Zika Vaccine Development Technology Roadmap

2018

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Background on Technology Roadmaps

Vaccine development technology roadmaps produced by the World Health Organization (WHO) aim to provide a strategic framework underpinning priority activities for vaccine researchers, funders and product developers, with the goal to address globally unmet medical needs.

WHO has led a series of initiatives to maintain continuous dialogue between developers, regulators and public health experts to identify how best to achieve rapid, robust, safe, and evidence-based licensing of Zika Virus (ZIKV) vaccines. The present roadmap states the vision and strategic goals for ZIKV vaccine development from WHO, with input from public health agencies, academia, industry, regulators, ethicists and financing bodies amongst others. The ZIKV vaccine ‘Vision’ articulates the prioritized public health need, and the ‘Strategic Goal’ describes a vaccination strategy that will enable realization of that vision. The roadmap also lays out priority activities in the categories of research, product development, key capacities and policy, commercialization and delivery. The objective of this framework is for the global ZIKV vaccine research and development community to accelerate timelines to licensure and use of ZIKV vaccines, especially in low- and middle-income countries where they are most needed. The present document is not intended to be product type-specific.
WHO will encourage implementation of the roadmap by the ZIKV vaccine community. Progress in the field will be monitored and the roadmap will be updated if there are significant changes that warrant reassessing the vision, strategic goals or priority activities.

**Introduction**

Zika virus (ZIKV) is a flavivirus mainly transmitted by *Aedes* spp mosquitoes, although human sexual transmission has also been reported. Discovered in 1947, ZIKV was only known to cause sporadic mild disease in Africa and Asia. In 2007, the first major outbreak occurred in Yap Island with an attack rate as high as 70% of the population. In 2013, during an outbreak in French Polynesia with a similarly high attack rate, the possible association with Guillain-Barré Syndrome was uncovered. By 2015, clusters of microcephaly as a result of pre-natal ZIKV infection were first described in Brazil. In February 2016, WHO declared the clusters of microcephaly and other neurological disorders, associated with ZIKV, a Public Health Emergency of International Concern (PHEIC), and called on the global research and product development (R&D) communities to prioritize the development of vaccines together with improved diagnostics, and innovative vector control strategies.

Although the PHEIC was declared over by the WHO Director-General in November 2016, ZIKV remains an enduring public health challenge requiring continued action, as outbreaks may re-emerge that put susceptible populations at risk. Many uncertainties remain with regard to disease epidemiology and transmission dynamics; hence projecting the future evolution of the ZIKV epidemic and further spread based on current knowledge is difficult.

This roadmap replaces the previous technical roadmap which primarily supported the development of a vaccine for outbreak use with the characteristics proposed within the Target Product Profile. This updated roadmap considers Zika vaccines for both outbreak and endemic use. If significant changes in the epidemic warrant reassessing this vision, the ZIKV vaccine roadmap will be updated again.

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**Vision**

Safe, effective and affordable Zika Virus (ZIKV) vaccines that prevent congenital ZIKV syndrome (CZS) and other serious ZIKV-associated clinical complications

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**Strategic Goals**

Support development, licensure and WHO-prequalification of high-quality, safe and effective ZIKV vaccines that prevent serious ZIKV-associated clinical complications, and ensure availability and affordability for use in countries where ZIKV circulates

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**Outbreak use:**

In the context of an ongoing epidemic or an imminent outbreak of ZIKV, a mass vaccination campaign may prevent ZIKV infection in women of child-bearing age. The primary public health objective of vaccination for outbreak use is the prevention of prenatal ZIKV infection

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and subsequent ZIKV-associated birth defects. Other populations, in particular men, may be included in emergency vaccination campaigns, if vaccine supply permits.

**Endemic use:**

Introduction of the vaccine into the routine immunization schedule of at-risk countries as a broad-based or universal vaccination campaign of the general population, extending from early childhood to adults, followed by routine immunization in childhood vaccination programs. The primary public health objective of vaccination for routine use is to establish population immunity to prevent CZS and other ZIKV-related complications.

**Priority Areas:**

**Research**

1. **Further quantify the unmet medical need for a ZIKV vaccine and its potential public health impact**

2. **Develop** a harmonized case definition for ZIKV surveillance purposes

3. **Urgently estimate** the regional and national burden of CZS in Asia, Africa and Latin America, including the presence or future risk for sustained endemic transmission

4. **Determine** whether ZIKV infection leads to long-term immunity to known ZIKV lineages

5. **Investigate** whether evolutionary changes in ZIKV have led to changes in transmissibility or risk of disease

6. **Investigate** the extent of population-wide immunity to ZIKV, including the effect of ZIKV-associated immunity on other flaviviruses and vice versa

7. **Better define** disease transmission dynamics, including the role of non-vector transmission

8. **Model** possible geographic spread and progression of ZIKV transmission

9. **Develop** predictive models for early detection of ZIKV outbreaks and **define** triggers to initiate outbreak use of ZIKV vaccines

10. **Urgently develop** models to determine the evolution of the burden of disease, the optimal age groups and target populations for vaccine introduction, and different dosing scenarios to inform the target product profile for endemic use and guide vaccine introduction for optimal impact

11. **(2) Better define the clinically relevant outcomes of ZIKV infections**

12. **Urgently define** and **address** epidemiological, biological, and environmental knowledge gaps related to CZS

13. **Develop** risk estimates for CZS by gestational age, asymptomatic versus symptomatic prenatal infection, and other factors that influence the risk

14. **Define** the full spectrum of CZS at birth and during at least the first 5 years of life, including delayed outcomes, long-term consequences and estimated life expectancy
Determine the full public impact of CZS with an estimation of DALYs

Determine the risk and clinical spectrum of ZIKV-associated neurological and other complications beyond CZS

Cross-Cutting Product Development Related Priority Areas

Refine animal models for evaluation of clinically relevant human disease outcomes

Develop and endorse standardization of virologic and immunologic assays for ZIKV vaccine development

Explore immunologic and virologic correlates of ZIKV vaccine-induced protection and surrogate efficacy endpoints for risk and protection of ZIKV infection

Prioritize improved surveillance tools that differentiate ZIKV infection from infections due to other flaviviruses

Develop more sensitive and specific diagnostic products defined by the ZIKV Target Product Profiles

Vaccine development

Vaccine candidates:

Establish a systematic approach for assessing vaccine candidates taking into account: safety (including in pregnancy); specificity, rapidity of onset, and duration of protective immunity; dosing regimen (volume, number, and schedule of doses); interactions with other relevant flaviviruses and flavivirus vaccines; key vaccine product attributes (e.g., storage and stability); immune correlates of protection and risk; head-to-head comparisons; and back-validation from clinical to nonclinical models

Outbreak use:

Characterize ZIKV vaccine candidates for safe use, including pregnant women

Develop a ZIKV vaccine suitable for outbreak settings, including rapid onset of protective immunity

Collect data pre- and post-licensure specific to safety and immunogenicity for all ZIKV vaccine candidates, including in pregnant women

Endemic use:

Develop a WHO Preferred Product Characteristics for ZIKV vaccines for routine use, including the need for long duration of protection, key age groups and target sub-populations

Explore combination vaccines to maximize vaccine coverage even at a time with low ZIKV infection incidence

Vaccine evaluation:

http://www.who.int/blueprint/what/research-development/zika-tpp.pdf?ua=1
Establish standardized definitions for adverse events of specific interest

Develop clinical development plans that include case definitions and endpoints for pivotal trials, systematic collection of relevant biomarkers, indicators and outcomes of safety and efficacy, including in pregnant women

Prepare clinical trial protocols and generic ethics approvals during the inter-epidemic period to accelerate implementation of a phase 3 efficacy trial at a time of a new outbreak

Make ZIKV vaccine trial results publicly available within 12 months of the last subject’s last visit pertaining to primary endpoint data (http://who.int/ictrp/results/reporting)

Develop points for consideration on alternative pathways to approve vaccines and other products for emerging pathogens when traditional clinical efficacy trials are not feasible

Urgently define accelerated regulatory pathways with immune correlates/surrogates as endpoint

Investigate the use of human controlled infection models in the development of ZIKV vaccine candidates

Key capacities

Build GCP Clinical Trial Capacity for vaccine evaluation, monitoring of AEFIs and vaccine effectiveness

Support capacity strengthening in ethical, regulatory and pharmacovigilance oversight of clinical vaccine trials and post-licensure activities

Research and establish baseline rates of disease and common adverse fetal outcomes to prepare for optimal safety and effectiveness surveillance

Strengthen and use existing recommendations and ongoing initiatives on safety surveillance for vaccines for use in pregnancy

Strengthen laboratory capacity for diagnostics for flavivirus infections

Develop diagnostic algorithms for CZS and ensure that affected areas have the capacity to follow such algorithms, including ultrasound capabilities in reproductive health care systems

Consolidate for each at-risk country relevant reproductive health data, such as age of sexual debut, age at first pregnancy, pregnancy spacing, age-specific rates for births, unplanned births, still births, neonatal deaths and other indicators that are relevant to inform immunization recommendations and to monitor vaccine impact

Strengthen birth defect surveillance in countries at risk

Strengthen surveillance for Guillain-Barre Syndrome

Establish or strengthen regional diagnostic reference laboratories for arboviruses

Ensure access to low cost vaccine manufacturing under current Good Manufacturing Practices (cGMP) for late stage development and commercial production
ZIKVA Vaccine Development Technology Roadmap, 13 December 2018
This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein
Not for implementation

Policy, commercialization and delivery

Establish cost-effectiveness and, dependent on outbreak or endemic situations, develop research and implementation financial investment scenario to support appropriate funding and policy decision-making at the global and national level.

Define scale-up needs and develop GMP manufacturing capacity to meet these needs.

Secure financing for procurement and deployment of ZIKV vaccines, including for and from stockpiles, respectively, once available.

Ensure post-licensure pharmacovigilance and effectiveness evaluations.

Develop advocacy and communication plans with stakeholders and partners to optimize vaccine uptake.