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Meeting Report: WHO consultation on considerations for regulatory expectations of Zika virus vaccines for use during an emergency

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ABSTRACT

On 1 February 2016, in the context of the ongoing Zika virus epidemic, the WHO declared that the recently reported clusters of microcephaly and other neurological disorders constituted a Public Health Emergency of International Concern (PHEIC). In response, WHO in collaboration with UNICEF and a working group of independent subject matter experts developed a Zika virus vaccine Target Product Profile (TPP) for use in an emergency, or in a future outbreak scenario. The drafting process of the Zika virus vaccine TPP included the opportunity for public comment, as well as consultation with epidemiologists, flavivirus vaccine subject matter experts, vaccine developers and global regulators to consider the regulatory expectations and potential emergency use pathways for a vaccine with the characteristics described in the TPP. This report summarizes an expert consultation held 6–7 June 2016 on the regulatory considerations for a Zika vaccine for emergency use.

1. Introduction

In February 2016, the World Health Organization (WHO) declared the clusters of microcephaly and other neurological disorders, possibly associated with Zika virus (ZIKV), a Public Health Emergency of International Concern (PHEIC) [1]. Although Zika presents as a mild illness in the majority of those infected, the advice of the declaration was based on the possible association of ZIKV infection and clusters of microcephaly, Guillain-Barré syndrome, and other possible neurological defects [2]. In the months following, the causal relationship with ZIKV infection and birth defects became accepted by the international community [3]. WHO and the broader public health community have prioritized vaccines together with improved diagnostics and innovative vector control strategies for ZIKV research and development [4]. At the time of the PHEIC declaration, ZIKV vaccine candidates had not been evaluated in clinical trials. As of this writing, approximately 30 vaccine candidates are in active preclinical development [5], the first paper evaluating ZIKV vaccine candidates in an animal model was published in June 2016 [6], and the first ZIKV vaccine candidate went into Phase 1 trials in July 2016 (NCT02809443).

While ZIKV vaccine research and development has progressed at a record pace, it is important to define the target population and acceptable product attributes to guide the development of ZIKV vaccine candidates. With this in mind, the Immunization, Vaccines and Biologicals department at the WHO formed a working group to draft a Target Product Profile (TPP) for ZIKV vaccines for use in an emergency context [7]. Following public consultation, the first TPP was finalized and published jointly with UNICEF. It will undergo updates as our knowledge on ZIKV evolves. The provision of appropriate regulatory oversight faces particular challenges when vaccines are being developed on an accelerated schedule in the context of a public health emergency and in the face of significant knowledge gaps. To support development of a vaccine with the characteristics proposed within the TPP, WHO held a consultation on considerations for regulatory expectations of ZIKV vaccines for use during an emergency 6–7 June 2016, in Geneva, Switzerland [8]. The meeting convened regulators, ZIKV vaccine developers, ZIKV/flavivirus vaccine subject matter experts, funders and other stakeholders from affected and non-affected countries. The objectives of the meeting were to discuss considerations with respect to regulatory expectations, based on the current understanding of the natural history of the disease, epidemiology and pathogenicity - and in the context of this, the potential data requirements, regulatory pathways and mechanisms to enable emergency use authorization by national regulatory authorities of a ZIKV vaccine. The TPP and these regulatory considerations for emergency use vaccines remain relevant, as the ZIKV emergency response has been modified into a sustained program of work since the PHEIC was declared over in November 2016.

2. Current status of knowledge about ZIKV with implications for vaccine development

ZIKV is a single-stranded RNA flavivirus. There are two genetic lineages, the African lineage and the Asian lineage, but these are believed to constitute only one serotype (with potentially 3 genotypes), suggesting a monovalent vaccine would be sufficient to offer coverage against all circulating ZIKV strains [9].

Most ZIKV infections (about 75%) are asymptomatic. Those cases that are symptomatic are typically mild with symptoms including low-grade fever, conjunctivitis, joint pain, headache, and a

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maculopapular rash. Although the case fatality rate is low, ZIKV infection can be associated with severe outcomes, in particular Guillain-Barré Syndrome (GBS), as well as other rare CNS pathologies [10,11]. Two mechanisms for GBS are postulated: molecular mimicry between ZIKV and naturally occurring glycolipids on host cells that lead to an autoimmune response to gangliosides; or viral neurotoxicity [12]. The rapid onset of neurological symptoms (in one study, approximately 6 days [10]) after symptoms consistent with ZIKV infection may favour the second hypothesis, but further work is needed to explore these possibilities.

The association between ZIKV infection during pregnancy and congenital neurological abnormalities (now termed congenital Zika syndrome [13]), including microcephaly, is another severe outcome of concern. How risk varies with gestational age at the time of infection is not fully understood, although data suggest the greatest risk in the first trimester [14,15]; the outcomes of fetal infection during the second or third trimester are less clear, although there are reports of immediate adverse outcomes [16] and there is a theoretical possibility of delayed adverse cognitive outcomes that may be initially inapparent. These associations have important consequences with respect to including vaccination of pregnant women as a priority target population and the relative risk to benefit balance of such a strategy, as well as for the acceptable minimum duration of immunity for the vaccine to protect during the entire duration of pregnancy. Furthermore, the relationship between viral load and fetal effects is still not fully understood. It has been hypothesized that adverse fetal effects may be more likely associated with higher viraemia, and thus symptomatic infection; the consequences of asymptomatic infection and virus transmission dynamics are less well understood however a recent case has been reported of ZIKV transmission from an asymptomatic male to his partner who had not visited a ZIKV endemic area [17]. The target population for vaccination will also depend on the relative importance of routes of transmission (e.g. sexual transmission), particularly in the context of limited vaccine supply [18].

Another key issue with implications for vaccine development and emergency use authorization is the interaction of pre-existing flavivirus immunity with neutralization and/or enhancement of ZIKV infection. In Latin America, over 10 flaviviruses co-circulate, including all four dengue virus (DENV) serotypes. Immune enhancement associated with more severe secondary heterologous DENV infections is well accepted [19]. While cross-reactivity has been documented between DENV- and ZIKV-induced antibodies [20], the relevance of sequential or pre-existing flavivirus immunity for subsequent infection and disease is not well understood. Four recent studies showed that anti-DENV human monoclonal antibodies (mAb) as well as DENV immune sera poorly neutralized and instead enhanced ZIKV infection in FcRII-bearing cells [21–24]. Another study found that DENV cross-neutralizing envelope dimer epitope 1 (EDE1) mAb strongly neutralized ZIKV and prevented infection in human monocytic cells as well as Vero cells and protected type I/II interferon receptor-knockout mice from ZIKV-associated morbidity and mortality; however, both convalescent primary and secondary DENV immune sera poorly neutralized ZIKV [25]. While previous DENV infection does not prevent ZIKV infection, the authors posit that a vaccine that elicits EDE1-like antibody could protect against both DENV and ZIKV infection [25]. The potential effects of vaccine-induced antibody may differ from immune responses to natural infection, and a stepwise evaluation of vaccines, starting in flavivirus-naïve subjects, is considered advisable. Clinical data that inform whether there could be any potential enhancement with multiple ZIKV and other flavivirus infections, such as from ongoing cohort studies in affected areas, are needed to reassure vaccine development efforts.

Diagnostics of ZIKV infection using serological assays based on the envelope proteins are challenging due to cross-reactivity with other flaviviruses. However, NS1 antigen-based serological tests tend to be specific for a given flavivirus, and recently a first diagnostic test became available for ZIKV [26]. Further evaluations of the performance of NS1-based serological assays using a broad spectrum of sera from affected countries are needed. Currently diagnostics of ZIKV rely primarily on viral detection using RT-PCR; however, due to transient viraemia, PCR-based diagnostics reliant on viral detection in the blood are limited to about 1 week from the onset of symptoms [27]. Potential viral detection in urine and saliva has shown promising results for the duration of viraemia as well as the sensitivity, and the U.S. Centers for Disease Control and Prevention currently recommend urine be collected and tested up to 2 weeks post-symptom onset [28], consistent with WHO recommendations [29].

ZIKV spread, like chikungunya virus, is highly epidemic, in other words unpredictable, focal, and periodic [30]. This presents a challenge in identifying sites for efficacy trials that would have suitable incidence rates to reasonably calculate efficacy at the time of the trial. It was recently estimated that the current epidemic could be over in 3 years; but future epidemics would be expected in subsequent years (potentially ~10 years) as a susceptible population is re-established [31]. It is currently unknown whether human-to-human endemic transmission could be sustained, or whether a sylvatic cycle will in the future contribute to periodic outbreaks in Latin America, as has been hypothesized for parts of Africa [32].

3. WHO ZIKV vaccine Target Product Profile (TPP)

Following declaration of a PHEIC, WHO initiated the process to develop a TPP for ZIKV vaccines use during an emergency [7]. The TPP describes the preferred and minimal product characteristics for a vaccine targeted to the proposed priority population during outbreak situations. It was initially drafted in consultation with an independent WHO working group of subject matter experts with diverse areas of expertise, and was posted for public comment. The TPP is specifically intended for ZIKV vaccines in the context of an ongoing epidemic or an imminent outbreak of ZIKV. The primary public health objective of vaccination stated in the TPP is the prevention of prenatal ZIKV infection associated microcephaly and other serious brain anomalies in infants. In this context, the vaccine is primarily targeted at women of childbearing age. It is stipulated that other populations, in particular men, may be included in emergency vaccination campaigns if vaccine supply permits. As with all vaccines, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization will advise on vaccination strategies once products reach maturity. The TPP outlines a number of characteristics with implications for regulatory assessment, which were discussed during the meeting.

4. Vaccine development status

There are approximately 30 ZIKV vaccine candidates under development by a range of developers including major pharmaceutical companies, smaller biotech companies, academia, and governmental research institutions, as documented in the WHO online vaccine pipeline tracker [5]. As of this writing, three candidates have U.S. Food and Drug Administration investigational new drug (IND) allowance for human Phase 1 study (NCT02809443, NCT02840487, NCT02963909), including one in an affected area (NCT02887482), and it is anticipated that a number of candidates will move into human trials later in the coming months.

Given the effective monovalent vaccines that have been developed against other flaviviruses (Yellow fever (YF) virus, Japanese encephalitis (JE) virus, and Tick-borne encephalitis (TBE) virus),

the development of a monovalent vaccine against ZIKV is thought to have a favourable probability of technical and regulatory success (PTRS). Vaccine platforms that have worked well for other flavivirus vaccines include live attenuated, live recombinant, and inactivated viral vaccines, but many other platforms have been tested and evaluated in animal models and some in humans, especially for dengue [33]. A recent preclinical challenge study in non-human primates suggests that development of an efficacious ZIKV vaccine is achievable [34].

All vaccine platforms have advantages and limitations to meet the needs of emergency deployment of a vaccine to protect women of child-bearing age (and others). To maximize the chances of success, and acknowledging different potential purposes of various platforms, pursuing all possible approaches was encouraged. Different vaccine technologies may have variable data requirements from a regulatory perspective, depending on the indication, specific construct aspects and existing safety database from previous clinical studies.

4.1. Vaccine platforms

Whole inactivated virus: Many commercial whole inactivated viral vaccines exist (e.g. influenza and polio), including vaccines against flaviviruses (JE and TBE). Inactivated vaccines are frequently the preferred product for special populations (e.g. pregnant or immunocompromised patients). Complete protection was recently demonstrated against detectable viraemia in Balb/c mice and rhesus macaques when challenged 4 weeks post-vaccination with alum-adjuvanted whole inactivated ZIKV vaccine candidate [6,34]. This candidate moved into Phase 1 trials in late 2016. Inactivated vaccines tend to be less immunogenic than their live attenuated counterparts and as such multiple doses or the use of adjuvants, possibly novel, may be required. Multiple doses are not ideal in an emergency situation and use of novel adjuvants would require a more comprehensive data package for evaluation than a well-known adjuvant.

Recombinant-derived subunit immunogen: Although several recombinant vaccines have been licensed, none has been fully developed for a flavivirus. Correct protein conformation is essential for vaccine potency and an adjuvant, such as an aluminium salt, is usually needed. Extensive physicochemical characterization of the vaccine antigen within the formulation (e.g. structure, level of posttranslational modifications, particle size and distribution) would be expected. The same immunogenicity considerations noted for an inactivated vaccine might be encountered by a subunit vaccine, including the need for multiple doses and adjuvants.

Live attenuated (including recombinant heterologous flavivirus-vectored) virus: Several live attenuated vaccines have been licensed and are in widespread use, many requiring only a single dose with long-lasting immunity. Production outputs can be increased with high yields of attenuated virus, which could help meet the public health need of mass preventive campaigns. In addition to the YF 17D vaccine, recombinant live vaccines against two other flaviviruses have been licensed with YF 17D vaccine virus as the backbone (IMOJEV against JE and DENGVAXIA against dengue). However, live attenuated vaccines are typically contraindicated in pregnant women, and in some cases for young children as well, although they have been given to women of child-bearing age (Measles-Mumps-Rubella, YF, polio) in situations of increased risk of exposure, and inadvertent vaccination of pregnant women does occur in mass vaccination campaigns. To date there is no evidence of increased adverse pregnancy outcomes due to immunization with currently licensed live attenuated vaccines [35]. Attenuation frequently involves a balance between safety and immunogenicity: a high level of attenuation might result in a good safety profile, but it could induce a weak immune response; on the other hand, a low level of attenuation may be associated with residual virulence, such as neurovirulence, viraemia, and undesirable side effects alongside a strong immune response. As ZIKV is a neurotropic virus and vaccine may be inadvertently given to pregnant women, the meeting considered that neurovirulence and reproductive toxicology testing are needed prior to approval for emergency use, as is demonstration of mosquito non-competence and genetic stability in production and clinical use. The risk of virus shedding and transmission would need to be addressed pre-approval. If the mechanism of ZIKV-associated GBS is direct viral attack, there could be implications for the design of neurovirulence testing of live attenuated vaccines.

Recombinant heterologous (non-flavivirus) vectored virus: Similar considerations apply for recombinant heterologous viral vectored vaccines as for live attenuated flavivirus-based vaccines, as discussed in the previous section. No non-flavivirus recombinant viral vectored vaccine has been licensed to date. A number of Ebolavirus vaccine candidates are viral vectored (e.g., on adenovirus, vaccinia, or vesicular stomatitis virus (VSV) backbones) and have demonstrated a satisfactory safety profile according to published studies, despite, in some cases, being relatively reactogenic in clinical trial participants [36]. A candidate with ZIKV pre-membrane and envelope (prM-E) expressed in the rhesus adenovirus serotype 52 viral vector recently showed complete protection against viraemia when challenged 4 weeks after vaccination with a single dose [34]. In the case of a viral vector used for other (non-ZIKV) candidate vaccines, the safety database may be supportive to judge the risk of the vector for the approval of clinical trials, but would be insufficient to support licensure.

Nucleic acid (mRNA/DNA): There are no licensed human vaccines based on an mRNA or DNA platform. Although generally found to be well-tolerated, these candidates have not been as immunogenic as other vaccine platforms in humans. There is the theoretical advantage of rapid development and production, and indeed the first ZIKV vaccine candidate to enter clinical development was a DNA-based construct. There may be requirements for new delivery systems or routes of immunization that would require training of personnel, and there is limited experience with commercial scale production. Recent studies found complete protection against viraemia induced by both lineages of ZIKV post-challenge of Balb/c mice and rhesus macaques vaccinated with a DNA candidate expressing full-length ZIKV prM-E, whereas deletion mutants were variably protective in mice [6,34]. E protein-specific antibody titers were higher, as was generation of ZIKV-specific neutralization antibodies, with the full-length prM-E DNA vaccine. High levels of protection against viraemia in rhesus macaques challenged with ZIKV were recently seen with two additional ZIKV/JEV prM-E DNA constructs, in which the prM signal sequence was replaced with the analogous JEV sequence to improve expression [37].

Adjuvants: Immunogenicity of inactivated vaccine candidates, recombinant/subunit candidates, and nucleic acid candidates may be significantly improved by the addition of an adjuvant. Adjuvants are not registered independently but rather as part of a product. Aluminium salts have been used as adjuvants in human vaccines for many years and have an extensive safety record. Other well-known and approved adjuvant systems could also be considered. Use of novel adjuvants would require non-clinical toxicology and safety studies, with a satisfactory human safety database as well.

5. Considerations for regulatory evaluation

5.1. Quality

As for any medical product, the potential for harm to vaccine recipients caused by inadequate control of the manufacturing process and/or insufficient quality control is not acceptable. However,

meeting participants considered that some options to accelerate timelines may be possible. For example, manufacturing scale-up to support product launch could be done at risk in parallel to the early stages of clinical development, prior to an indication of vaccine safety and immunogenicity. This strategy enables earlier characterization testing of the clinical trial materials that will be used in late-stage clinical evaluation, in parallel to phase 1/2 clinical testing. Characterization tests that take several months, such as real time stability studies, neurovirulence (depending on vaccine platform) and reproductive toxicology testing, are anticipated to be necessary even for emergency use, and the timeline for these must be considered early to avoid delaying authorization. Another option for emergency use approval is that the evaluation of three commercial-scale consistency batches within the late-stage clinical evaluation studies could be reconsidered; if data on only 1 or 2 batches were needed this could significantly reduce the timeline to vaccine availability. Data on the remaining consistency batches could be generated subsequent to emergency approval to support vaccine licensure; however, potency models and assays should be validated prior to late-stage clinical evaluation as recommended by ICH guidelines.

The current TPP requests stability for at least up to 6 months at 2–8 °C as a minimal requirement although additional data to support storage and use over longer periods and at higher temperature are preferred. Six months is considered the minimal time required to release, package and deliver the vaccine to the point of use, although this will be logistically challenging and so a 6-month shelf-life will risk vaccine doses being discarded. Accelerated stability data at elevated temperatures can be indicative of stability at 2–8 °C beyond 6 months, and would de-risk the use of a vaccine with such a limited real-time stability profile. It was agreed that −20 °C storage is difficult to sustain in the environments in which a ZIKV vaccine might be needed for emergency use and would not be applicable to an alum-adjuvanted vaccine.

5.2. Non-clinical studies and proof-of-concept models

A relevant animal model that recapitulates human pathogenesis and effects on fetal development following ZIKV infection will help to elucidate the underlying mechanisms of disease, and demonstrate vaccine proof-of-concept. In recent months there have been significant advances in the development of preclinical models for ZIKV virus infection, including models of congenital infection.

ZIKV has been shown to be lethal in immunocompromised mice deficient in either IFN-α/β receptors or both IFN-α/β and IFN-γ receptors [38–40] and recently the Asian ZIKV strain SZ01 was shown to replicate efficiently in embryonic in E13.5 ICR mouse brains by directly targeting different neuronal lineages [41]. An in utero transmission model of infection has been established in which ZIKV infects placental cells and results in intrauterine growth restriction [42]. Furthermore, Cugola et al. demonstrated that a 2015 Brazilian strain of ZIKV is able to infect foetuses, causing intrauterine growth restriction, including signs of microcephaly, in mice [43].

Rhesus macaques may be a more relevant model for infection and transmission in the immunocompetent state, and infection with the Asian lineage resulted in detection of ZIKV RNA in plasma, saliva, urine and cerebrospinal fluid at one day post infection in 8 animals, 2 of which were pregnant [44]. Viraemia remained for 21 days in non-pregnant animals, and 57 days in pregnant animals. Detectable virus was not found in any animals following re-challenge at 10 weeks, indicative of acquired protective immunity against homologous strains. Recently, three vaccine candidates were successfully evaluated in rhesus macaques [34]. The model also allows to study the effect of pre-existing immunity against heterologous flaviviruses, such as dengue.

Passive transfer studies in mice have been used to substantiate measures of protection for other flavivirus vaccines [45], and recently adoptive transfer of purified IgG from mice vaccinated with a ZIKV plasmid DNA vaccine conferred passive protection [6]. Protection against viraemia post-challenge by adoptive transfer studies was again demonstrated for an inactivated ZIKV vaccine in mice and rhesus macaques [34].

Given the targeted age group of women of child-bearing age, reproductive toxicology studies will be needed to inform on potential risks to women who are inadvertently vaccinated in early stages of pregnancy, even in the case of the emergency use scenario where the vaccine is not explicitly targeted to pregnant women. Such studies would need to be completed ideally prior to late-stage clinical evaluation and would be required for all vaccine platforms. Early engagement between developers and regulators is needed to agree on an appropriate non-clinical model and study design. Given that ZIKV infection is associated with teratogenic effects in humans, the availability of a validated non-clinical animal model able to measure these effects could be a significant advantage on the pathway to licensure. Such nonclinical models are in early development and appear promising. Neurovirulence testing would be important for all vaccine platforms using replicating viruses; in contrast, recombinant protein-based or non-replicating vaccines may not require neurovirulence testing.

From a regulatory perspective, preclinical challenge studies are not required for Phase 1 trial approval; that said, preclinical studies that provided evidence of safety and immunogenicity would be required. It was acknowledged that for funders and developers evidence of preclinical proof-of-concept might be set as a potential stage gate to inform candidate selection. If available, these data would then be of interest for the regulators. Part of the rationale for not requiring preclinical challenge data before staring clinical trials is that the disease animal models for ZIKV disease are still being developed and characterized, and protection against viraemia is an imperfect proxy for protection against disease in humans. This position, however, may evolve as development and characterization of preclinical models, particularly challenge models for ZIKV, advance. Although preclinical studies may inform dose-finding, the optimal dose and scheduling will still need to be evaluated in humans.

5.3. Clinical trials

Safety, immunogenicity, and dose-finding are the main objectives of early stage clinical evaluation (Phase 1 and 2 clinical studies), with some studies usually performed in affected/endemic populations. That said, safety and immunogenicity assessment should be first evaluated in a Phase 1 study of flavivirus-umlaut individuals. The plaque reduction neutralization test (PRNT) is the likely neutralization assay of interest from a regulatory perspective to establish a surrogate marker or correlate of protection. The need for reference materials for calibration of assays was highlighted as an urgent priority. Reference materials are critical to ensure comparability of results across a range of assays from different developers, to interpret vaccine immunogenicity data, and eventually to establish a correlate of protection. This would include an international serum reference, e.g. from blood transfusion centers. A centralized laboratory service that could conduct standardized PRNT assays was seen as highly desirable.

For all clinical trials, a placebo control is optimal, especially given the hypothetical risk of GBS. As the TPP stipulates a lower age limit of 9 years, age de-escalation will be needed.

In light of many uncertainties in ZIKV epidemiology and evolving diagnostic assays, a definite clinical trial endpoint could not be provided at the time of the meeting. Potential options for clinical trial endpoints that would be supportive for emergency use

authorization include disease endpoints (in the vaccinated individual or infants born to vaccinated mothers), infection endpoints, and/or immunological endpoints based on PRNT (Table 1). There are advantages and disadvantages to the various approaches, and subsets within trials may be used to study secondary endpoints for which data are more difficult to collect. Although GBS is too rare to be considered as an endpoint in a clinical trial (background rate estimated at 0.62–2.66 per 100,000 person-years depending on age [46]), it should be designated as an adverse event of special interest (AESI).

A working case definition of virologically-confirmed Zika illness is available [47]. There is no known correlate of protection for ZIKV. Although relatively low antibody titers, as measured by PRNT, are accepted as surrogates of vaccine-induced protection against JE, TBE, and YF [48], this has not been the case for the licensed dengue vaccine [49], albeit this is a more complicated tetravalent formulation. Relevant clinical endpoints are useful to allow regulators to better assess risk/benefit balance in vaccinated individuals. With the public health goal to reduce congenital Zika syndrome in infants through vaccination, immune responses in adult vaccinees are an indirect measure of the desired outcome. As such, efforts to determine the feasibility of evaluating more direct clinical benefit from vaccination should be diligently sought. One study suggested rates of microcephaly as high as 15% [14], which could make clinical trials with congenital Zika syndrome as a clinical trial endpoint potentially feasible, although still very challenging because of protracted efficacy study timelines and cost.

Efficacy against ZIKV infection (as measured by seroconversion) or reduction in viraemia (e.g. through frequent specimen collection) is another option. Although detectable viraemia in blood has a short duration (approximately 10 days), recent studies suggest detectable virus lasts longer in saliva and urine samples, which are also easier to collect [32]. One strategy could be to look at the protection against infection or reduction in viraemia among vaccinated participants in a subset of an efficacy trial with the primary endpoint of clinical disease.

5.4. Challenge trials

Work is ongoing to develop a human challenge model for uncomplicated ZIKV infection building on recent work on challenge studies in humans for dengue [50,51]. Pending approval by competent authorities, human challenge trials with ZIKV may be useful research tools to identify possible correlates of protection, duration of viraemia and viral shedding, and potentially down-select vaccine candidates. Although human challenge studies are an informative tool, due to the serious complications of ZIKV infection (congenital Zika syndrome and GBS) and an incomplete understanding of human-to-human transmission of ZIKV, human challenge trials should proceed with caution. There are ethical considerations for challenge trials: some have argued that it is ethical only in affected areas where infection in the trial could be protective for future exposure; on the other hand, concerns about interacting flavivirus immunity cannot be excluded at this time, so an incremental approach, starting in flavivirus-umlaut populations, would be most prudent. Just as immune responses to flavivirus vaccination are different among flavivirus-umlaut and -experienced populations, the results of challenge trials in umlaut populations would be similarly limited in their generalizability to populations exposed to co-circulating flaviviruses. Regulatory views on the acceptability of human challenge trials in areas suitable for ZIKV transmission may vary by country and should be explored early. Risks of mosquito transmission and sexual or other potential modes of human-to-human transmission of the challenge virus must be mitigated. Potential participants with other risk factors for GBS (e.g. older age and history of autoimmune disease, including GBS) should be excluded.

5.5. Ethical considerations for Zika vaccine research

A consultation hosted by the Pan American Health Organization in April 2016 highlighted specific ethical issues relevant to research and the ZIKV epidemic, including the potential role of pregnant women in research and vaccine development [52]. Special considerations for the performance of ZIKV vaccine clinical trials were also discussed at the WHO meeting, and the issues highlighted included the ethical concerns of testing in women who may be unknowingly pregnant at the time of vaccination and the evolving assessment of vaccine risk vs. clinical benefit to both mother and feotus, in the context of the need to accelerate evaluation within the target population that resides in resource-constrained settings. Additional work in the ethical considerations for vaccine development of ZIKV vaccines is ongoing under a collaboration between the University of North Carolina, Johns Hopkins University and the University of Kwazulu-Natal.

Table 1
Advantages and limitations of potential endpoints for clinical trials of ZIKV vaccines in support of emergency use.

Clinical trial endpoint	Advantages	Limitations
Immunogenicity	• Easily measured • Does not enlarge sample size • Short timeline to collect (e.g. 28 days post-vaccination) • Could be done in a range of epidemiological settings	• Limitations of PRNT assay • Unclear relationship between immunogenicity and protection (no correlate of protection established) • Must be linked to convincing animal data, such as passive protection studies • Effectiveness data must be collected post-introduction
ZIKV infection (viraemia or seroconversion)	• Asymptomatic infection may be relevant for congenital Zika syndrome • Sterilizing immunity would constitute an all-encompassing endpoint • Smaller sample size needed	• As few vaccines confer sterilizing immunity, high bar for vaccine success • Limitations of RT-PCR assays (duration of viraemia) • Uncertainties of specimens needed • Unpredictability of disease transmission • Might need frequent sampling to detect asymptomatic infections, causing burden to trial participants
Laboratory-confirmed Zika disease	• Standard for efficacy trials in absence of a correlate of protection • Hypothesis that symptoms, viraemia, and transmission to infants are correlated	• Case definition unvalidated • Large sample size requirements • Unpredictability of disease transmission
Congenital Zika syndrome	• Outcome of greatest interest for public health	• Largest sample size requirements • Longest time for results to be available • Focus on enrolling women • Unpredictability of disease transmission

5.6. Post-authorization risk-management plans

Necessary post-authorization studies will be dependent upon the clinical development plan and associated findings. For example, if a vaccine is authorized for emergency use based on endpoints other than clinical efficacy, then proof-of-effectiveness will need to be established post-licensure. Pregnancy registries are critical to follow up women who are inadvertently vaccinated while pregnant. Sample sizes and follow-up times may also be more limited if approved for emergency use, necessitating special post-licensure studies, particularly for safety and durability of protection.

There will also remain some questions that can only be evaluated post-authorization. GBS, which may be associated both with ZIKV infection as well as vaccination, will be a critical outcome to study. Surveillance for GBS must be in place where a vaccine is deployed under emergency use, and lessons could be learned from experiences with international collaboration for influenza and GBS studies with draft protocols [53]. The Brighton Collaboration has developed standard case definitions for GBS as an adverse event following immunization [54]. Clear protocols should be in place to assess reports from individuals with neurological manifestations. The interaction of vaccine-induced immunity and disease caused by other flaviviruses can only be studied to a limited degree in the context of a clinical trial. While natural history of disease cohort studies may generate evidence on this matter, longer term follow-up of vaccine recipients will be needed to document any beneficial or detrimental effects resulting from interactions with vaccination.

6. Regulatory pathways for emergency use

A review of regulatory pathways for emergency use in selected countries has been carried out by WHO [55]. Fast tracking of regulatory procedures in case of a public health emergency while maintaining public safety requires a case-by-case approach and consideration of the actual benefit-risk balance. Many lessons can be learned from the experience with rapid development and access to the Ebola virus vaccine. Regulatory agencies facilitated this process through expedited review of chemistry, manufacturing and controls (CMC) information, preclinical and clinical protocols, and clinical trial data, where available, for Ebola virus vaccine candidates. Agencies held numerous meetings with sponsors to discuss CMC issues, clinical development programs, and pathways to licensure of Ebola virus vaccines that contributed to the accelerated timelines. A key factor was international collaboration among regulatory agencies in reviews, with the goal of regulatory convergence, which WHO facilitated. Additional strategies to accelerate regulatory assessments include rolling submissions and priority review.

Some regulatory authorities have legal provisions for expedited review or even use of authorized use of unapproved medicinal products, while others do not have formal mechanisms but may use traditional pathways for conditional approval. Generally speaking, access may occur through expanded access options for unapproved products, emergency use authorizations, or accelerated/conditional approvals. Among various pathways available in the United States, regulation for approval by the so-called "Animal Rule" is not relevant to ZIKV vaccine development. Regulatory authorities have in place criteria and provisions for the different pathways as well as sponsor obligations in the context of use. Emergency use authorizations are time limited until further data are collected and evaluated to permit a decision on licensure.

Following the 2014 Ebola outbreak and the urgent need for new diagnostic and therapeutic tools to be available in the context of the public health emergency, WHO developed the Emergency Use Assessment and Listing Procedure (EUAL) [56]. The WHO EUAL is a list of unlicensed products for which an assessment has been made based on the quality, safety and efficacy/performance for use during and potentially following a PHEIC, in the context an ongoing emergency. National regulatory authorities are still responsible for authorizing the use of the listed vaccines during an emergency.

7. Conclusions

Participants highlighted a number of considerations for regulatory expectations throughout the course of the meeting (Box 1). Given the many uncertainties that remain with regard to disease epidemiology and pathology, the rapidly evolving development of preclinical models, and considerations that will be specific to the emerging vaccine candidates, a definitive regulatory strategy could not be recommended at this early stage. However, there are a number of considerations that may facilitate definition of regulatory expectations of ZIKV vaccines for use during an emergency, and global stakeholders are committed to continuing to work collaboratively to develop these in order to advance the availability of these candidates as expeditiously as possible.

Box 1 Points to consider for regulatory expectations of ZIKV vaccines for use during an emergency.

- Current understanding of disease epidemiology, pathology and mechanisms of immunological protection is incomplete, but evolving at rapid pace;
- A definitive regulatory strategy cannot be recommended at this stage;
- Careful benefit-risk assessment will be essential in any approval for accelerated vaccine development and use;
- While the public health objective of a vaccine is the prevention of congenital Zika syndrome, the indication could relate to prevention of confirmed ZIKV illness or possibly infection;
- Contraindication of vaccination of pregnant women should be avoided;
- Demonstration of immunogenicity in relevant animal models is needed to progress into clinical studies, and animal challenge studies are advisable;
- Challenges studies in non-human primates may be of particular interest but are currently not essential to progress to clinical trials, as are pregnancy models in mice or non-human primates;
- PRNT is the critical immunological readout, but other immunological measures may provide supportive evidence of immunogenicity;
- Data from a PRNT assay performed by a central service using an optimized assay protocol is highly recommended, to allow comparison across studies;
- When available, immunological reference reagents and standard challenge viruses should be used;
- Clinical efficacy endpoints are the preferred option if feasible: prevention of ZIKV infection as well as prevention of virologically-confirmed ZIKV illness represent the two most likely options;
- If clinical efficacy trials are not feasible, immunological endpoint studies combined with passive protection studies in animals, and possibly human challenge study results, may represent acceptable data sets for initial emergency use authorization;
- Safety evaluation needs particular attention in relation to reproductive toxicology, and AESI's will include GBS and the risk of enhanced disease due to pre-existing immunity to related flaviviruses.

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