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World Health Organization

Current Zika Product Pipeline

3 March 2016

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Current Zika Product Pipeline

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Introduction

As part of the broader response to Zika WHO has initiated an emergency research and development plan. This is the first effort following the West-Africa Ebola epidemic to implement the WHO's R&D Blueprint.

Established in 2015 at the request of the WHO Executive Board, and subsequently welcomed by the World Health Assembly, the R&D Blueprint aims to develop and implement a roadmap for R&D preparedness, and to enable roll-out of an emergency R&D response as early and as efficiently as possible for emerging pathogens for which there are no, or insufficient, preventive and curative solutions. In December 2015 WHO convened a workshop to identify a short-list of pathogens to be prioritized immediately. Zika was identified as a serious risk, necessitating further action as soon as possible.

The emergency research and development plan has been tailored to the current state of understanding of Zika fever and addresses research and development needs for novel means of vector control, diagnostics, vaccines, and therapeutics. The plan further includes coordination of supportive research activities such as the establishment and validation of appropriate animal models, and sharing of information. WHO remains committed to convening and working with all actors in relevant research and development efforts to contribute solutions to this international health concern.

Diagnostic development for Zika virus

Due to the high visibility of the Zika outbreak, a number of In vitro diagnostic (IVD) manufacturers have already expressed an interest in developing assays to support the outbreak. More than 30 IVDs have been developed or are at various stages of development. Of the few IVDs commercially available, even fewer have undergone regulatory premarket assessment.

The strong response from IVD companies to the Zika outbreak is encouraging , however a number of barriers remain to allow for the rapid availability and use of quality IVDs. In order to speed up and facilitate the development and then implementation of IVDs for Zika, WHO is working to provide:

- better definition and prioritization of the needs (i.e. for patients presenting symptoms, surveillance, research, patient monitoring, when and where will the tests be used, multiplex tests). WHO is developing target product profiles (TPPs) in collaboration with multiple partners and conducting a pipeline analysis.
- access to standardized reference materials (to design/validate/calibrate the tests). WHO is coordinating the development of these reference materials in collaboration with partnering organizations.

The variability of quality and performance of assays developed in similar circumstances for Ebola virus highlighted the critical need for independent assessment of these assays and their manufacture. In response to that need, WHO has established the Emergency Use Assessment and Listing (EUAL) Procedure for evaluation of Zika diagnostics. The purpose of the WHO EUAL Procedure is to provide guidance on diagnostic quality, safety and performance to interested United Nations procurement agencies and national regulatory authorities (NRAs) of relevant WHO Member States.

Anti-virals, host-directed therapeutics, and other therapeutic interventions

Given our current lack of understanding of Zika virus infection, clinical progression and pathogenesis, it is not at all certain where there is a role for therapeutic products. As our understanding of the disease progresses we may find that there is such a role in specific target groups (potentially including congenitally infected infants, long-term carriers, auto-immune, etc.).

Given the complexity of testing and using novel therapeutic drugs in pregnant women, it is unlikely at this stage that therapeutics will constitute a priority activity. There could however be a role for small-molecule prophylaxis, similar to malaria prophylaxis, as well as passive immunization with monoclonal antibodies. For such prophylactic interventions, the safety of long-term use will be key, as will the ease of administration and affordability. Other factors that will need to be taken into account for candidate prioritisation will be the target population and also the mechanism of action leading to microcephaly, Guillain-Barré Syndrome and other complications.

Vaccine development against Zika virus diseases

Zika virus (ZIKV) belongs to the family of flaviviridae and to the antigenic complex Spondweni. It is also closely related to the four dengue viruses, as evidenced by strong serologic cross-reactivity. Genotyping and geographical analysis have revealed an African and an Asian lineage, but sequence homology is high and the clinical and serologic relevance is unclear. It is assumed that a ZIKV vaccine can be developed building on the same technologies that have been successfully used to develop human flavivirus vaccines (Yellow Fever, Tick-Borne Encephalitis, Japanese Encephalitis, Dengue).

WHO has conducted a landscape analysis of approaches taken by commercial, governmental, academic and any other known entities towards the development of ZIKV vaccine candidates. This information is being updated continuously with available information.

The landscape analysis revealed 18 active programmes (including 5 academic groups and 15 commercial entities, some working in collaborative partnership). A few additional institutions are still considering options. Several developers are pursuing different strategies in parallel. Vaccine approaches include purified inactivated virus, nucleic acid based vaccines (DNA, RNA), live vectored vaccines, subunit vaccines, VLP technologies and live recombinant approach. Most are building on existing flavivirus vaccine technology and know-how.

All programmes are at an early preclinical stage of development but some have been ongoing for several months, and others expect to be able to progress very quickly. Phase 1 clinical studies are expected to begin as of end of 2016. Common obstacles to ZIKV vaccine development have been surveyed and will be presented.

WHO has initiated a consultative process to develop a target product profile for a Zika vaccine for use in the emergency context and targeted at the protection of women in child-bearing age and pregnant women.

New tools for Vector control

Vector-borne diseases (VBDs) account for 22 % of the estimated global burden of communicable diseases. No effective vaccine or medication is available for some diseases, and vector control is the only option. Vector control strategies have a proven track record of successfully reducing or interrupting disease transmission when coverage is sufficiently high.

This landscape analysis identifies new tools under development for:

- Mechanical approaches, such as in ovitraps;
- Chemical approaches, such as in outdoor residual spraying, insecticides with both adulticidal and lavicidal properties, the replacement of chemical compounds with plant extracts, insect growth regulators, the use of sugar baits, and alternative delivery approaches;
- Biological approaches, such as in the use of bacterial control measures (e.g. *Bacillus thuringiensis israelensis* and Wolbachia), fungal control measures, and the use of copepods as predators; and
- Genetic approaches, such as the Sterile Insect Technique, the release of insects carrying a dominant lethal gene (RIDL), RNAi-boosted insect immune responses, and homing endonuclease genes (gene drives).

Vector control methods could be made more efficient, effective and ecologically sound through a combination of approaches, for example: basing decisions increasingly on local determinants, using a range of interventions, covering several diseases and using existing systems and local human resources.[1]

The Vector Control Advisory Group (VCAG) on new tools was constituted by WHO as an advisory body on new forms of vector control for malaria and other vector-borne diseases.[2] The VCAG meets annually to determine whether the evidence about new tools is sufficient to justify its potential application for public health use in one or more environmental settings. An emergency meeting of VCAG to review new tools relevant to the Zika public health emergency of international concern is scheduled for March 2016.

[1] http://apps.who.int/iris/bitstream/10665/44765/1/9789241502788_eng.pdf
[2] http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/

Product pipelines:

WHO has been mapping the R&D pipeline for Zika countermeasures in order to prioritize medical products and approaches that should be fast-tracked into development. These will be reviewed by expert advisory committees as soon as possible.

Diagnostic Pipeline: PCR and Serology Tests

DISCLAIMER: Information source: public domain and or provided by developers and manufacturers. [Not verified by WHO]
(As of 2 March 2016)

I. Lab based use: nucleic acid test kits

Test Developer /Manufacturer	Brief description	Regulatory Approval/Commercialization Plans
Genekam Zika virus PCR Genekam Biotechnology AG	PCR kits: Zika virus (Single Check) PCR kit FR325 Zika virus (Double Check) PCR kit FR340 Zika virus, Dengue virus and Chikungunya virus (multiplex) PCR kit FR342: IN DEVELOPMENT	Kit FR325 and FR340 are currently available under RUO Data is being prepared for submission to regulatory authorities (e.g. CE, FDA and WHO EUAL for approvals.)
ZIKV PCR kit by Fast-track Diagnostics	PCR based in vitro test for the qualitative detection of Zika viral nucleic acid. The assay targets the NS5 genomic region of the Zika virus genome and it is designed to detect both the Asian and the African lineage of Zika virus. FTD Zika includes Streptococcus equi (S equi) as an internal control.	Currently available under RUO, CE-label received Feb 2016. Planning to submit to the US FDA EUA
RealStar®Zika Virus RT-PCR Kit 1.0 (Altona, Germany)	PCR kit for detection of Zika virus specific RNA	CE/IVD certified on Feb 2016 Submitted to WHO EUAL
GenArraytion/Luminex Multiflex bead-based assay panel	Multiplex end-point detection for “Mosquito-borne Panel” Zika Virus (4 targets) Dengue Virus Serotypes 1-4,Chikungunya Virus, West Nile	

	Virus, Yellow Fever Virus, Plasmodium falciparum	
Genesig® Advanced Kit (Genesig, UK)	PCR kit for Zika Virus polyprotein gene	
MyBioSource Zika PCR Kit (USA)	PCR kit for Zika virus RNA	
Statens Serum Institut (Denmark)	PCR test service (sample submission to SSI)	
Zika Real time PCR kit (Liferiver, China)	PCR kit for Zika virus RNA	Submitted to WHO EUAL
Co-Diagnostics, Inc.	Qualitative PCR kit for the detection of Zika virus nucleic acids.	Available as RUO initially with commercialization plans under discussion. Plan to submit US FDA, India Regulatory, and WHO EUAL
Kit Nat by Fiocruz (Brazil)	Zika, Dengue and Chikungunya multiplex PCR kit	
Experimental Therapeutics Centre (ETC) Singapore	Developing a multiplex PCR assay that will be used in hospital laboratories. The targets are dengue virus, chikungunya virus and Zika virus.	Plan to submit to Health Sciences Authority (Singapore), EU and US FDA.
Vela Diagnostics Zika RT-PCR test (VELA Diagnostics, Singapore)	PCR kit – Zika PCR assay to be added to current multiplex PCR kit containing Chikungunya and Dengue (Tropical Infections Panel)	
Vista NanoBioSensor Vista Therapeutics, USA	Identification of viral particles using nanotechnology	
Thermo Fisher		
Siemens Healthcare Diagnostics		
SD Biosensors	Zika PCR Kit	
SolGent	Zika, Dengue and Chikungunya multiplex PCR kit	

II. ELISA based tests

Test Developer/Manufacturer	Brief description	Regulatory Approval/Commercialization Plans
Euroimmune (Germany) IIFT Arboviral Fever Mosaic 2 (IgG/IgM)	Anti-Zika Virus IIFT (IgM or IgG) utilise Zika virus-infected cells as the antigenic substrate. Positive and negative results are evaluated by fluorescence microscopy.	Received CE labelling Approved by the Brazilian authorities (ANVISA). Available as Research Use Only (RUO) in the US Registration in process in: Australia, Venezuela, Peru, El Salvador, Canada, Paraguay, Ecuador, Mexico and Serbia
Euroimmune (Germany) (Anti-Zika) IgM ELISA	Anti-Zika Virus ELISA (IgM) provide fully automated antibody detection using microplates coated with a recombinant protein from Zika virus.	Received CE labelling Registration in Brazil (ANVISA) has been requested. Submitted to WHO EUAL Available as RUO in the US Registration in process: Australia, Venezuela, Peru, El Salvador, Canada, Paraguay, Ecuador, Mexico and Serbia
Euroimmune (Germany) (Anti-Zika) IgG ELISA	Anti-Zika Virus ELISA (IgG) provide fully automated antibody detection using microplates coated with a recombinant protein from Zika virus.	Received CE labelling Registration in Brazil (ANVISA) has been requested. Submitted to WHO EUAL Available as RUO in the US Registration in process: Australia, Venezuela, Peru, El Salvador, Canada, Paraguay, Ecuador, Mexico and Serbia
Zika Virus IgG (ZK-IgM) Elisa kits by MyBiosource (USA)	Double-antigen sandwich ELISA for Human ZV-IgM	
Zika Virus IgG (ZV-IgG) ELISA Kit (MyBiosource, USA)	Double-antigen sandwich ELISA for Human ZV-IgG	

US Center for Disease Control and Prevention CDC (USA)	Zika IgM Antibody Capture ELISA (Zika MAC-ELISA)	US FDA EUA (Feb 26, 2016). Available only to qualified labs (domestic and international); not for US hospitals or other primary care settings. For presumptive detection of Zika virus specific IgM in human sera or CSF alongside a patient matched serum specimen from individuals meeting CDC Zika virus clinical and epidemiological criteria
SD Biosensors	Under development – Zika Antigen, IgM, IgG	

I. RDT type tests

Test Developer/Manufacturer	**Brief description**	**Regulatory Approval/Commericalization Plans**
Biocan Diagnostics (Canada)	Mix of ZIKV NS1 and Envelope protein (for IgM and IgG detection)	Approved for sale in Brazil
Biocan Diagnostics	Cassette format: Dengue IgG/IgM, NS1 Ag +Chikungunya IgG/IgM Ab + Zika IgG/IgM Combo	
Orangelife	Ag/Ab based test for Zika With smart reader	
NG Biotech Z.A.	Under development: RDT to detect Zika antibodies	Plan to submit to CE and US FDA

InBios	Developing an antigen detection test (during acute/febrile phase and an IgM/IgG test for convalescent phase samples.	Will be initially available as RUO. Plan to submit for CE licensing, WHO EUAL and US FDA EUA
SD Biosensors	Under development: Zika NS1 Ag Test Kit, Zika Ab Test Kit , Zika IgG/IgM Test Kit	Plan to submit to MFDS (Ministry of Food and Drug Safety, Korea) for Free sales certificate and to the WHO EUAL

Note: A number of additional diagnostic developers and companies are considering or actively developing Zika diagnostics including: Biomerieux, Alere, Cepheid, Hema diagnostic system, Altomo diagnostics, Orasure, Access Bio, Chem Bio, DiaSorin, Inc., Siemens but details have not been provided.

Therapeutics

Therapeutic	Activity against Zika (or other Flavi's)	In Vitro and In Vivo data (EC50s, Specificity index, cell type)	Safety/ Use in pregnant women	Availability/ Feasibility
Amodiaquine	not known	Dengue EC90=2.7uM SI ~10 on BHK-21 cells.	Not thought to be teratogenic. Occasional SAE (neutropenia, agranulocytosis, hepatotoxicity) with long-term use in populations with CYP2C8 gene variants.	Widely used for malaria prophylaxis. Thought to have had benefit in Ebola patients through antiviral activity.
Chloroquine	Dengue: no decrease in viraemia in adults	Dengue: 0.5 ug/ml in vero cells. No effect in C6/36 cells.	Safe	Was widely used for malaria prophylaxis. Readily available.
Ribavirin	Not effective for dengue in NHPs. Decrease YF mortality in hamsters.	Zika: EC50 = 140 ug/ml Vero SI >55 Dengue: EC50 = 20 ug/ml Vero SI >400. YF: EC50=42ug/ml vero SI =174	Teratogenic	Readily available.
Interferon a	No effect on JEV in infants.	JEV: EC50=4.8 IU/ml Vero. Zika: EC50= 34 IU/ml Vero.		
BCX4430 (Biocryst, USA)	dose-related decreases in YF mortality in hamsters	YF: EC50= 8.3 ug/ml Vero SI = ~5 DENV: EC50=13ug/ml WNV: EC50=16 ug/ml	Phase 1 safety completed. No information on teratogenicity.	
GS-5734 (Gilead, USA)	-	under investigation. Likely.	Phase 1 safety completed. No information on teratogenicity.	

NITD008	DENV-2 in mice: dose-dependent reduction in viraemia and mortality	DENV: EC50 = 3uM WNV: EC50=5 uM YF: EC50=3uM	no human safety data.	time to human safety data likely to be long.
Monoclonal antibodies	Passive immunization is expected to provide short-term protection		Passive immunization with monoclonal antibodies unlikely to present any safety issues unless there is antibody-mediated pathology.	Short half-life, high cost, and difficult administration (i.v. or possibly i.m.) may make this unsuitable for broad population. Approaches to increase half life may be considered.

Vaccines

(alphabetic order, status 3 March 2016)

Institution	Technology	Status & timelines	Collaboration
Bharat	Inactivated purified virus as priority project ; VLP with pRME protein	Preclinical work ongoing, GMP lots 3Q2016	
Bio-Manguinhos / Fiocruz	Inactivated purified ; YF17DD chimeric ; VLP ; DNA	Work initiated	Under consideration
Butantan	Live dengue recombinant ; inactivated purified	Work initiated	Collaboration with US NIH
US CDC	DNA plasmid expressing VLP ; live recombinant adenovirus	Work initiated	
Hawaii Biotech	Insect cell line produced recombinant proteins plus Alhydrogel or proprietary adjuvant fom collaborator	Work initiated. GMP lots 4Q2016	Under discussion
InOvio/GeneOne	DNA – electroporation; work initiated	Preclinical work initiated	
Institut Pasteur	Lentivirus-vectored, measles vectored	Work initiated	Measles vectored work in collaboration with Themis
NewLink	Purified Inactivated virus	Work initiated, clinical evaluation 2018	
US NIH	Zika targeted mutation live attenuated (longer-term), DNA, live VSV recombinant	Work initiated	Various
Novavax	E protein – nanoparticles	Preclinical work initiated	
Replikins	Synthetic replilink peptides	Preclinical work initiated	
Sanofi	ChimeriVax (YF17D) ; other undisclosed technologies	Work initiated	Under consideration
Themis Bioscience	Measles vaccine virus vector (live)	Work initiated	Institut Pasteur
Valneva	Purified inactivated vaccine	Work initiated	

In addition, the following institutions have communicated about their active consideration of the field or have committed planning/discovery stage activities: CureVac, Geovax, GlaxoSmithKline, Institut Pasteur, Johnson & Johnson, Merck, Oxford University, Pax Vax, Pfizer, Profectus Biosciences, Protein Sciences, Sementis, Sinergium, Takeda.

Preclinical work refers to animal studies

Vector Control Methods

This review does not cover community-based or environmental control approaches, such as removing containers of standing water

Control Approach	Specific control	Development	Location(s)
Mechanical	Ovitraps – including demonstration of impact on disease transmission rated with other flaviviruses (i.e. Dengue), ongoing efforts to improve the efficacy of traps through the use of baits and attractants as well as insecticides.		Bangladesh, Brazil, Malaysia, Peru, Puerto Rico, Thailand.
Chemical	Ongoing development of chemical agents, including trials in novel approaches for outdoor residual spraying, the development of insecticides with both adulticidal and lavicidal properties, the replacement of chemical compounds with plant extracts, the use of insect growth regulators, the use of sugar baits, and development of alternative delivery mechanisms.		Cameroon, Colombia, India, Malaysia, Peru, Republic of Korea, USA Venezuela
Biological	*Bacillus thuringiensis israelensis* (Bti)	Field trial testing the effectiveness of a space-sprayed Bti formulation in the control of dengue in two hotspots using truck-mounted Ultra Low Volume generators and mist blowers demonstrated notable decreases in cases of the disease. Other field trials have demonstrated combined efficacy with other biocontrols agents, such as spinosads.	Malaysia
	Wolbachia	Field trial of the repeated release from two sites of *Aedes aegypti* infected with wMel *Wolbachia* demonstrated increasing frequency of infection. Follow-up field trials established the longer-term persistence of virus-blocking in *Wolbachia*-infected mosquitoes after their release and establishment in wild populations. *Wolbachia* have been considered as a possible control mechanism for Zika in *Aedes aegypti* but the ability of this bacteria to block the zika virus has yet to be demonstrated.	Australia
	Fungal control measures	Laboratory trials of *Metarhizium anisopliae* as a biocontrol agent for *Ae. Aegypti* demonstrated notable larvicidal activity. It has received regulatory approval as a biopesticide in the USA. Laboratory and semi-field trial of *Beauveria bassiana* as a biocontrol agent for *Ae. Aegypti* demonstrated varied levels of mosquito survival and fecundity. This agent has also been used in concert with insect growth regulators in ovitraps.	Australia, United Kingdom
	Copepods as predators	Semi-field and field trials of copepods have demonstrated notable reductions of larvae and adult mosquitoes.	USA, Viet Nam

Genetic	Sterile Insect Technique	The sterile insect technique is a proven and environment-friendly technology which has been applied to control insect pests and disease vectors for over 50-60 years now, on all continents. The SIT has been an extremely successful strategy, always as a component of an Area-Wide Integrated Pest Management or Integrated Vector Management (IVM) approaches. The SIT relies on the mass-rearing of a target species, the separation of males from females in the case of disease vectors, the sterilization of males by means of ionizing irradiation, and the handling, transport and release of sterile males in target areas where we ask these males to compete with wild males for mating to wild females. Since the released males are sterile, these matings will also be sterile, so the wild females will have no viable offspring. Over time, and through the systematic and continuous releases of sterile males, the targeted population will diminish and will get suppressed. In other words, the SIT is a type of "insect birth control. The SIT-based approach has been developed for Aedes aegypti and Aedes albopictus	Italy, Indonesia and Mauritius
	Release of insects carrying a dominant lethal gene (RIDL)	Field trial of genetically modified male mosquitoes with RIDL demonstrated that modified mosquitoes can successfully compete with wild males in terms of finding and mating with wild females. Modelling experiments have been used to improve release strategies for population suppression. A year-long field trial of RIDL resulted in notable decreases in adult and larvae *Aedes aegypti* populations. A second field trial of adult male mosquitoes (both RIDL and a wild-type laboratory strain) showed similar field longevity but reduced dispersal compared to the unmodified strain.	Brazil, Cayman Islands, Malaysia
	RNAi-mediated sterility	Laboratory trials in *Aedes aegypti* larvae have demonstrated RNAi-mediated sterility and inhibition of female development.	Canada
	RNAi-boosted insect immune response	Lab trial where *Aedes aegypti* were genetically modified to exhibit impaired vector competence for dengue type 2 viruses.	USA
	Homing endonuclease Genes (gene drives)	Laboratory trials determined homing endonucleases can be used to manipulate the genome of *Aedes aegypti*. A strategy was developed to apply advances in genome editing (CRISPR-CAS9) to earlier work on gene drives. In particular, progress in developing drives to control *Anopheles gambiae* was highlighted. Laboratory trials of a CRISPR-CAS9 mediated gene drives confered genes associated with an ability to transmit the malaria pathogens in *Anopheles stephensi*. Laboratory trials of a CRISPR-CAS9 mediated gene drive to confer a recessive female-sterility phenotype in *Anopheles gambiae*.	France, Italy, USA