Zika Vaccine Development Technology Roadmap

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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 developments, 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.

This roadmap is only related to ZIKV vaccines for outbreak use. It is the first step towards a broader roadmap for ZIKV research and product development.
**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 for ZIKV research and development.

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.

In light of the global decline in cases in the year 2017, combined with poor understanding of all the factors needed to sustain endemic ZIKV transmission, this technical roadmap will primarily support development of a vaccine for outbreak use with the characteristics proposed within the Target Product Profile.\(^1\) If significant changes in the epidemic warrant reassessing this vision, the ZIKV vaccine roadmap will be updated.

**Vision**

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

**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 is circulating.

**Outbreak use:**

In the context of an ongoing epidemic or an imminent outbreak of ZIKV, a mass vaccination campaign may prevent ZIKV-associated disease in women of child-bearing age. The primary public health objective of vaccination for outbreak use is the prevention of prenatal ZIKV infection to prevent ZIKV-associated birth defects. Other populations, in particular men, may be included in emergency vaccination campaigns if vaccine supply permits.

**Routine use:**

\(^1\)http://www.who.int/immunization/research/development/WHO_UNICEF_Zikavac_TPP_Feb2017.pdf?ua=1
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
ey 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**

- Urgently define the regional and national burden of CZS in Asia, Africa and Latin America
- Investigate the extent of population wide immunity to ZIKV including the effect of ZIKV-associated immunity on other flaviviruses and vice versa
- Better define disease transmission dynamics including the role of non-vector transmission
- Model possible geographic spread and progression of ZIKV transmission
- Develop predictive models for early detection of outbreaks and define triggers to initiate a ZIKV vaccination program in response to a ZIKV outbreak

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

- Urgently define and address epidemiological, biological, and environmental knowledge gaps related to CZS
- Develop risk estimates for CZS by gestational age, asymptomatic versus symptomatic prenatal infection, and other factors that influence the risk
- 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 and duration of protective immunity, interactions with other relevant flaviviruses, number of doses, rapidity of onset of protection, stability, immune correlates, back-validation from clinical to nonclinical models and head-to-head comparisons

**Outbreak use:**

Characterize candidate 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

**Routine use:**

Develop a Target Product Profile for ZIKV vaccines for routine use including the need for long duration of protection

**Vaccine evaluation:**

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 trial at a time of a new outbreak

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

Explore accelerated regulatory pathways with immune correlates/surrogates as endpoint

Investigate the potential of human controlled infection models in the development of ZIKV vaccines

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

2 http://www.who.int/blueprint/what/research-development/zika-tpp.pdf?ua=1
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

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

**Strengthen and use** existing adapted 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 had 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

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 to enhance vaccine uptake