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Overview of Arbovirus vaccines

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Declaration of interests

I am an inventor of patents for Dengvaxia

I have shares in Sanofi

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Arboviruses

Arbovirus is the short name for **ar**thropod-**bo**rne virus.

Arboviruses are viruses that are spread by invertebrate animals (arthropods), most commonly blood-sucking insects.

Many arboviruses have complex life cycles and use birds as the primary host with vertebrate animals including man as the dead-end host.

Arboviruses that are occurring as a global epidemic have adapted to humans as the primary host.

Arboviruses by mode of Transmission

Virus Family	Viral Genus	Virus	Vector Species
	Orthobunyavirus	California serogroup viruses	Mosquito (Aedes sp.)
	Phlebovirus	Rift Valley Fever virus	Mosquito (various)
Bunyaviridae	Phlebovirus	Toscana virus	Sandfly (Phelbotomus sp.)
	Phlebovirus	Phlebotomus fever virus	Sandfly (phelbotomus)
	Phlebovirus	Sandfly Fever Naples virus	Sandfly (phelbotomus)
	Phlebovirus	Sandfly Fever Sicilian virus	Sandfly (phelbotomus)
	Phlebovirus	Heartland virus	Tick (A. americanum)
	Phlebovirus	Severe fever with thrombocytopenia syndrome virus	Tick (H. longicornis)
	Nairovirus	Crimean Hemorrhagic Fever virus	Tick (Hyalomma sp.)
Flaviviridae	Flavivirus	Dengue Virus	Mosquito (Aedes sp.)
	Flavivirus	Zika virus	Mosquito (Aedes sp.)
	Flavivirus	Yellow fever virus	Mosquito (Aedes sp.)
	Flavivirus	West Nile Virus	Mosquito (Culex sp.)
	Flavivirus	St. Louis Encephalitis virus	Mosquito (Culex sp.)
	Flavivirus	Japanese encephalitis virus	Mosquito (Culex sp.)
	Flavivirus	Murray Valley encephalitis virus	Mosquito (Culex sp.)
	Flavivirus	Usutu	Mosquito (various)
	Flavivirus	Omsk Hemorrhagic fever virus	Tick (dermacentor)
	Flavivirus	Kyasanur Forest Diesease virus	Tick (Haemaphysalis sp.)
	Flavivirus	Tick-borne encephalitis virus	Tick (Ixodes and Haemaphysalis sp.)
	Flavivirus	Powassan virus	Tick (Ixodes sp.)
Orthomyxoviridae	Thogotovirus	Bourbon virus	Tick (A. americanum)
Reoviridae	Coltivirus	Colorado tick fever	Tick (dermacentor)
Rhabdoviridae	Vesiculovirus	Vesicular Stomatitis (New Jersey) virus	Sandflies (Lutz. Sp) | Mosquitos (various)
	Vesiculovirus	Chandipura	Sandlfy (Phlebotomus Sp.)
Togaviridae	Alphavirus	Barmah Forest Virus	Mosquito (Aedes and Culex sp.)
	Alphavirus	Chikungunya virus	Mosquito (Aedes sp.)
	Alphavirus	Venezuelan equine encephalitis virus	Mosquito (Culex sp.)
	Alphavirus	Sindbis virus	Mosquito (Culex sp.)
	Alphavirus	Equine encephalitis virus	Mosquito (Culex sp.)
	Alphavirus	Mayaro virus	Mosquito (Haemagogus sp.)

Schneider, C.A.; Calvo, E.; Peterson, K.E. Arboviruses: How Saliva Impacts the Journey from Vector to Host. *Int. J. Mol. Sci.* **2021**, *22*, 9173. https://doi.org/10.3390/ijms22179173

Clinical Syndromes of the Arboviruses

Systemic Febrile Illness

- Chikungunya, O'nyong-nyong, Ross River, Dengue, Oropouche.

Fever with Arthritis

- Chikungunya, Ross River, O'nyong-nyong.

Encephalitis

- Japanese encephalitis, West Nile virus, Venezuelan equine encephalitis, Western equine encephalitis, Murray Valley encephalitis, Tick-borne encephalitis.

Hemorrhagic Fever

- Yellow Fever, Dengue, Rift Valley Fever, Chikungunya, Korean hemorrhagic fever, Crimean-Congo Hemorrhagic Fever.

Congenital malformations

- Zika, Oropouche?

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Climate change could shift disease burden from Malaria to Arboviruses in Africa

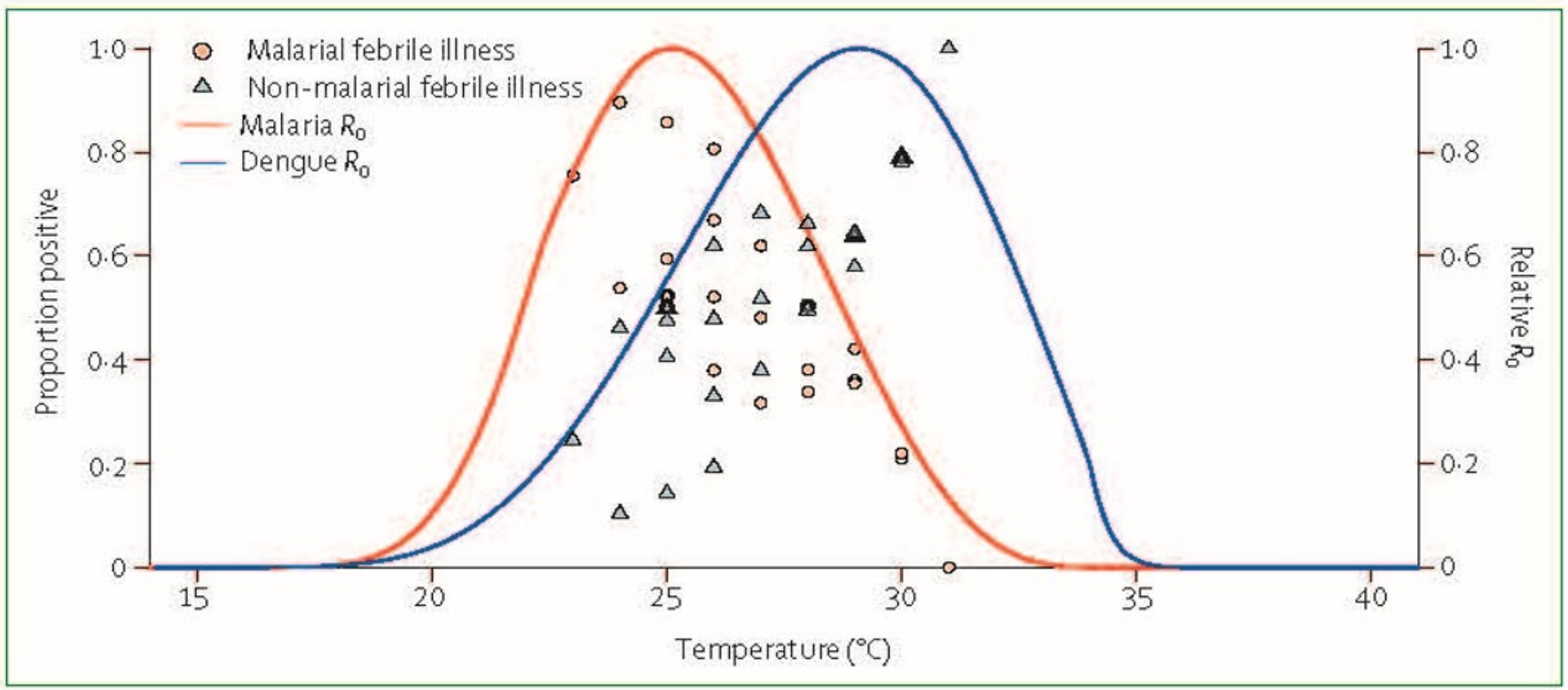

Figure 1: **Malarial and non-malarial fever among Kenyan children from 2014 to 2018 versus temperature, overlaid on R_0 curves for malaria and dengue**

Erin A Mordecai, Sadie J Ryan, Jamie M Caldwell, Melisa M Shah, A Desiree LaBeaud. Climate change could shift disease burden from Malaria to Arboviruses in Africa: Lancet Planet Health 2020; 4: e416–23

Licensed and approved flavivirus and alphavirus human vaccines

Virus	Vaccine (manufacturer)	Construct Type	Target Population	Approval Status (year of first approval)
Flavivirus vaccines				
Dengue virus (DENV serotypes 1-4)	Dengvaxia (Sanofi Pasteur)	Quadrivalent, live-attenuated, YFV-17D backbone, Vero cell-derived	9–45 years, with previous DENV infection	Licensed (2015)
	Qdenga (Takeda)	Quadrivalent, live-attenuated, DENV2 backbone, Vero cell-derived	>4 years	Licensed (2022)
Yellow fever virus (YFV)	YF-VAX (Sanofi Pasteu; Stamaril)	Live-attenuated, YFV-17D, produced in chicken embryos	>9 months	Licensed (1986)
	17DD-YFV vaccine (Bio-Manguinhos/Fiocruz)			WHO-prequalified manufacture since 2000
Japanese encephalitis virus (JEV)	IMOJEV (Sanofi Pasteur)	Live-attenuated, YFV-17D backbone, Vero cell derived	>9 months	Licensed (2010)
	SA14-14-2 (Chengdu Institute of Biological Products)		>1 year	Licensed (1988)
	IXIARO/JESPECT (Valneva)	Inactivated, alum adjuvant	>2 months	Licensed (2009)
Tick-borne encephalitis virus (TBEV)	FSME-Immun or TicoVac (Pfizer)	Inactivated, alum adjuvant	>16 years; junior formulation >1year	Licensed (1976)
	Encepur (Bavarian Nordic)		>12 years	Licensed (1992)
Alphavirus vaccines				
Chikungunya virus (CHIKV)	IXCHIQ/VLA1553 (Valneva)	Live-attenuated, CHIKV LR2006-OPY1 with 61-amino-acid deletion in non-structural protein 3	>18 years	Approved by FDA under the Accelerated Approval pathway (2023)
	Vimkunya (Bavarian Nordic)	VLP	>12 years	Approved by FDA under the Accelerated Approval pathway (2025)

Daniel J. Rawle, Leon E. Hugo, Abigail L. Cox, Gregor J. Devine & Andreas Suhrbier Generating prophylactic immunity against arboviruses in vertebrates and Invertebrates. *Nature reviews immunology*, Volume 24, Sept 2-24, 621-636

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Licensed and approved flavivirus and alphavirus animal vaccines

Virus	Vaccine (Manufacturer)	Construct Type	Target Population	Approval Status
West Nile virus (WNV)	PreveNile (Intervet)	Live-attenuated, YFV-17D backbone, Vero cell derived	Horses	Licensed (2006)
	INNOVATOR (Zoetis)	Inactivated, MetaStim adjuvant		Licensed (2003)
	RECOMBITEK (Merial)	Recombinant canarypox		Licensed (2004)
Salmon pancreas disease virus (SPDV)	Clynav (Elanco Animal Health)	DNA vaccine	Atlantic salmon (Europe)	Licensed (2017)
	AquaVac PD3 (MSD Animal Health)	Trivalent, including inactivated SPDV, light liquid paraffin adjuvant	Licensed (1983)	
Venezuelan equine encephalitis virus (VEEV)	Equivac TC-83 (Productora Nacional de Biológicos Veterinarios)	Live-attenuated	Horses (Mexico)	FDA emergency use authorization for US Army (1963)
Eastern and Western equine encephalitis viruses (EEEV and WEEV), WNV + VEEV	Core EQ INNOVATOR+V (Zoetis)	Six-valent, inactivated, MetaStim adjuvant	Horses (USA)	Licensed (2018)
JEV+Getah virus (GETV)	JEV/GETV combined vaccine (Nisseiken)	Inactivated	Horses (Japan)	Used since 1979

Daniel J. Rawle, Leon E. Hugo, Abigail L. Cox, Gregor J. Devine & Andreas Suhrbier. Generating prophylactic immunity against arboviruses in vertebrates and Invertebrates. *Nature reviews immunology,* Volume 24, Sept 2-24, 621-636

FDA, Food and Drug Administration; WHO, World Health Organization.

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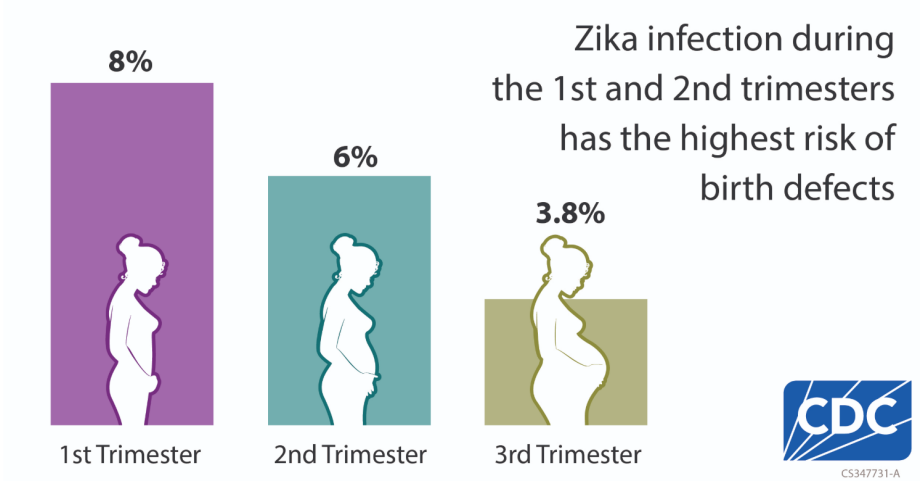
Zika vaccine development



Risk of birth defects is highest in the first and second trimesters.

Vaccine type	Vaccine name	Antigen	Phase	Developer(s)	Adjuvant
Inactivated vaccines	ZPIV	Whole virus	I	NIAID/WRAIR/BIDMC	Alum
	PIZV/TAK-426	Whole virus	I	Takeda Pharmaceuticals	Alum
	VLA1601	Whole virus	I	Valneva Austria GmbH	Alum
	BBV121	Whole virus	I	Bharat Biotech International	Alum
DNA vaccines	VRC5288	prM/E	I	NIAID, VRC	None
	VRC5283	prM/E	II	NIAID,VRC	None
	GLS-5700	prM/E	I	GeneOne Life Science/Inovio Pharmaceuticals	None
Live-attenuated vaccine	rZIKV/D4Δ30–713	rZIKV/D4Δ30–713	I	NIAID	None
mRNA vaccines	mRNA 1325	prM/E	II	Moderna Therapeutics	None
	mRNA 1893	prM/E	II		None
Viral vectored vaccines	MV-ZIKA-RSP	prM/E	I	Themis Bioscience GmbH	None
	MV-ZIKA	prM/E	I	Themis Bioscience GmbH	None
	ChAdOx1 ZIKA	CprME/NS	I	University of Oxford	None
	Ad26.ZIKV.001	ZIKV M-Env	I	Janssen Vaccines and Prevention B.V.	None

Abbreviations: ZPIV, ZIKV, PIZV purified inactivated vaccines. VRC, Vaccine Research Center. prM, premembrane. E, envelope. WRAIR, Walter Reed Army Institute of Research. NIAID, Natioinal Institute of Allergy and Infectious Diseases (USA). BIDMC, Beth israel Deaconess Medical Center. ChAdOx1, Chimpanzee adenovirus Oxford 1. MV, measles virus vaccine

Peng ZY, Yang S, Lu HZ, Wang LM, Li N, Zhang HT, Xing SY, Du YN, Deng SQ. A review on Zika vaccine development. Pathog Dis. 2024 Feb 7;82:ftad036. doi: 10.1093/femspd/ftad036. PMID: 38192053; PMCID: PMC10901608

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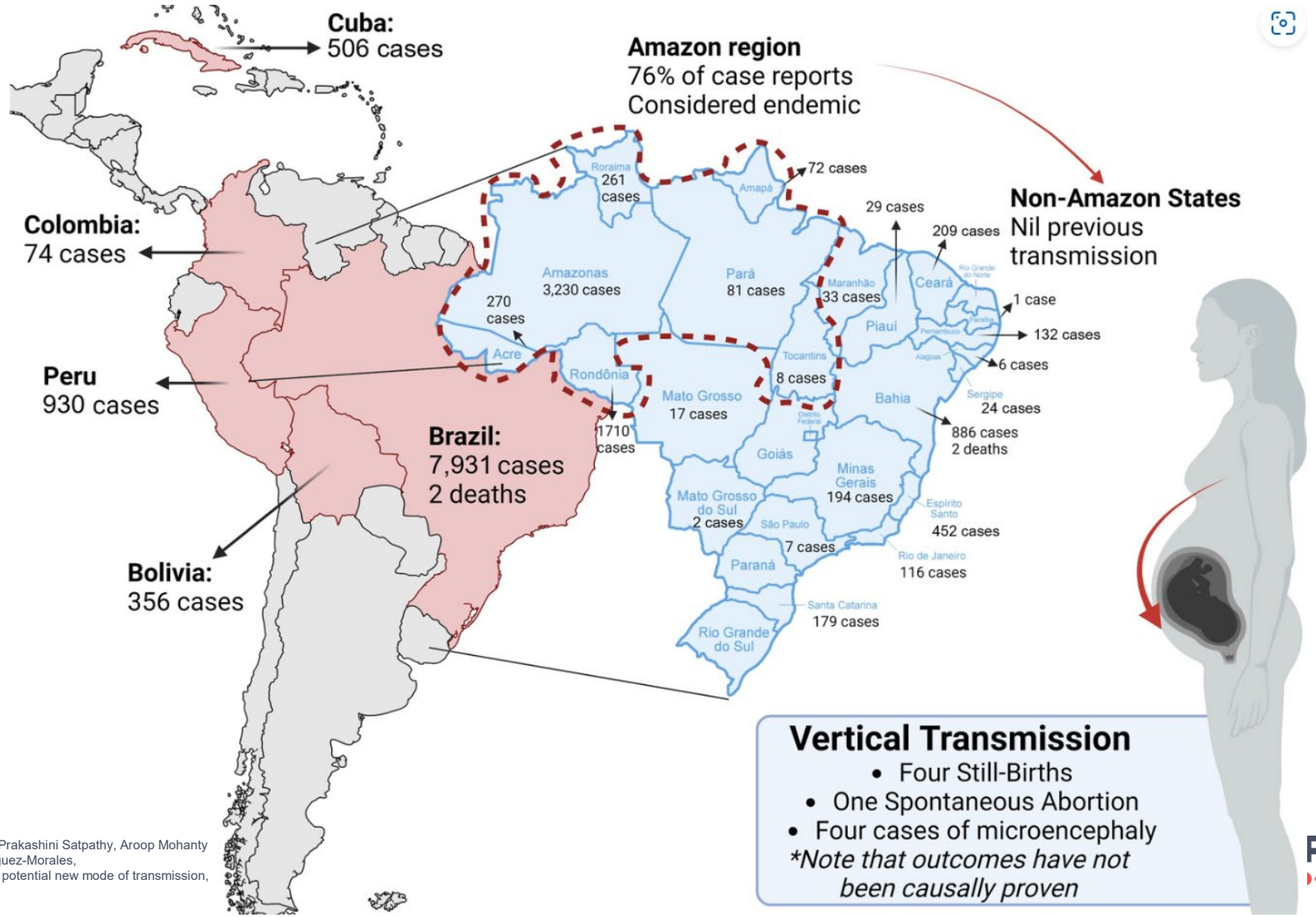
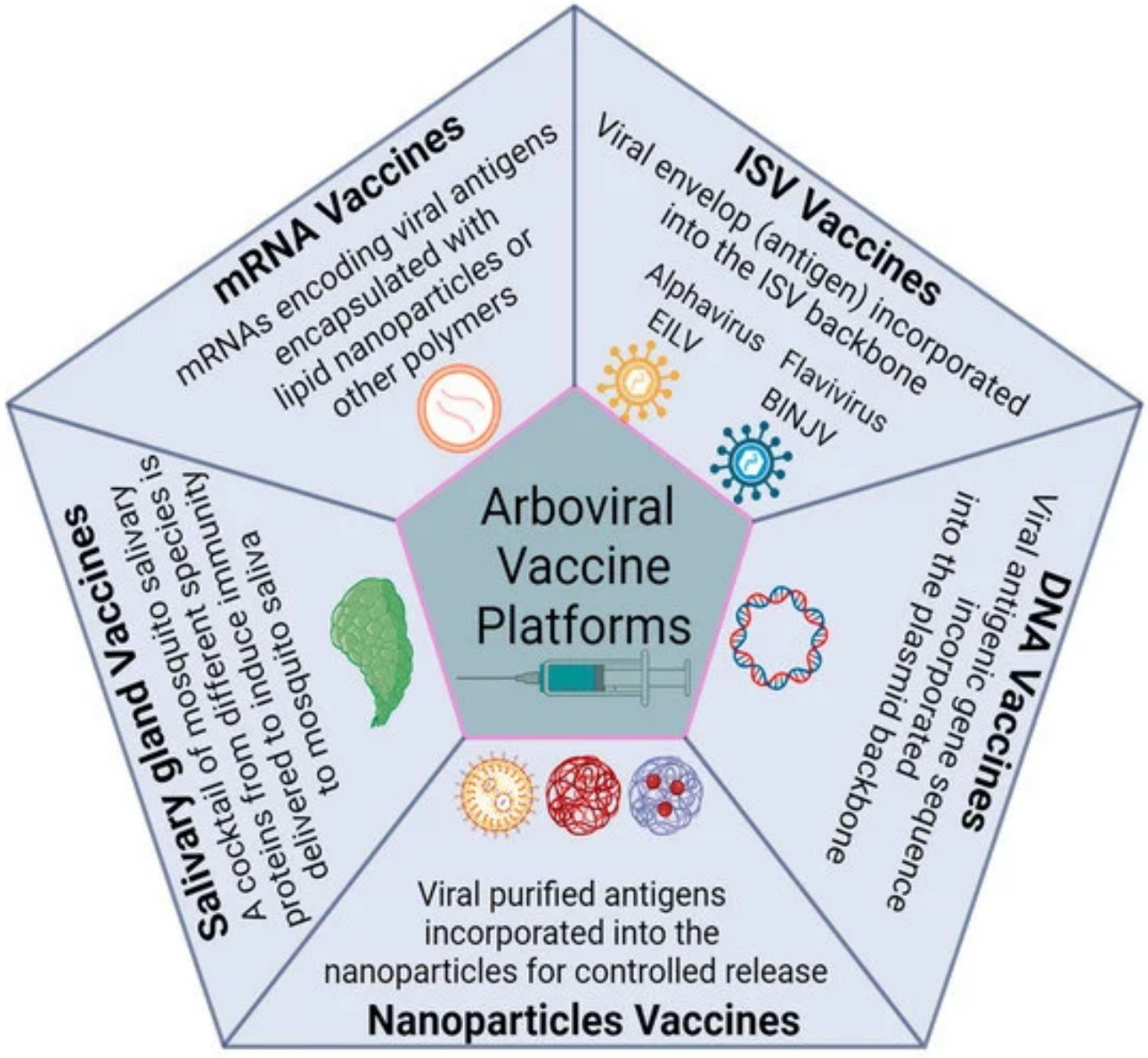
Oropouche virus: Case fatalities and vertical transmission in Latin America: Implications of a potential new mode of transmission?



Ranjit Sah, Shriyansh Srivastava, Rachana Mehta, Sharib Raza Khan, Sachin Kumar, Prakashini Satpathy, Aroop Mohanty , Carolina Ferraz, Jack Feehan, Vasso Apostolopoulos, Camila Luna, Alfonso J. Rodriguez-Morales,
Oropouche fever fatalities and vertical transmission in South America: implications of a potential new mode of transmission,
The Lancet Regional Health - Americas,
Volume 38, 2024, 100896,

Emerging platform technologies for Arbovirus vaccines



Pujhari, S. Recent Advances in Arboviral Vaccines: Emerging Platforms and Promising Innovations. *Biologics* **2024**, *4*, 1-16. https://doi.org/10.3390/biologics4010001

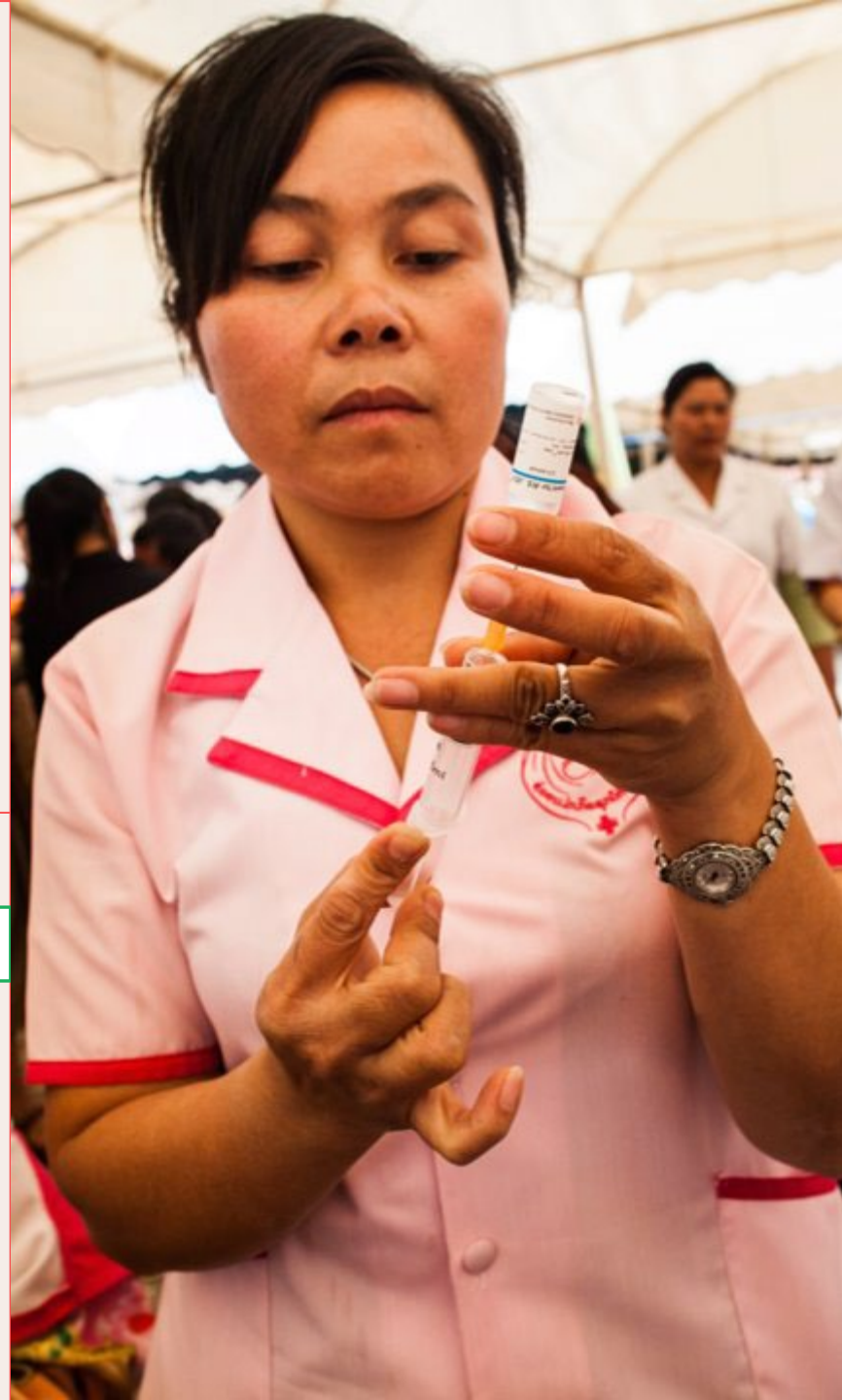
How can Arboviruses be integrated into a Crowded Immunization Schedule?

The growing number of vaccines to deliver at each visit is causing challenges for health care workers and making it harder for countries to consider new vaccine introductions.

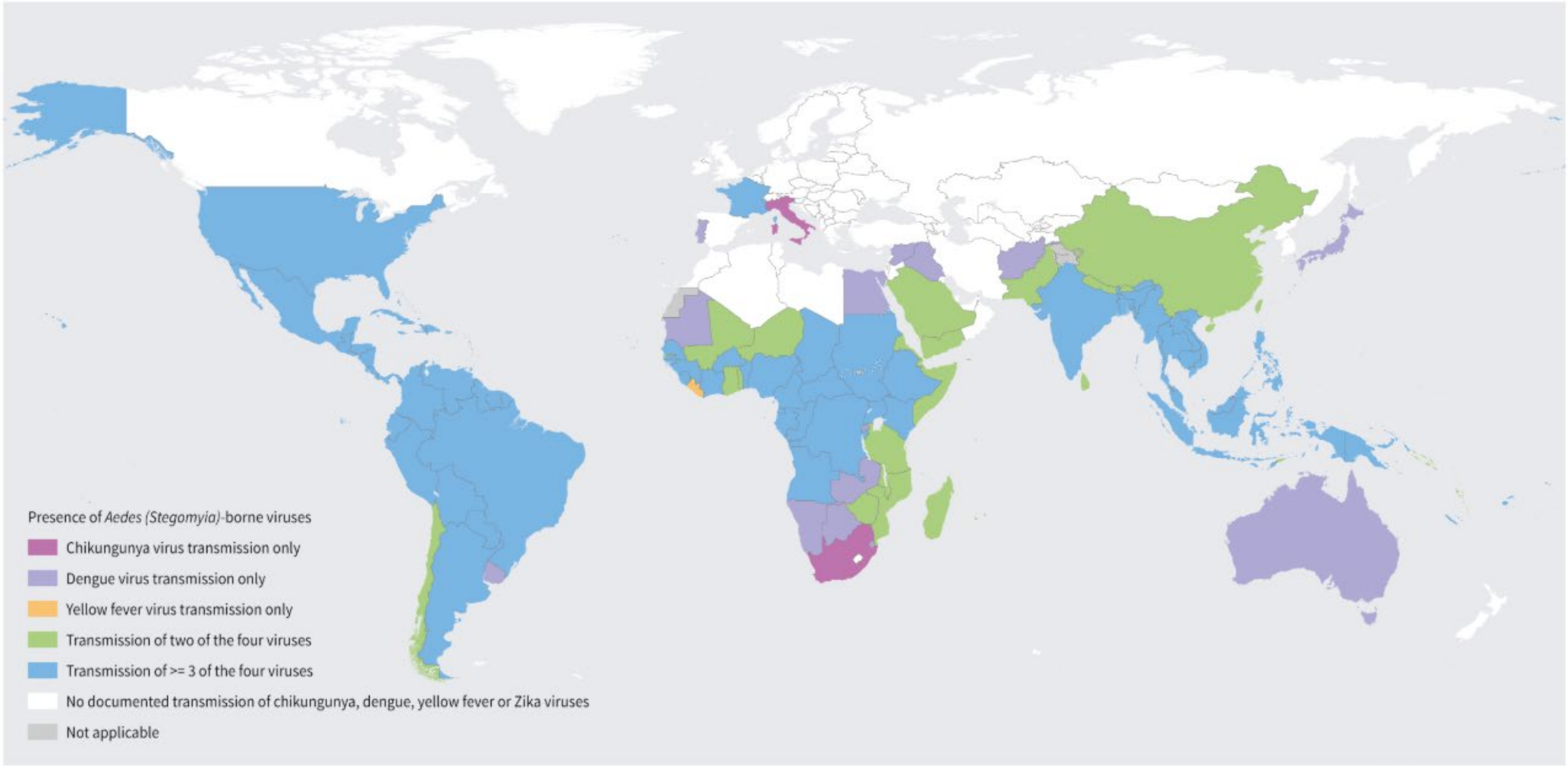
Challenge

Opportunity

Innovations in development, policy, and regulatory approaches are critical to advance combination vaccines.



Countries and territories with current or previous transmission of chikungunya, dengue, yellow fever or Zika viruses



The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: WHO Health Emergencies Programme
Request ID: RITM00065

World Health Organization

Prioritization of novel combination vaccine candidates

PATH, in collaboration with WHO's Immunization, Vaccines and Biologicals Policy Unit, Gavi, and Regional Immunization Technical Advisory Groups (RITAGs), is creating a robust and transparent process for evaluation and prioritization of novel combination vaccine candidates to help guide future vaccine development efforts and investments.

The effort includes:

- ✓ Modeling focused on one specific combination vaccine, MR/YF, to assess its potential cost of delivery, compared to the separate vaccines.
- ✓ Developing a broader set of health impact and economic metrics that are relevant to LMIC settings to evaluate and help in prioritization of combination vaccines.
- ✓ Designing a framework by which to evaluate and identify priority combination vaccines, and to use that framework and the metrics to evaluate a select group of combination vaccine candidates.
- ✓ Supporting a WHO-convened Combination Vaccine Technical Advisory Group (TAG) that will provide technical and strategic insight into this project.

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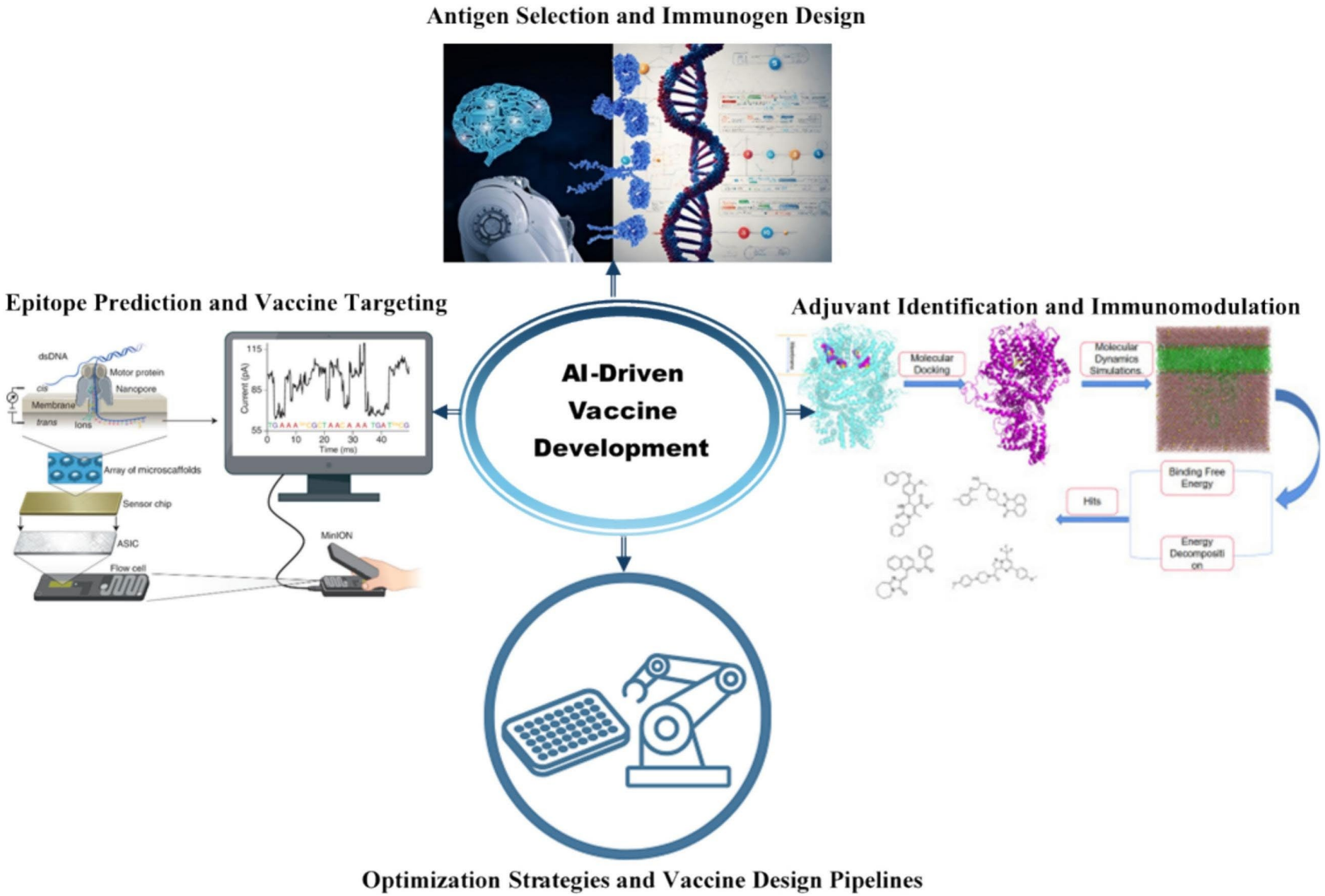

David B. Olawade, Jennifer Teke, Oluwaseun Fapohunda, Kusal Weerasinghe, Sunday O. Usman, Abimbola O. Ige, Aanuoluwapo Clement David-Olawade, Leveraging artificial intelligence in vaccine development: A narrative review, Journal of Microbiological Methods,Volume 224,2024, 106998, ISSN 0167-7012, https://doi.org/10.1016/j.mimet.2024.106998.

Key considerations in Arbovirus vaccine development

Licensure challenges through conventional regulatory pathways	• Outbreak nature of disease make pivotal efficacy studies a challenge for licensure
Correlates of protection	• Some flaviviruses have correlates (based on PRNT) • Chikungunya used correlates to support licensure
Risk of enhanced disease	• Poorly neutralizing antibody can promote entry of virus in the cell • Previous infection with DENV serotype can result in more severe disease with secondary infection • Postulated that previous DENV infection exacerbates ZIKV infection and disease • Cross reactive ZIKV antibodies potentially mediate ADE for DENV

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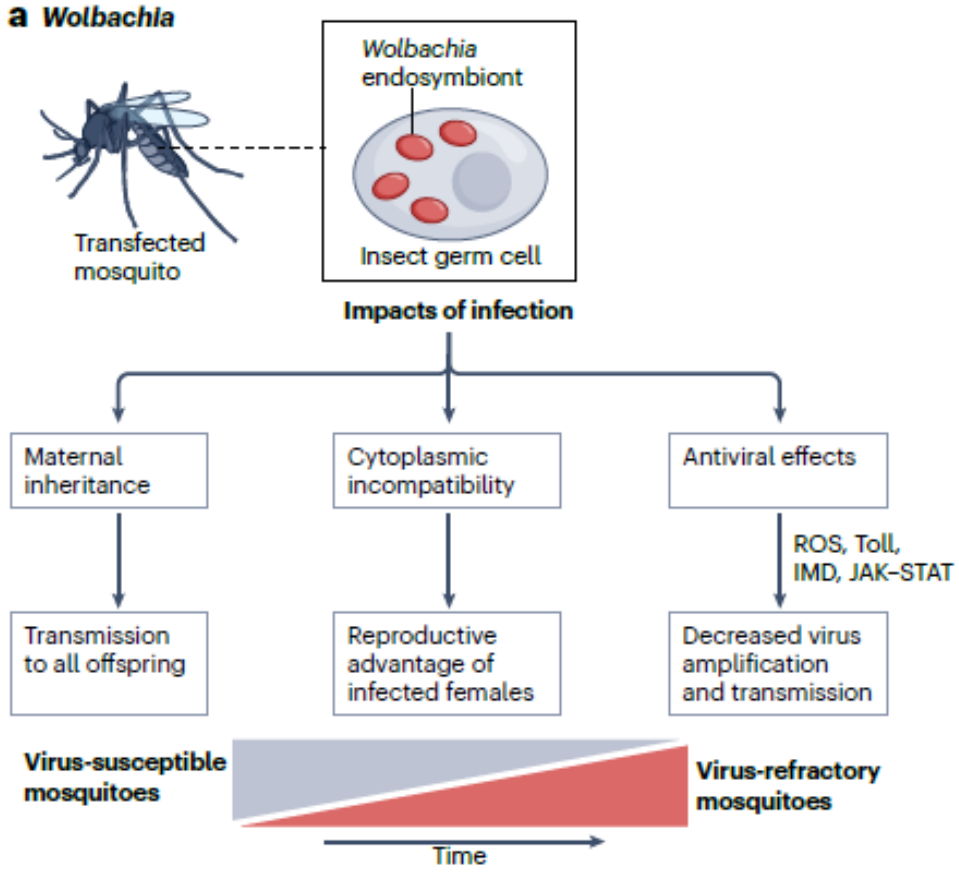
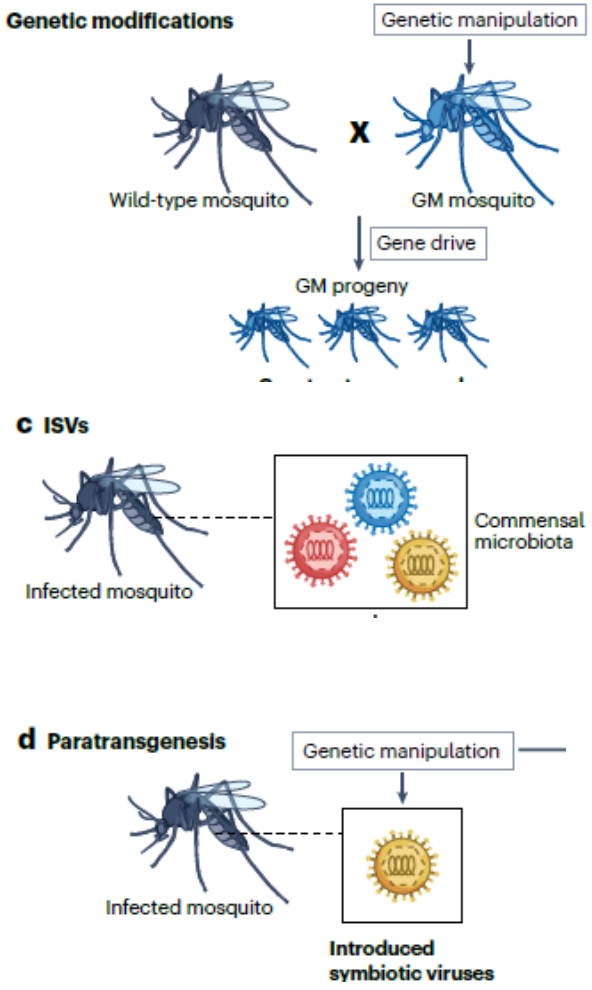
Approaches to inhibit Flavivirus and Alphavirus transmission





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