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 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 established. 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 WHO Director-General declared an end to the PHEIC in November 2016, ZIKV remains an enduring public health challenge requiring continued action, as low level transmission may continue, and 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.[1] 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.

>>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 circulates.

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

[1] http://www.who.int/immunization/research/development/WHO_UNICEF_Zikavac_TPP_Feb2017.pdf?ua=1

health objective of vaccination for outbreak use is the prevention of prenatal ZIKV infection and subsequent ZIKV-associated birth defects, with women of child-bearing age being the primary target group, although men should 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 through 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

Further refine a harmonized case definition for ZIKV surveillance purposes

Estimate the regional and national burden of CZS in Asia, Africa and Latin America, including the presence or future risk for sustained endemic transmission

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

Investigate whether evolutionary genetic changes in ZIKV have led to changes in transmissibility or risk of disease

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 ZIKV outbreaks and **define** triggers to initiate outbreak use of ZIKV vaccines

Develop models to determine the burden of disease, and the optimal age groups and target populations for vaccine introduction, to inform the target product profile for endemic use and guide vaccine introduction for optimal impact

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

Define and **address** epidemiological, biological, and environmental knowledge gaps related to CZS

Develop risk estimates for CZS by gestational age, asymptomatic versus symptomatic pre-natal 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 and long-term consequences

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 **identify and validate** 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[2]

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 use in pregnant women as pregnant women may be an important target group during an outbreak (depending on risk-benefit assessment) and women may not know they are pregnant at the time they are vaccinated

Develop a ZIKV vaccine suitable for outbreak settings, including rapid onset of protective immunity in accordance with the target product profile[1]

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

Endemic use:

Develop 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 (eg ZIKV in combination with other flavivirus vaccines) and

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

co-administration with more than one vaccine to maximize vaccine coverage even at a time with low ZIKV infection incidence

Vaccine evaluation:

(1) Clinical efficacy 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 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)

(2)Alternative pathways for vaccine evaluation beyond the conduct of classic clinical efficacy trials[3]

Define accelerated regulatory pathways with immune correlates/surrogates as endpoint, animal rule, or combinations thereof

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

Key capacities

Build 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 the diagnosis of 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,

[3] Vannice K et al. Demonstrating vaccine effectiveness during a waning epidemic: a WHO/NIH meeting report on approaches to development and licensure of a Zika vaccine candidates. Vaccine 2019; 4; 37:6: 863-868

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 the development, procurement and deployment of ZIKV vaccines, to include the establishment of a vaccine stockpile

Ensure post-licensure pharmacovigilance and effectiveness evaluations

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

Engage local National Immunization Technical Advisory Groups (NITAG) to work on routine immunization recommendation and advocacy