting ZIKV infection and immunological responses. The issue of flavivirus cross-reactivity was noted in B-cell and antibody responses, as well as T-cell immunity. The DENV CD4/CD8 responses differ from those of ZIKV, and epitope mapping suggested differences in the T-cell targets of DENV and ZIKV. Significant progress has been achieved in the diagnostic tools for assessing ZIKV infection and efforts are ongoing to develop and validate new immunoassays, including assays for evaluating sexual transmission of ZIKV. The importance of reference reagents and the development of an international reference standard for ZIKV vaccine-related assays was noted.

Session 3 included a review of current animal models for ZIKV infection, with a focus on mouse and NHP models. Current vaccine strategies were reviewed, including protective efficacy and adoptive transfer studies in both mice and monkeys. Preclinical data with DNA vaccines, PIV vaccines, and Ad vectored vaccines were discussed. Immune correlates for other flavivirus vaccines were also presented. While it was agreed that the evidence points to a neutralizing antibody correlate of protection, it was debated whether the protective titer was higher for ZIKV than for other flaviviruses. The possibility of ADE for ZIKV was also discussed, and the consensus was that data to date suggest that this is primarily an *in vitro* phenomenon, and possibly in mice. Nonhuman primate data and human epidemiologic studies show no obvious evidence to date. Regulatory aspects of Zika vaccine clinical development and licensure were also discussed with attention focused on the complexities of testing and licensing vaccine candidates in women of childbearing age and pregnant women.

Session 4 began with discussions on the WHO's Global R&D Blueprint for action to prevent epidemics and its application to ZIKV. It is unlikely that a single efficacy trial design would suffice for all nine WHO priority pathogens. Therefore, tools, such as decision trees, that identify options for development of vaccines and other countermeasures are important to accelerate efficacy evaluation plans. In the case of ZIKV, clinical endpoints include infection, clinical disease, and, possibly, congenital infection. The use of CHIM to down-select candidate vaccines in early clinical development and to answer key scientific questions in humans was presented as a potential option; however, ethical assessments of ZIKV human challenge trials are pending. A key point that will drive vaccine research will be the predictability of future ZIKV outbreaks. The proposed accelerated, adaptive clinical trial design will likely emerge as a primary approach for safety evaluation of potential Zika vaccine candidates.

Closing

NIAID and WHO leadership thanked participants for participating in this consultation on ZIKV vaccine development. The need for international coordination of study sites was a cross-cutting theme of the 2-day meeting, and such coordination could be done under the umbrella of the Global R&D Blueprint. While significant progress has been made in ZIKV research resulting in the development of several innovative vaccine candidates, additional research is needed on ZIKV epidemiology, pathogenesis, Zika disease and its complications, as well as improved immunoassays and animal models.

WHO & NIAID Scientific Consultation on Zika Virus Vaccine Development

10 & 11th January 2017

NIAID facility at 5601 Fishers Lane in Rockville, MD

Day 1: Tuesday, 10 January 2017

Time	Title	Presenter
8:00-8:30	Welcome and opening statements	Anthony S. Fauci, NIAID, NIH Marie-Paule Kieny, WHO-HQ
Session 1: Zika epidemiology and vaccine efforts Co-chairs: Laura Rodrigues and Eva Harris		
8:30-9:15	Dynamics of Zika 1. Data from Brazil and the Pacific Islands, 15 min. 2. Data from other countries in the Americas, 15 min. 3. Data from Singapore/Asia, 15min.	Laura Rodrigues, LSHTM and MERG Sylvain Aldighieri, PAHO Leo Yee Sin, Institute of Infectious Disease and Epidemiology, Communicable Disease Centre
9:15-10:00	Congenital Zika Syndrome and Guillain-Barre Syndrome 4. Congenital Zika Syndrome as relevant for vaccine efforts, 15 min. 5. GBS as relevant for adverse events of vaccination, 15 min. 6. Discussion, 15 min.	Demócrito de Barros Miranda-Filho, University of Pernambuco, Recife, Brazil Carlos Pardo, Johns Hopkins School of Medicine, Baltimore
10:00-10:30	Tea break	
10:30-11:00	Sero-epidemiology and Modelling 7. The interplay between immunology and epidemiology, 15 min. 8. Predicting the future of the epidemic using mathematical models, 15 min.	Eva Harris, School of Public Health, University of California, Berkeley Neil Ferguson, Imperial College
11:00-12:30	Vaccine Efforts 9. Public health performance characteristics for vaccines, 15 min. 10. Zika vaccine opportunities and challenges: a developer's perspective, 15 min. 11. Zika vaccine pipeline overview, 15 min. 12. Discussion, 45 min.	David Kaslow, PATH Thomas Monath, NewLink Genetics Armen Donabedian, BARDA
12:30-13:30	Lunch break	

Day 1, continued

Time	Title	Presenter
Session 2: Detecting Zika virus infection and immunological responses Co-chairs: Aravinda de Silva and Philip Minor		
13:30-14:00	What do we know about the human immune response to ZIKV infection and detecting by PCR? 13. B-cell and Ab responses to ZIKV infection, 15 min. 14. T-cell immunity to ZIKV, 15 min.	 Gavin Screaton, Imperial College London Alessandro Sette, La Jolla Institute for Allergy and Immunology
14:00-15:25	The status of PCR and serology assay development 15. The status of PCR assays as infection endpoints, 15 min. 16. The status of ELISA development for vaccine development, 15 min. 17. NS1 serological assays, 15 min. 18. The status of neutralizing antibody assay development, 20 min. 19. Discussion, 20 min.	 Uwe Scherf, US FDA Jane Basile, US CDC Eva Harris, School of Public Health, University of California, Berkeley Ted Pierson, US NIH
15:25-15:45	Tea break	
15:45-17:00	Development of reference reagents, and considerations for assay validation 20. Development of an international reference standard for ZIKV vaccine development, 10 min. 21. Development of other reference materials, 10 min. 22. Perspectives from industry, 10 min. 23. Perspectives from regulators, 10 min. 24. Panel discussion, 35 min.	 Mark Page, NIBSC Cristina Cassetti, US NIH Hansi J. Dean, Takeda Yuansheng Sun, PEI Hansi Dean (Takeda), Yuansheng Sun (PEI), Jon Heinrichs (Sanofi Pasteur), Nikos Vasilakis (UTMB), Mark Page (NIBSC), and Cristina Cassetti (NIH)
17:00	End of Day 1	

Day 2: Wednesday, 11 January 2017

Time	Title	Presenter
Session 3: Animal models Co-chairs: Stephen Thomas and Dan Barouch		
8:30-9:20	Overview of animal models for Zika pathogenesis 25. Review of small animal development, 20 min. 26. Review of large animal development, 20 min. 27. Discussion, 10 min.	Michael Diamond, Washington University David O'Connor, University of Wisconsin
9:20-10:10	Opportunities for efficacy and correlates of protection using animal models 28. Preclinical vaccine efficacy studies, 15 min. 29. Correlates of protection studies, 20 min. 30. Discussion, 15 min.	Dan Barouch, Harvard Medical School Alan Barrett, UTMB
10:10-10:40	Tea break	
10:40-11:00	Studies to understand the role of pre-existing flavivirus immunity/disease enhancement 31. The role of pre-existing flavivirus immunity/disease enhancement in Dengue, 10 min. 32. The impact of pre-existing flavivirus immunity/disease enhancement in Zika, 10 min.	Aravinda de Silva, UNC Stephen Thomas, SUNY
11:00-12:20	Regulatory considerations 33. Clinical development pathways for licensure, emergency use authorization, and expanded access, 20 min. 34. Preclinical safety/toxicology studies, 15 min. 35. Panel with regulators, 45 min.	Marion Gruber, US FDA Kirk Prutzman, US FDA Yuansheng Sun (PEI), Flavia Sobral (ANVISA), Francisco Sierra Estaban (INVIMA), and Vasquez Albores (Cofepris)
12:20-13:20	Lunch break	

Day 2, continued

Time	Title	Presenter
Session 4: Efficacy evaluation Co-chairs: David Kaslow and Srilatha Edupuganti		
13:20-14:50	Tailoring trial designs to Zika clinical and epidemiological characteristics 36. R&D Blueprint for action to prevent epidemics, 15 min. 37. R&D Blueprint for action to prevent epidemics: case study on ZIKV vaccine trial design, 30 min. 38. Considerations and practical issues in the selection of clinical trial endpoints, 15 min. 39. Discussion, 30 min.	Ana Maria Henao, WHO-HQ Momodou Jasseh, MRC Gambia Steven Bellan, University of Georgia Ira Longini, University of Florida Stephen Thomas, SUNY
14:50-15:10	Tea break	
15:10-15:55	Current experiences and future plans: human challenge trials 40. Opportunities and challenges for ZIKV human challenge studies, 15 min. 41. Ethical considerations on human challenge studies: report from a consultation, 15 min 42. Invited remarks and facilitated discussion, 15 min	Anna Durbin, Johns Hopkins University Seema Shah, University of Washington Abha Saxena, WHO-HQ
15:55-17:10	Current experiences and future plans: Phase 2b/Phase 3 clinical trials 43. VRC plans for efficacy evaluation, 15 min. 44. Sanofi Pasteur plans for efficacy evaluation, 15 min. 45. Valera plans for efficacy evaluation, 15 min. 46. Round table of vaccine developers, 20 min. 47. Discussion, 10 min.	Julie Ledgerwood, US NIH Fernando Noriega, Sanofi Pasteur Mike Watson, Valera Scott White (GeneOne/Inovio), Alexander Roberto Precioso (Instituto Butantan), and Theodore Tsai (Takeda)
17:10-17:30	Wrap up and closing 48. Report back from Session Chairs, 15 min. 49. Closing, 5 min.	Session 1-4 Co-Chairs
17:30	End of Day 2	

**National Institute of Allergy and Infectious Diseases (NIAID) and
World Health Organization (WHO)**

**Consultation on the Zika Virus Vaccine Development
10-11 January 2017, Rockville, Maryland**

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