World Health Organization

WHO consultation on Chikungunya vaccine evaluation

29 November 2018, Geneva, Switzerland

Meeting report (DRAFT)

R&DBlueprint

Powering research to prevent epidemics

On November 29 2018, the WHO R&D Blueprint convened a group of experts to discuss methodological issues and agree *a priori* on principles in the design, conduct and analysis of Phase2b/Phase 3 clinical trials to evaluate Chikungunya vaccines, based on key epidemiological considerations, driven by vaccine needs from a public health perspective, and also recognizing current epidemiological gaps. The group of experts included national representatives from countries affected by Chikungunya, experts in Chikungunya virology and epidemiology as well as members of the R&D Blueprint working group on clinical trial design.

Epidemiological considerations

This section does not intend to summarize all the current knowledge on Chikungunya clinical manifestations and epidemiology but intends to provide main epidemiological considerations for the design of clinical trials for Chikungunya vaccines evaluation, based on the group discussions.

Chikungunya is an arboviral disease, mainly transmitted to humans by *Aedes aegypti and Aedes albopictus.* Chikungunya disease is caused by Chikungunya virus, an alphavirus, a class of virus prone to strong arthrotropism in humans. The virus has been identified in over 60 countries in Asia, Africa, Europe and the Americas, under three different lineages (Asian, Indian, ECSA), and has caused significant outbreaks over several months, particularly in urban settings. The burden of Chikungunya outbreaks is biphasic and is split between an acute stage, associated with brutal disability in daily life, and a chronic stage associated with long-term sequelae. Both stages cause significant socio-economic disruption in the short-, mid- and long-term.

Transmission patterns have been extremely heterogeneous across regions, countries and continents and depend on complex environmental (e.g. elevation, rainfall), ecological (e.g. type of Aedes, enzoonotic cycle), epidemiological (e.g. population susceptibility, viral lineage) and social (e.g. population mobility in urban settings, lifestyle) conditions that influence the distribution of *Aedes* and human populations and drive disease transmission in a given area. Chikungunya epidemiology is characterized by large introductions in epidemiologically naïve populations which may be followed by granular transmission causing micro-epidemics in small clusters of susceptible population. Major epidemiological gaps remain and chikungunya epidemiology should be extrapolated from other arboviruses with caution. In particular, additional sero-prevalence studies are needed to better understand the distribution of past cases and where we may anticipate new cases in the future to inform site selection for vaccine trials. Clinical records could also be leveraged to understand better the distribution of past outbreaks. Lastly, it was noted that clinical surveillance is much more sensitive and appropriate than entomological surveillance for Chikungunya.

Chikungunya infections result in about 80% of symptomatic cases. A significant number of symptomatic patients stay in bed or are hospitalized and present within two weeks with severe fever and arthralgia along with non-specific clinical manifestations (e.g. rash, myalgia, asthenia). Rarely, neurologic complications may occur and case fatality rate is typically less than 1%. Adults, especially elderly people and patients with co-morbidities (e.g. chronic organ failure, immunosuppression), are the most vulnerable to the disease and its complications as well as newborns via vertical or neonatal transmission, while children cases are less symptomatic on average. Although viraemia is typically cleared in patients' blood within nine days, a large majority of these patients develop in the following months post-acute symptoms with clinical persistence or relapse and transient immune changes towards a chronic stage where, for instance, persistence of joint inflammation and rheumatic (e.g. musculoskeletal) disorders is observed in 20-50% of patients at least over two years, but rarely with arthritis. It was recognized that the real burden of the chronic stage is difficult to assess and to compare across outbreaks and regions, which underscores the need for standardized methodological description of the disease. Lastly, the role of the lineage in clinical severity remains unclear.

Clinical trials to evaluate the safety and efficacy of Chikungunya vaccines

Overview of investigational Chikungunya vaccines

This section does not intend to provide the full overview of vaccines candidates developed to prevent Chikungunya-related burden of disease but intends to highlight the main characteristics of the most advanced agents that currently exist and that could be considered for efficacy trials and to illustrate the motivation behind current vaccine design.

There are currently no licensed Chikungunya vaccines. Several candidates vaccines are in clinical development. A wide variety of platforms ranging from live-attenuated, chimeric vector-based (e.g. measles-, alphavirus-, vaccinia-, adeno-, vesiculovirus-based), protein-based (e.g. VLP, subunit) are under development. Three candidates vaccines (1 live attenuated, 1 vector-based vaccine and 1 protein-based) have undergone Phase 2 clinical trials and another candidate vaccine (protein-based) is about to start a Phase 2 trial, and which has shown protection across various Chikungunya lineages in preclinical data. Various other candidates are in Phase 1 clinical trials or at the preclinical level. Generally, advanced candidate vaccines elicit similar immune response to wild-type infection but their comparison is hampered by the lack of standardization of assays used across studies. Lessons learned from other alphaviruses vaccine development and passive immune transfer Chikungunya studies have illustrated the key role in protection of neutralizing antibodies against Chikungunya virus. However, it remains unclear whether a defined threshold of neutralizing antibodies titres can be identified as a correlate of protection. Lastly, the role of cellular immunity in protection remains also unclear.

Chikungunya vaccine development is also associated with important safety concerns. A live attenuated Chikungunya vaccine has shown to cause arthralgia at various degrees of severity in a Phase 2 study and its development has been stopped. The study also revealed that pre-existing alphavirus immunity may interfere with subsequent neutralizing antibody response to a live attenuated heterologous vaccine. It was further noted the impact of pre-existing immunity to the vector on the immune response must be assessed in the case of a vector-based approach.

Considerations on Chikungunya diagnostics

Currently, both molecular and serological diagnostics could be leveraged for vaccine clinical trials. Quantitative molecular assays, such as RT-PCR, could be used to confirm Chikungunya cases by detecting viraemia in blood within 8 days of symptoms onset. Serological assays, such as ELISA or neutralization assays (e.g. PRNT, micro-neutralization, flow cytometry) could be used to study the immune response elicited, such as IgM or neutralizing antibodies, by a candidate Chikungunya vaccine, to establish a correlates of protection, or to detect Chikungunya cases after 8 days of symptoms onset. However, IgM ELISA may cross-react with other alphaviruses at various levels. Therefore, neutralization assays remain the most important functional serological assays for its higher specificity and because neutralizing antibodies are thought to be key in protection, although they require more resources than ELISA, and may require a BSL3 laboratory to be able to manipulate live chikungunya virus. Finally, it is unclear at this stage whether those serological assays could help distinguish between Chikungunya vaccination and wild-type infection.
Rapid diagnostic tests (e.g. lateral flow assay) could be used to inform preliminary participant inclusion to be subsequently confirmed with a more definitive test in the trial reference laboratory.

Overview of trial design methodological elements

The design of vaccine trials for Chikungunya is challenged by the epidemiology, mainly because it is extremely difficult to identify trial sites where enough transmission will occur to satisfy realistic sample sizes and reach conclusive evidence on vaccine efficacy. The group suggested an approach whereby a Phase 3 vaccine trial properly informed by addressing current epidemiological gaps would be the preferred approach. A Phase 2b trial would be useful to gather information about the potential of the vaccine to prevent disease and long term disabilities, but with intrinsic risk of being poorly informative if not able to collect sufficient number of cases due to the limited size of the trial and in view of uncertainties on epidemiology.

The group underscored the need for a Phase 3 Master Protocol that would be flexible to simultaneously address a preventive and a reactive setting, i.e. in response to an outbreak, in any country where an outbreak may arise. In a reactive setting, it was noted that Chikungunya outbreaks are of relatively long duration, typically one or two years, with serial intervals of about 23 days, which increases the feasibility of a vaccine trial and potential use of a vaccine in this setting.
Likewise, engaging stakeholders under a Master Protocol would potentially increase chances of answering research questions deemed to be the most relevant from the widest public health perspective and would also serve as a framework to transparently select the most appropriate vaccine candidates for evaluation.

Overall, the suggested trial design to evaluate a Chikungunya vaccine is a **Phase 3 prospective, double-blind, placebo-controlled, efficacy trial.** The next sections provides more details on the choice of endpoints, target population, and comparator.

1. **Primary endpoint**

Option 1 – Laboratory-confirmed acute clinical Chikungunya illness
Option 2 – Co-primary endpoints: laboratory-confirmed acute clinical illness and an indicator of chronic symptoms, where the false positive error would be shared between the analyses of these two endpoints.

Participants recognized that a Chikungunya vaccine that would significantly reduce the risk of laboratory-confirmed acute clinical Chikungunya illness would also be expected to have an impact on the risk for major long-term morbidity. This reasoning contributed to support of Option 1. In Option 1, an indicator of chronic symptoms would be a critical secondary endpoint. In this design, a trial with 62 primary endpoint events and a 5% false positive error rate would have 90% power to rule out a hazard ratio of 0.7 when the true hazard ratio was 0.3. Positivity at 2-sided p=.10 would occur with an estimated hazard ratio 0.45 and at the traditional 2-sided p=0.05 would occur with an estimated hazard ratio 0.41, the latter corresponding to estimated vaccine efficacy of 59%.

It cannot be excluded that a vaccine could reduce the probability of acute clinical illness without having a large effect on the rates of chronic manifestations. For example, if a trial of a Chikungunya vaccine were to yield statistically positive results by Option 1, with estimated vaccine efficacy in the range of a 55% to 60% reduction in acute clinical Chikungunya illness, and if long-term sequelae in the control group would be expected to be approximately 40%, which may vary in different regions and with different strains, it cannot be assumed that such a vaccine would be preventing 55 to 60% of the long-term chronic manifestations, since the vaccine could be selectively preventing anywhere from very few to most of the cases that would later develop chronic manifestations. Similarly, a vaccine with 55 to 60% vaccine efficacy regarding laboratory-confirmed acute clinical Chikungunya illness could have anywhere from little effect to a profound effect on chronic manifestations. Given that the risk of developing chronic manifestations appears to be rather high, Option 2 is appealing due to the clinically compelling importance of obtaining definitive evidence about vaccine effects on chronic manifestations and due to

the increase in statistical power when evaluating a Chikungunya vaccine that provides substantial reductions not only regarding risk of acute clinical Chikungunya illness but also regarding long-term chronic manifestations.

To illustrate the important increase in sensitivity of Option 2, suppose a clinical trial's 2.5% false positive error rate would be shared equally between ruling out the hypothesis of 30% vaccine efficacy regarding the endpoint, 'laboratory-confirmed acute clinical Chikungunya illness' and ruling out the hypothesis of no effect on the endpoint, 'chronic manifestations'; further, suppose the trial with a 2:1 randomization between the vaccine and placebo arms has 62 participants having laboratory-confirmed acute clinical Chikungunya illness and has an estimated 50% vaccine efficacy on that endpoint, and yet also has 40% participants developing chronic manifestations in the control arm and an estimated risk reduction in chronic manifestations of at least 70%, (a plausible scenario); in that setting, the trial would yield a negative conclusion about vaccine efficacy when using Option 1 and yet would yield the positive conclusion of a statistically significant effect on chronic manifestations when using Option 2.

The table in Appendix 1 gives power calculations for an additional set of simulations. The seventh column of the table shows the statistical power to rule out that Vaccine Efficacy is less than or equal to 30% (equivalent to a relative risk of 70% or higher) under option 1, based on only the relative incidence of acute clinical Chikungunya illness, assuming a two-sided type 1 error rate of .05. The last column, also in bold, gives the statistical power to reject either the null hypothesis that vaccine efficacy is ≤ 30% for Chikungunya illness or the null hypothesis that vaccine efficacy is ≤ 0 for chronic manifestations, option 2, assuming a two-sided type 1 error rate of .025 for each comparison. While not meant to represent all possible scenarios of interest, for all scenarios examined here the statistical power is either the same or higher for option 2 as for option 1.

It was agreed that more in depth discussion is needed about the relative merits of these two options, enlightened by further simulations and statistical calculations under various scenarios regarding sample sizes of trials and numbers of participants having laboratory-confirmed acute clinical Chikungunya illness events, rates of long-term chronic manifestations, true levels of vaccine efficacy for effects on these two endpoints, and, for Option 2, regarding approaches for sharing the false positive error rates between the two analyses and regarding a range of null hypotheses for the chronicity endpoint, (such as ruling out no effect or, instead, requiring stronger evidence that also rules out small effects on chronicity).

It also was noted that a case definition of 'laboratory-confirmed acute clinical Chikungunya illness' must be defined – especially on what *acute* means - and needs to be standardized across countries that would operate under the Master Protocol, building on the case definitions recommended by WHO regional offices. Laboratory confirmation will be performed using a RT-PCR that detect Chikungunya virus in the blood.
Moreover, case definition for chronic sequelae and appropriate timing of assessment for chronic manifestations are also not defined carrying uncertainties with regards to definition of endpoints and assumptions for Option 2.

Given the high symptomatic rate, infection was not proposed as a pertinent endpoint.
Subacute illness was also suggested as secondary endpoint. In order to investigate correlates of protection, relevant samples need to be collected at baseline and some days – to be defined – after administration of the vaccine. All trial participants need to be bled at baseline to determine their seropositivity to Chikungunya, or to another alphavirus, recognizing that the vaccine effect and vaccine safety profile may depend on seropositivity status. Baseline samples could also contribute to determine an immune correlate of protection. Ideally, the trial will be conducted in areas where participants seropositivity is low but where we anticipate disease transmission. Restricting the primary analysis to seronegative subjects at baseline was suggested as a reasonable option.

2. **Target population** – **Healthy adults and children**
excluding pregnant and lactating women, people with co-morbidities (e.g. immunodeficiencies, rheumatic conditions, diabetes)

Chikungunya affects the general population at all age groups and targeting the general population would maximize any potential herd immunity associated with the future use of a vaccine in preventing transmission to ineligible or unimmunized people.
Study populations need to be enrolled in multiple sites and multiple countries, under the Master Protocol, mainly to increase chances of generating conclusive evidence. Vaccine trial site selection is challenged by the difficulties of anticipating where Chikungunya transmission is likely to occur, and to accrue enough cases in order to answer the primary questions defined under the Master Protocol.

3. **Randomization and comparator – 2:1 individual randomization placebo-controlled** within sites

Under the Master Protocol, the trial structure should allow new sites in affected areas to be added and within each site, participants would be individually randomized to receive either the vaccine or a placebo with a 2:1 randomization schedule, in order also to learn more about the vaccine safety profile.
The measure of vaccine efficacy would result from the combined incidence rate with respect to the primary endpoint across all sites.
Multiple vaccines could also be tested against a single placebo arm with as many hypothesis tests, comparing each vaccine against the placebo arm.
Finally, participants and investigators must remain blinded.

Data Monitoring Strategy

It was agreed that study data would not be released unless the trial was stopped, for efficacy or futility, under close DSMB oversight, or by reaching its targeted number of endpoints, to preserve the integrity of the trial and to prevent any prejudgment. Interim analyses to assess efficacy or futility can be timed to occur at after reaching a targeted amount of events.
Only seronegative individuals will contribute to the primary analysis.

Next Steps

1. Address current epidemiological gaps: serosurveillance and modelling studies to better understand the disease burden, better assess the feasibility of a Phase 3 vaccine trial, while building research capacity for trial sites.

Serological studies must be conducted in Chikungunya population where outbreak have occurred or are likely to occur in order to better assess the disease burden, derive cumulative attack rates, and to identify potential trial sites, where transmission is likely to occur and where a vaccine trial is likely to be feasible. Additional studies are also needed to better assess the burden of the chronic stage of the disease and emphasis should be put on the need for standardized methodologies, especially to be able to compare disease chronicity across regions.
Such studies could be complemented by the use of mathematical models of infectious diseases that would simulate the spread of Chikungunya disease given current understanding of transmission patterns and control measures.

2. Establish a collaborative and transparent framework for selecting candidate vaccines to be tested in efficacy trials.
An independent working group will be formed to establish a framework for selecting the most promising vaccine candidates to be tested in efficacy trials, based on all the available evidence for each candidate vaccines and on a target product profile for chikungunya vaccines. The group will be charged to define criteria for candidate selection, and to review and assess all the available evidence on each candidate.

3. Write a generic protocol for Chikungunya vaccine evaluation based on the preliminary recommendations outlined in this document.

Appendix A

Table 1: Sample power calculations to compare Option 1 (primary endpoint of Chikungunya infection only) with Option 2 (co-primary endpoints of Chikungunya infection and chronic manifestations)

All calculations based on 10,000 simulations/row, n=400 in placebo and n=800 in treatment arm; normal approximation to log(RR) ; rule out VE<30% for acute, VE=0% for chronic; all chronic occur among acute people

Probability of Chikungunya illness		**VE, Chikungunya illness**	**Probability of chronic (among acutes)**		**VE, chronic manifestations**	**Power for Option 1: illness only***	**Power for Option 2: either illness or chronic manifestations****
Trt	**Ctrl**		**Trt**	**Ctrl**			
.1	.07	30%	.4	.4	0%	**.025**	**.14**
.1	.07	30%	.4	.3	25%	**.025**	**.36**
.1	.07	30%	.4	.2	50%	**.025**	**.70**
.1	.05	50%	.4	.4	0%	**.34**	**.46**
.1	.05	50%	.4	.3	25%	**.34**	**.67**
.1	.05	50%	.4	.2	50%	**.34**	**.87**
.1	.03	70%	.4	.4	0%	**.93**	**.93**
.1	.03	70%	.4	.3	25%	**.93**	**.96**
.1	.03	70%	.4	.2	50%	**.93**	**.98**

* “illness only” at two-sided α=.05 (rule out 30% VE)
** illness at two-sided α=.05; chronicity at 2-sided α=.05

WHO Headquarters in Geneva

Avenue Appia 20
1202 Geneva
Telephone: +41-22-7912111

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