Vaccines for Vector Borne Diseases

Neil Rellosa, MD

Attending Physician, Division of Pediatric Infectious Disease

Nemours Children's Hospital, Delaware

Assistant Professor of Pediatrics, Sidney-Kimmel Medical College/Thomas Jefferson University

Delaware Immunization Summit 2025

NEMOURS CHILDREN'S HEALTH

Disclosures

- I have no relevant financial relationships with industry to disclose
- I will not discuss off label use and/or investigational use in my presentation

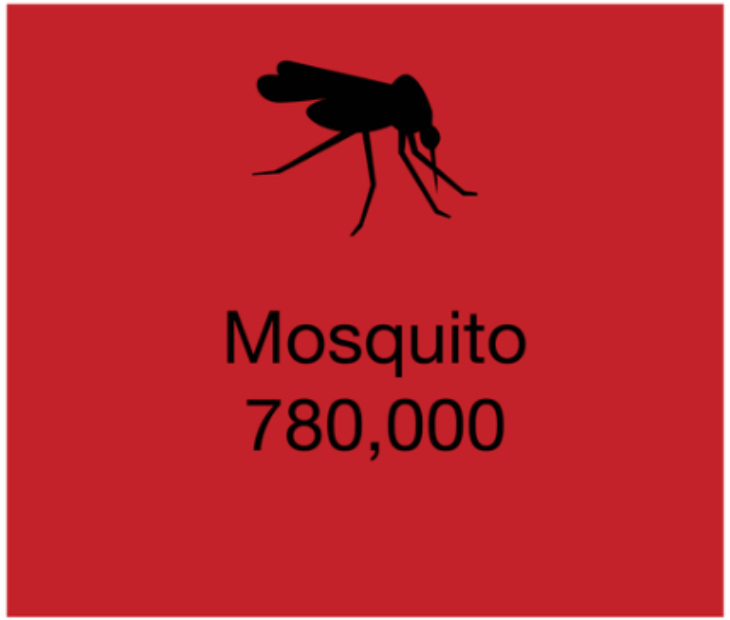
NEMOURS CHILDREN'S HEALTH

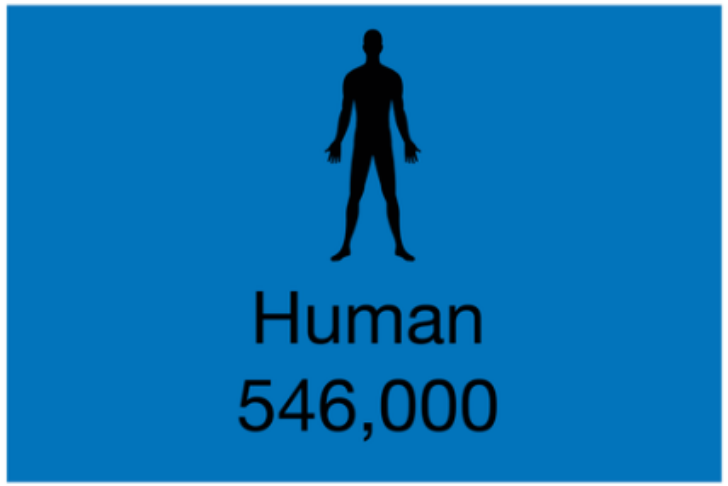
Definition of Vector-Borne Disease: Illness or disease caused by a pathogen (bacteria, virus, parasite) transmitted to humans and other animals through a bite or contact with an arthropod such as a tick, mosquito or flea

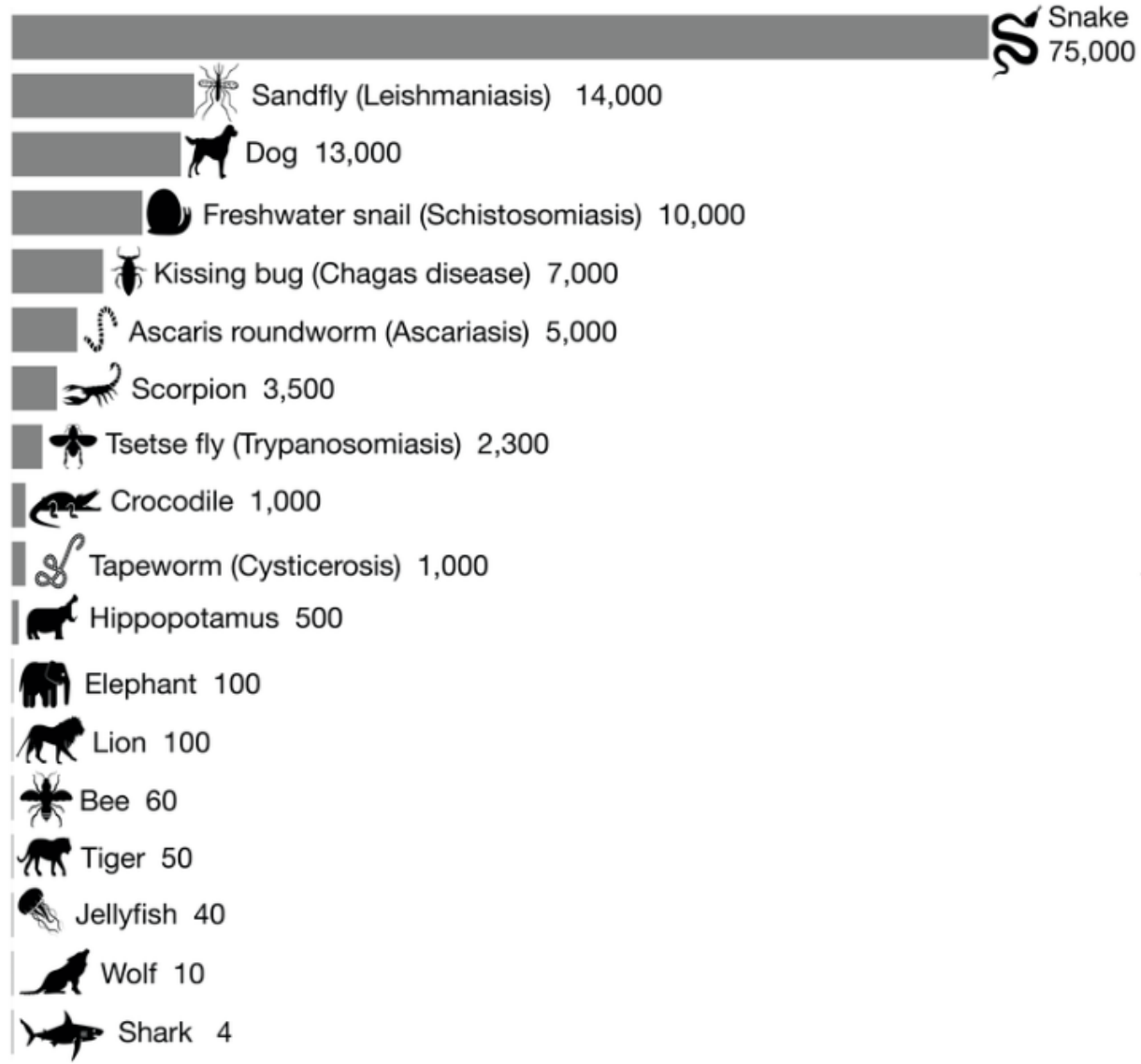
NEMOURS CHILDREN'S HEALTH

Deadliest animals: global deaths by animal, 2016

Our World in Data







Based on data by IHME, WHO, Shark Attack File, CrocBITE, GatesNotes, National Geographic, UN FAO, WWF. Logo source: Noun Project.
Global estimates for some animals have a significant error margin, but expected to be representative of relative magnitude.
The data visualization is available at OurWorldinData.org. There you find research and more visualizations on this topic.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 73 / No. 6
February 15, 2024

Surveillance for Lyme Disease After Implementation of a Revised Case Definition — United States, 2022

Kiersten J. Kugeler, PhD[1]; Austin Earley, MPH[1]; Paul S. Mead, MD[1]; Alison F Hinckley, PhD[1]

Abstract

Lyme disease, a tickborne zoonosis caused by certain species of *Borrelia* spirochetes, is the most common vectorborne disease in the United States. Approximately 90% of all cases are reported from 15 high-incidence jurisdictions in the Northeast, mid-Atlantic, and upper-Midwest regions. After the implementation of a revised surveillance case definition in 2022, high-incidence jurisdictions report cases based on laboratory evidence alone, without need for additional clinical information. In 2022, 62,551 Lyme disease cases were reported to CDC, 1.7 times the annual average of 37,118 cases reported during 2017–2019. Annual incidence increased most in older age groups, with incidence among adults aged ≥65 years approximately double that during 2017–2019. The sharp increase in reported Lyme disease cases in 2022 likely reflects changes in surveillance methods rather than change in disease risk. Although these changes improve standardization of surveillance across jurisdictions, they preclude detailed comparison with historical data.

relies almost exclusively on serologic testing for antibodies to *B. burgdorferi* using a two-tier process (*1*).

Before 2022, national surveillance for Lyme disease required the collection of clinical information, most often coupled with laboratory evidence of infection, to classify cases. As the number of Lyme disease infections has increased, the workload associated with collecting clinical information has proven prohibitive in several high-incidence jurisdictions, leading to the adoption of modified, jurisdiction-specific surveillance practices, including in New York and Massachusetts (*2*, *4*–*6*). These divergent approaches often precluded the reporting of cases to CDC and prevented accurate comparison of trends across jurisdictions and over time (*3*,*7*).

To address this challenge, effective January 1, 2022, the Council of State and Territorial Epidemiologists (CSTE), in partnership with CDC, revised the national surveillance case definition for Lyme disease.† The revised case definition provides for reporting of cases from high-incidence jurisdictions based on laboratory evidence alone, without the need to collect addi

Vital Signs: Trends in Reported Vectorborne Disease Cases — United States and Territories, 2004–2016

Ronald Rosenberg, ScD[1]; Nicole P. Lindsey, MS[1]; Marc Fischer, MD[1]; Christopher J. Gregory, MD[1]; Alison F. Hinckley, PhD[1]; Paul S. Mead, MD[1]; Gabriela Paz-Bailey, MD[1]; Stephen H. Waterman, MD[1]; Naomi A. Drexler, MPH[1]; Gilbert J. Kersh, PhD[1]; Holley Hooks, MPH[1]; Susanna K. Partridge, MPH[1]; Susanna N. Visser, DrPH[1]; Charles B. Beard, PhD[1]; Lyle R. Petersen, MD[1]

On May 1, 2018, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

Abstract

Introduction: Vectorborne diseases are major causes of death and illness worldwide. In the United States, the most common vectorborne pathogens are transmitted by ticks or mosquitoes, including those causing Lyme disease; Rocky Mountain spotted fever; and West Nile, dengue, and Zika virus diseases. This report examines trends in occurrence of nationally reportable vectorborne diseases during 2004–2016.

Methods: Data reported to the National Notifiable Diseases Surveillance System for 16 notifiable vectorborne diseases during 2004–2016 were analyzed; findings were tabulated by disease, vector type, location, and year.

Results: A total 642,602 cases were reported. The number of annual reports of tickborne bacterial and protozoan diseases more than doubled during this period, from >22,000 in 2004 to >48,000 in 2016. Lyme disease accounted for 82% of all tickborne disease reports during 2004–2016. The occurrence of mosquitoborne diseases was marked by virus epidemics. Transmission in Puerto Rico, the U.S. Virgin Islands, and American Samoa accounted for most reports of dengue, chikungunya, and Zika virus diseases; West Nile virus was endemic, and periodically epidemic, in the continental United States.

Conclusions and Implications for Public Health Practice: Vectorborne diseases are a large and growing public health problem in the United States, characterized by geographic specificity and frequent pathogen emergence and introduction. Differences in distribution and transmission dynamics of tickborne and mosquitoborne diseases are often rooted in biologic differences of the vectors. To effectively reduce transmission and respond to outbreaks will require major national improvement of surveillance, diagnostics, reporting, and vector control, as well as new tools, including vaccines.

Table 1. Critical Vector-Borne Diseases (VBDs) and outbreaks[a].

Vector Species		Type of VBD	Pathogen/Parasite/ Virus	Vaccines/Drugs	Estimated Outbreaks[b]
Mosquitoes	Aedes mosquito	Dengue fever	Dengue virus (DENV)-1 to -4	Dengvaxia® (CYD-TDV) (Phase III trial)	3.9 billion cases/128 countriesc
		Yellow fever	Yellow fever virus	YF-Vax	200,000 cases globally
		Chikungunya	Chikungunya virus (CHIKV)	Measles Virus (MV-CHIK) and VRC-CHCKVLP059-00-VP (Phase I trial)	265,000 suspected cases in Brazil[c]
		Zika	Zika virus (ZIKV)	VRC-ZKADNA085–00-VP or VRC-ZKADNA090–00-VP (DNA; Phase I trial) GLS-5700 (DNA; Phase I trial) mRNA-1325 (Phase II trial) ZIKV PIV or BBV121 (Inactivated whole target organism; Phase I trial)	439 cases per 100,000 population in Guna Yala[c]
	Culex mosquitoes	West Nile fever	West Nile virus	ChimeriVax (Phase II trial)	1,757 cases in Columbia district[d]
		Malaria	*Plasmodium (P.) vivax* *P. falciparum* *P. ovale* *P. malariae*	Drugs: Amodiaquine plus sulfadoxine-pyrimethamine Vaccine: Mosquirix™	212 million cases[c]
		Lymphatic filariasis	*Wuchereria bancrofti* *Brugia malayi* *Brugia timori*	Diethyl Carbamazine, Doxycycline	856 million cases/52 countries[c]
	Haemagogus mosquitoes	Yellow fever	Yellow fever virus	YF-Vax	200,000 cases[c]
Ticks	Ixodes pacificus (bear tick)	Lyme disease	*Borrelia (B.) burgdorferi* *B. mayonii* *B. afzelii* *B. garinii*	Doxycycline Ceftriaxone Tetracycline Penicillin	532,125 cases[c]
	Hyalomma tick	Crimean-Congo hemorrhagic fever	Crimean-Congo hemorrhagic fever virus (CCHFV)	Ribavirin	40% fatality rate[c]
	Dermacentor variabilis	Rocky Mountain spotted fever	*Rickettsia rickettsia*	Doxycycline	500–2,500 cases per year in USA[c]
	Ticks or other insects (unclear)	Bourbon disease	Bourbon virus	Not available	Limited numbers in Midwest and Southern USA[d]
Mites	Leptotrombidium deliense	Scrub typhus	*Orientia tsutsugamushi*	Doxycycline, Rifampicin, Azithromycin	One billion cases[c]

- More than a billion people are infected by vector-borne diseases each year
- Continue re-emerge in new geographic areas
- Impacted by climate change
- Significant financial and economic burden globally
- Vaccination may be the most cost-effective strategy to prevent and control vector-borne diseases

Kim KS, Curr Med Chem, 2019

NEMOURS CHILDREN'S HEALTH

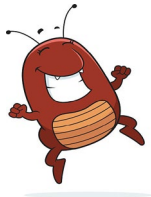
Vector-Borne Diseases

Ticks

- Lyme
- Tickborne Encephalitis
- Babesiosis
- Anaplasmosis
- Rocky Mountain Spotted Fever
- Ehrlichiosis
- Tularemia
- Powassan virus
- Tickborne Relapsing Fever
- Alpha-gal Syndrome

Mosquitoes

- Malaria
- Chikungunya
- Dengue Virus
- Japanese Encephalitis Virus
- Yellow Fever
- Zika Virus
- West Nile Virus
- Other arthropod-borne encephalitides (La Crosse, Eastern equine, Western equine, etc.)



Fleas

- Cat scratch disease
- Plague (Yersinia pestis)
  - Bubonic
  - Pulmonic
- Murine typhus

NEMOURS CHILDREN'S HEALTH

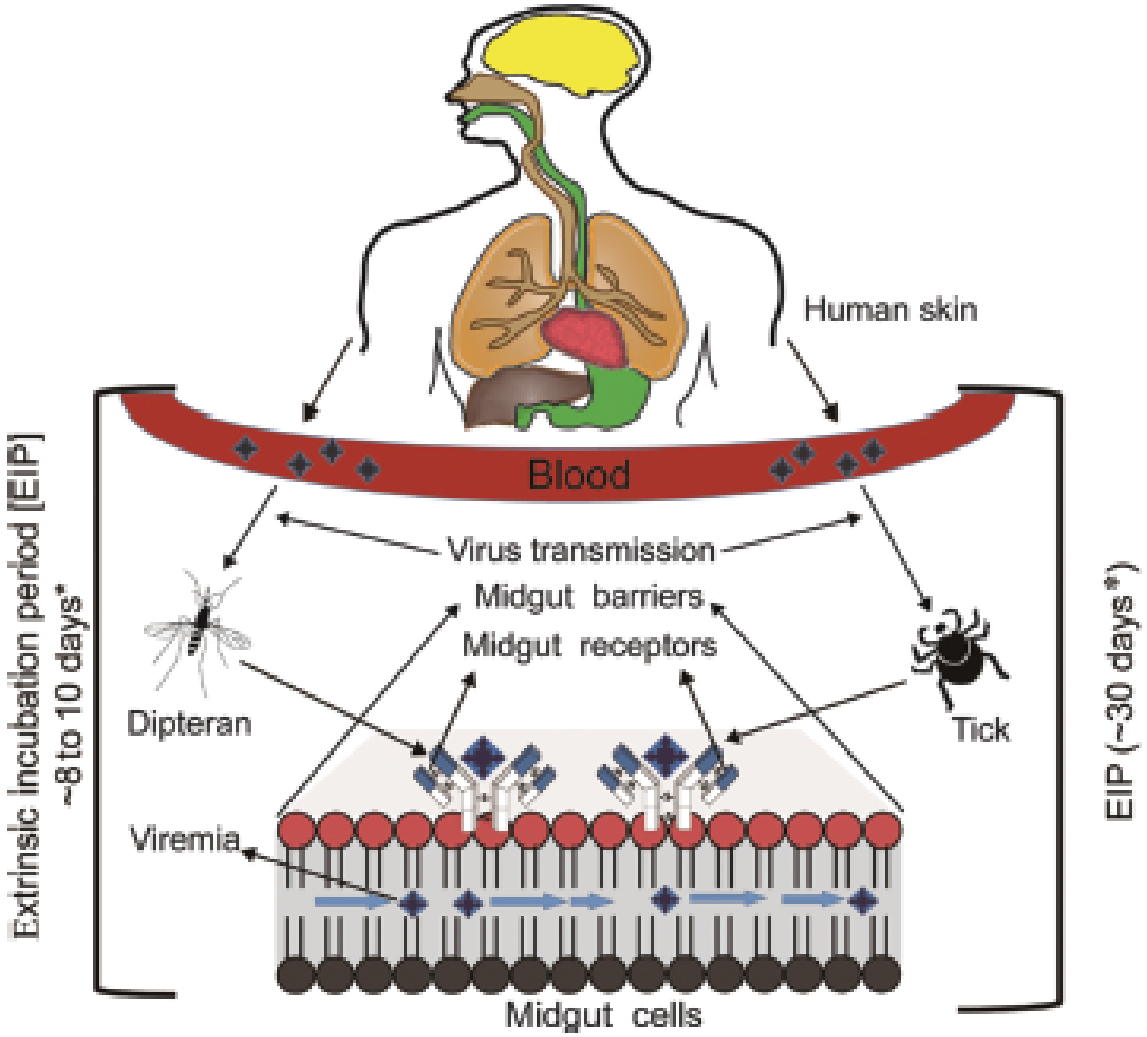


Fig. (1). Extrinsic incubation of dipteran and tick vectors. [*] denotes that the extrinsic incubation period varies according to temperature.

- Pathogen transmission by vectors is highly dependent on feeding rate, temperature changes, and the Extrinsic Incubation Period (EIP)
- EIP shorter at higher temperatures and longer at lower temperatures
- Durations are longer in ticks because ticks feed only once from a single host per feeding life stage and require time to transmit an infection

Kim KS, Curr Med Chem, 2019

NEMOURS CHILDREN'S HEALTH

AAP Redbook General Protective Measures

- Understand which arthropod-related infections are common in your area
- Eliminate standing water sources that attract mosquitoes
- Reduce exposure to mosquitoes
- Reduce exposure to ticks
- Wear appropriate protective-clothing
- Consider treatment of clothing and gear (0.5% Permethrin)

  www.epa.gov/insect-repellents/repellent-treated-clothing

  www.epa.gov/mosquitocontrol/permethrin-resmethrin-d-phenothrin-sumithrinr-synthetic-pyrethroids-mosquito

NEMOURS CHILDREN'S HEALTH

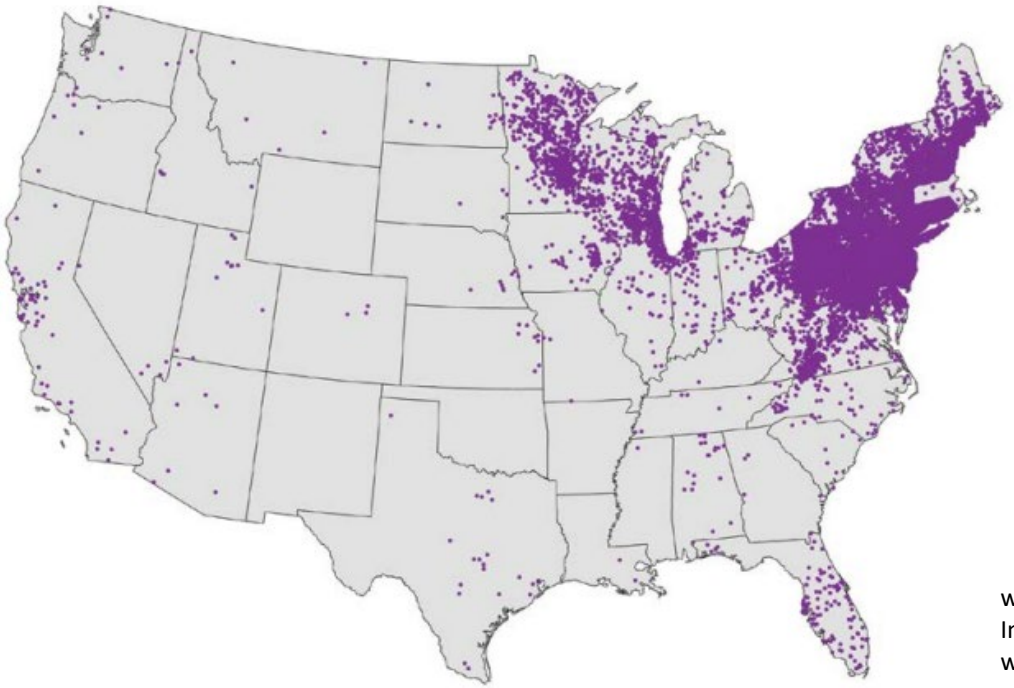
Issues with Developing Vaccines for Vector-borne Diseases

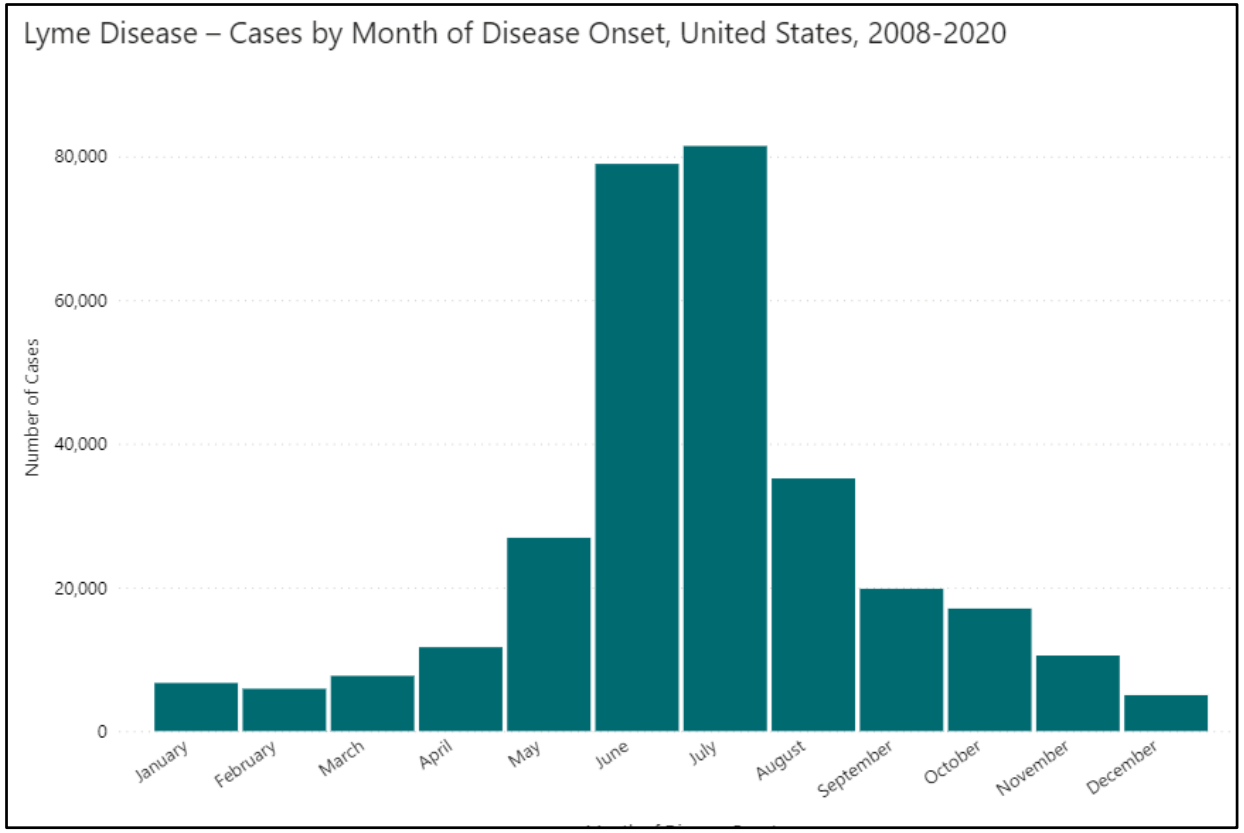
- Complex life cycles of pathogens within vector vs human
- Immune evasion
- Host-vector-pathogen interface
- Limited animal models
- Pathogen variability and antigen targets
- Difficulty defining what constitutes immunity
- Identifying population to protect
  - Geography/Endemic areas
  - Seasonality
  - Diversity of subjects

NEMOURS CHILDREN'S HEALTH

Lyme Disease

Vector: Blacklegged tick (*Ixodes scapilaris)*
Pathogen: Borrelia burgdorferi or B. mayonii





Lyme disease patients are most likely to have illness onset in June, July, or August and less likely to have illness onset from December through March

www.cdc.gov/vector-borne-diseases
Infectious Diseases Society of America
www. Idsociety.org/practice-guideline/all-practice-guidelines

NEMOURS CHILDREN'S HEALTH

Stages of Clinical Manifestations of Lyme Disease

Early Localized Disease	Early Disseminated Disease	Late Disseminated Disease
3 to 30 days	Several Weeks	Several more weeks-months

• Erythma migrans (EM) lesion at the site of tick bite (70-80% of people)
• EM most common manifestation in children
• Painless, non-pruritic, annular, erythematous, central clearing, ≥5 cm
• Malaise, headache, mild neck stiffness, myalgia, arthralgia, fever
	• Progresses to disseminated disease in 60% of people
	• Multiple EM lesions
	• Cranial nerve palsies (CN VII)
	• Lymphocytic meningitis
	• Carditis with AV block (less common in children)
	• Low-grade fever, arthralgia, myalgia, HA, fatigue
		• Arthritis
		  • Mono- or pauciarticular
		  • Large joints (knees)
		  • Swelling out of proportion to pain
		  • Baker's cyst
		• Polyneuropathy, encephalopathy, encephalitis (Rare)

APP Red Book 2018

History of Vaccine for Lyme Disease

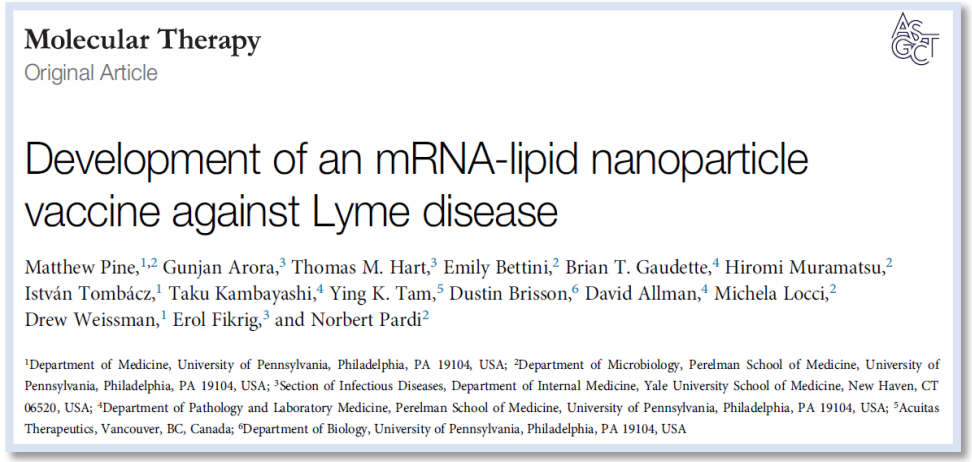
- OpsA antigen vaccines developed in early 1990s by Sanofi and GSK, but only GSK vaccine licensed by US FDA in 1998
- Given in 2 doses during 1st year and 3rd dose in 2nd year; efficacy of 71-76% following last dose
- Concern for arthritic reaction; controlled studies showed no difference in arthritic-symptoms between vaccinated vs controls & no higher frequency seen in vaccinated compared to expected age-specific frequencies in the population
- Speculated that genetically susceptible individuals were reacting to vaccine; concern for latent autoimmunity
- Requirement for 3 doses, no approval for children, and reports of associated arthritis-> decreased vaccine uptake ->withdrawal of vaccine by GSK

Plotkin SA & Shapiro ED, CID, 2025

NEMOURS CHILDREN'S HEALTH

Lyme Disease → *Borrelia burgdorferi*

Penn Medicine



Molecular Therapy
Original Article

Development of an mRNA-lipid nanoparticle vaccine against Lyme disease

Matthew Pine,[1,2] Gunjan Arora,[3] Thomas M. Hart,[3] Emily Bettini,[2] Brian T. Gaudette,[4] Hiromi Muramatsu,[2] István Tombácz,[1] Taku Kambayashi,[4] Ying K. Tam,[5] Dustin Brisson,[6] David Allman,[4] Michela Locci,[2] Drew Weissman,[1] Erol Fikrig,[3] and Norbert Pardi[2]

[1]Department of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [2]Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [3]Section of Infectious Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520, USA; [4]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [5]Acuitas Therapeutics, Vancouver, BC, Canada; [6]Department of Biology, University of Pennsylvania, Philadelphia, PA 19104, USA

Moderna: *The Canopy Trial (June 2023 – Mar 2026)*

A Clinical Trial of a Lyme Disease Vaccine for Adults

Pipeline: two novel mRNA vaccine candidates against Borrelia species (Lyme disease)

mRNA-1982

monovalent vaccine targeting prevalent US serotype

mRNA-1975

multivalent, includes 7 RNAs targeting 7 European serotypes

Europe - Phase 1/2 study, 800 subjects
Anticipate results informing immunogenicity in 2024

Pfizer and Valneva partnership

- July 2017: Fast Track designation by US FDA (Valneva)
- April 2020: Collaboration agreement between Valneva and Pfizer to co-develop VLA15

VLA15-221 Phase 2 study showed a strong anamnestic antibody response for all serotypes in pediatric (5 to 11 years of age) and adolescent participants (12 to 17 years of age), as well as in adults (18 to 65 years of age), one month after administration of a booster dose (month 19).

"Safety and tolerability profile of VLA15 after a booster dose was consistent with previous studies as the vaccine candidate was **well-tolerated in all age groups** regardless of the primary vaccination schedule."

"**No vaccine-related serious adverse events** (SAEs) and **no safety concerns** were observed by an independent Data Safety Monitoring Board (DSMB)."

www.pfizer.com/news/announcements/valneva-and-pfizer-report-positive-pediatric-and-adolescent-phase-2-booster

Lyme Disease → *Borrelia burgdorferi*

VLA15 (Pfizer/Valneva) – **Phase III trials**

Investigational multivalent protein subunit vaccine - Targets outer surface protein A (OspA) of *B. burgdorferi*

- OspA: surface protein expressed by *B. burgdorferi* when present in a tick; blocking OspA limits transmission
- Vaccine covers 6 most common OspA serotypes (*B. burgdorferi sensu lato* species prevalent N. America, Europe)
- Alum-adjuvanted formulation; administered intramuscularly

An Efficacy, Safety, Tolerability, Immunogenicity, and Lot-Consistency Clinical Trial of a 6-Valent OspA-Based Lyme Disease Vaccine (VLA15) (VALOR)

ClinicalTrials.gov ID: NCT05477524
Sponsor: Pfizer Last Update Posted: 2024-07-26

https://clinicaltrials.gov/study/NCT05477524

Phase 3 trial
3-dose primary vaccination series at about 0, 2, and 5 to 9 months and then receive a booster dose about 12 months later.

…primary series completed before peak Lyme disease season followed by a booster dose just prior to beginning of second Lyme disease season.

Safety Study of a Vaccine to Help Protect Against Lyme Disease in Healthy Children

ClinicalTrials.gov ID: NCT05634811
Sponsor: Pfizer Last Update Posted: 2024-05-22

Initiated Dec 2022, estimated completion mid-2025

Phase 3, randomized, placebo-controlled, observer-blinded trial to evaluate the safety of a **6-VALENT OspA-BASED LYME DISEASE VACCINE (VLA15)** in healthy children 5 through 17 years of age

Anticipate 2026…

NEMOURS
CHILDREN'S HEALTH

Tick-borne Encephalitis

Table 1. List of tick-borne flaviruses associated with encephalitis

Virus	Vector	Susceptible hosts	Distribution
Alkumra haemorhagic fever virus	*Ornithodoros* spp.	Humans	Arabian Peninsula
Kyasanur forest disease virus	*Haemaphysalis spinigera*	Primates	India
Louping ill virus	*Ixodes ricinus*	Sheep, grouse	British Isles
Powassan virus	*Ixodes* and *Dermacentor* spp.	Humans	North America, East Asia
Tick-borne encephalitis virus (multiple subtypes)	*Ixodes* spp.	Humans, horses, dogs, livestock	Eurasia
Spanish goat encephalitis virus	*Ixodes* spp.	Ovine	Spain
Spanish sheep encephalitis virus	*Ixodes* spp.	Ovine	Spain
Greek goat encephalitis virus	*Ixodes* spp.	Ovine	Greece
Turkish sheep encephalitis virus	Vector unknown	Ovine	Turkey

Approximate distribution of tick-borne encephalitis as of January 20, 2024.

- Biphasic disease; 1st phase-flu-like symptoms; 2nd phase-CNS encephalitis, meningitis
- Illness onset occurs median 8 days (range 4 to 28)
- No antiviral therapy; supportive care

Johnson N, et al. Curr Opinion, 2023.
Pavli A & Maltezou HC. Travel Med & Infect Dis. 2022.

- Single-Stranded RNA *Flavirus;* multiple subtypes
- Vector: *Ixodes* ticks
- Endemic to focal areas of Western/Central Europe, Russia and Asia (China, Japan, Kazakhstan, Kyrgyzstan, Mongolia & South Korea)
- Mostly in summer (April-Nov)
- 1 case per 10,000 person-months of exposure
- **Pre-travel vaccine for travelers exposed outdoors in rural endemic areas during transmission period**

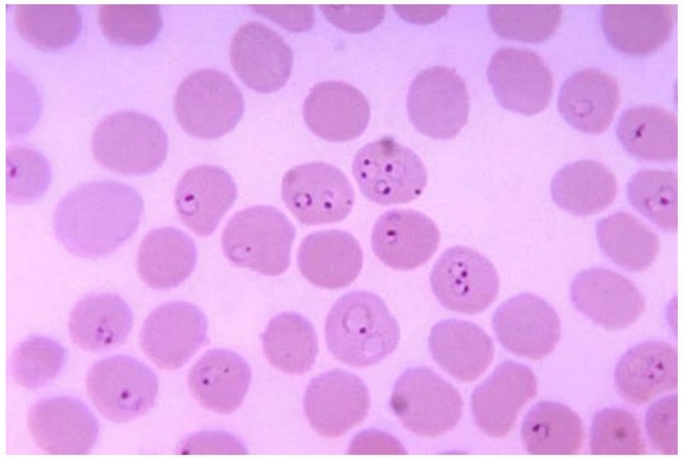
NEMOURS CHILDREN'S HEALTH

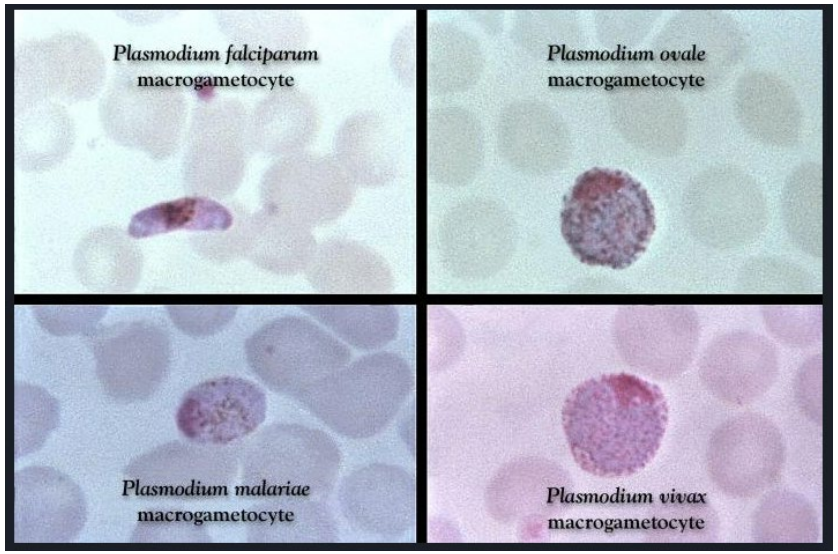
TBE Vaccine

- In US, inactivated vaccine (Ticovac) for adults and children ≥1 year
- Recommended for those traveling or moving to are where endemic and have extensive exposure to ticks through outdoor activities
- Multiple inactivated vaccines available in Europe and Russia and one in China
- Mass vaccination been undertaken in Austria with at least 96% protection rate; routine primary vaccination series requires ≥6 months for completion

Johnson N, et al. Curr Opinion, 2023.
Pavli A & Maltezou HC. Travel Med & Infect Dis. 2022.
Barrett RN, Schober-Bendizen S, Ehrlich HJ. Vaccine, 2003.

NEMOURS CHILDREN'S HEALTH



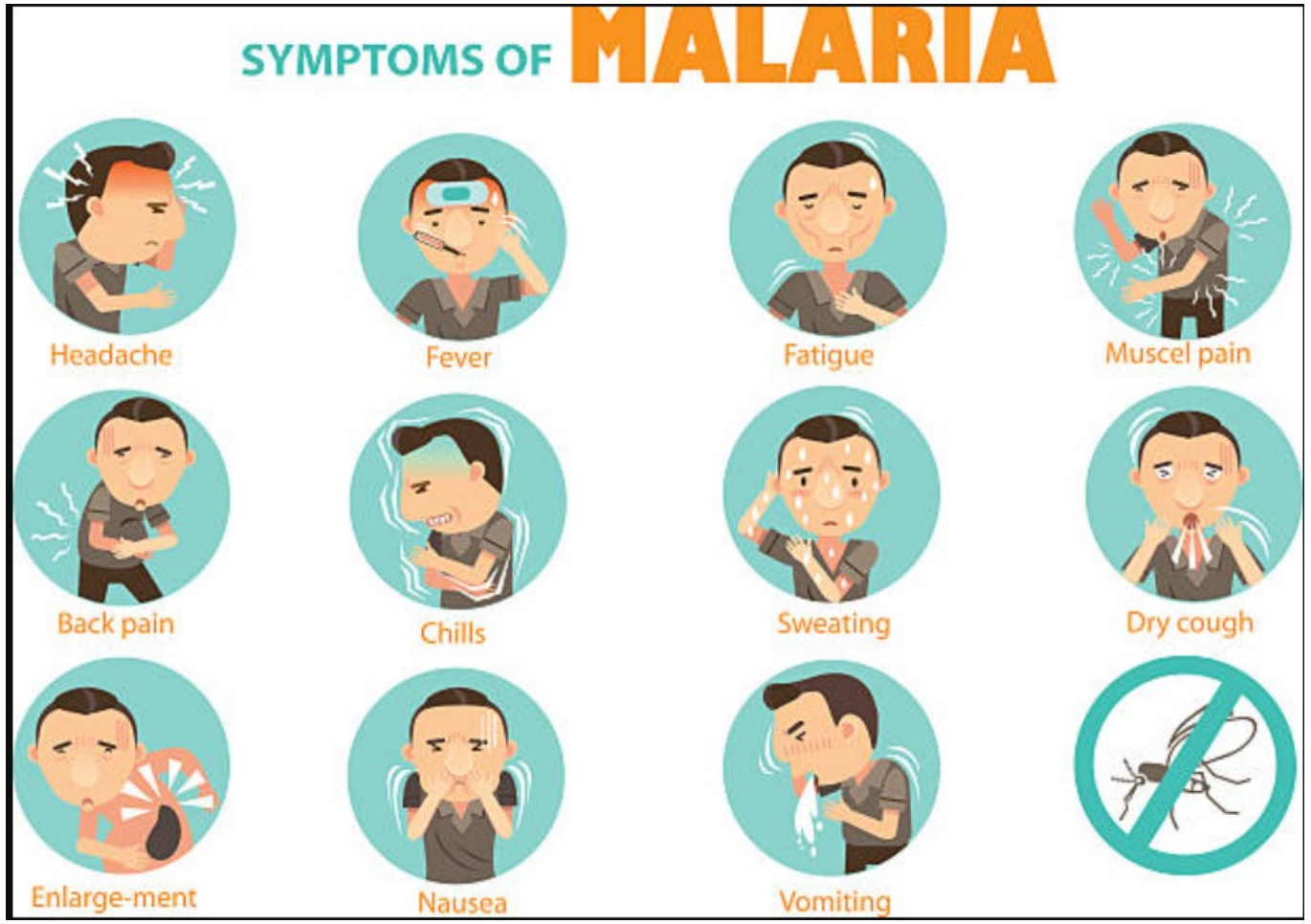


Malaria

- *Plasmodium* genus: *P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi*
- Vector: Female Anopheles genus of mosquito
- Highest risk: Sub-Saharan Africa, Papua New Guinea, & Solomon Islands; Intermediate risk: Indian subcontinent; Low risk: Southeast Asia and Latin America
- Intra-erythrocyte parasite that infects liver and spleen and rapidly replicates and disseminate
- Incubation time: 7-30 days; relapse can occur within weeks to months

https://www.cdc.gov/malaria/index.html

NEMOURS CHILDREN'S HEALTH



Prevention:

- Bite protection: repellent, clothing, nets
- Chemoprophylaxis
  - Referral to travel clinic
  - CDC Yellow Book
  - Multiple options-based on travel, age, medical history

Severe findings:

- Cerebral: Altered MS, seizures
- Anemia, metabolic acidosis, hypoglycemia
- Acute kidney injury; nephrotic syndrome
- Pulmonary edema & ARDS
- Shock
- Jaundice, HSM

Diagnosis: Blood smear (thick & thin [%parasitemia]); rapid diagnostic testing and PCR

Treatment: antimalarial med based on species and drug resistance
Severe malaria may need IV artesunate

Malaria Vaccine

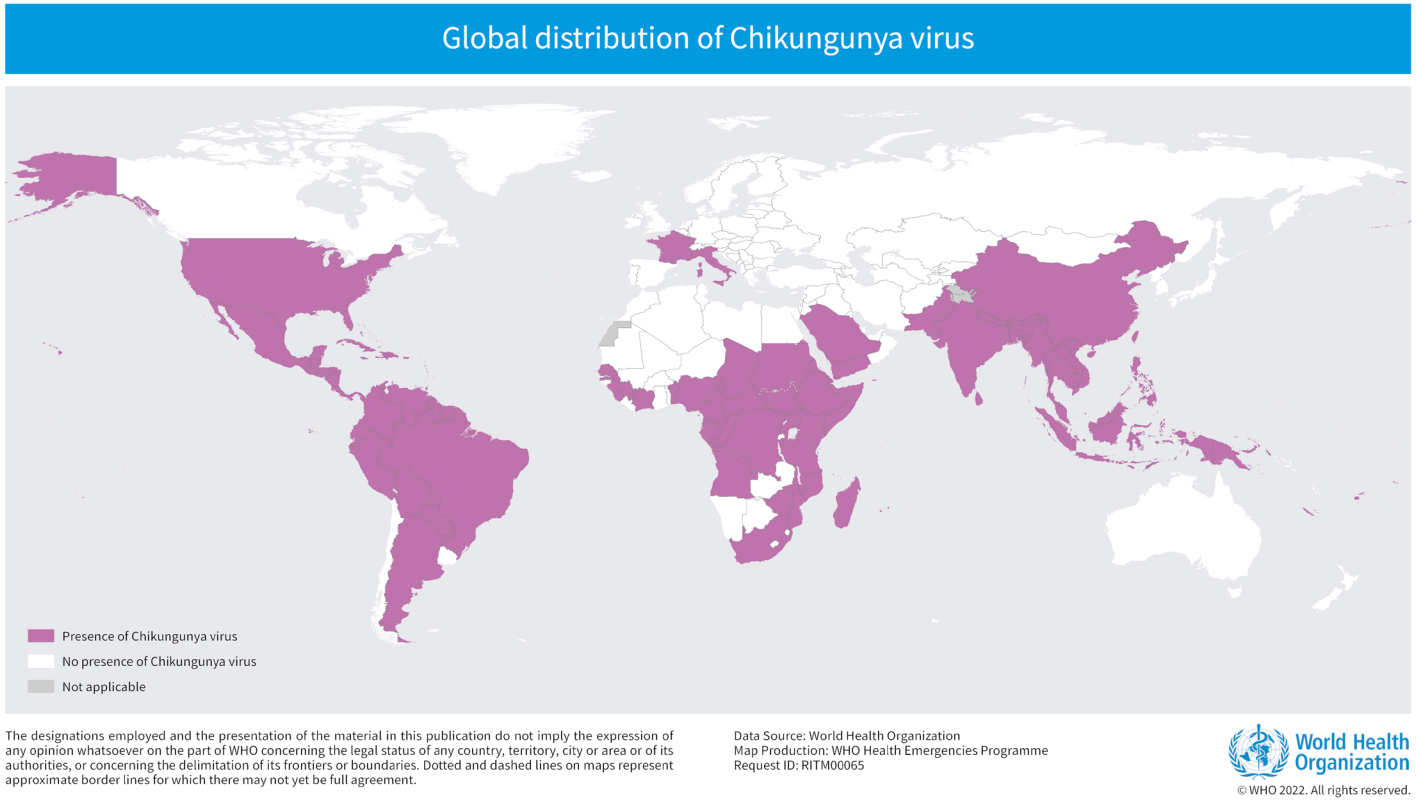
- Vaccine development has been slow because of vector and pathogen diversity and variability; finding targets for different stages of life cycle
- Goal of prevention of disease vs eradication
- Vaccines developed focused on the pre-erythrocytic stage (parasite entering into human bloodstream and infected liver cells)
- RTS,S/AS01 vaccine-approved in WHO in October 2021 for children in areas with moderate to high transmission; moderately efficacious for prevention
- Targets circumsporozoite antigen on surface of parasite
- Other vaccines in development but more interventions needed for eradication

Kim KS, Curr Med Chem, 2019.
Laurens MB, Human Vaccines & Immunotherapeutics, 2021.

NEMOURS CHILDREN'S HEALTH

Chikungunya

- RNA virus
- Vector: *Aedes albopictus*
- Congenital transmission rare
- Africa, Asia, Europe, Indian & Pacific Oceans
- Reported in FLA, Puerto Rico, TX & US Virgin Islands



- Most infected become symptomatic
- High fever, polyarthralgia, myalgia, maculopapular rash, headache, N/V/D
- Diagnosis: clinical, PCR & serology
- Treatment: Supportive; ?antirheumatic medications
- Prevention: **Vaccine approved for 18 years and older at high risk (no longer available in US)**

NEMOURS CHILDREN'S HEALTH

https://www.cdc.gov/chikungunya/about/index.html

Chikungunya Virus (CHIKV)

www.thelancet.com Vol 401 June 24, 2023

www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00641-4/fulltext

Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial

Martina Schneider, Marivic Narciso-Abraham, Sandra Hadl, Robert McMahon, Sebastian Toepfer, Ulrike Fuchs, Romana Hochreiter, Annegret Bitzer, Karin Kosulin, Julian Larcher-Senn, Robert Mader, Katrin Dubischar, Oliver Zoihsl, Juan-Carlos Jaramillo, Susanne Eder-Lingelbach, Vera Buerger, Nina Wressnigg

VLA1553 is a live-attenuated vaccine

for active immunization and prevention of disease caused by chikungunya virus

March 2022: Phase 3 data reported in 4,115 adults aged 18 years and above showing a 98.9% seroresponse rate at 28 days with single vaccination

June 2023: Results published in Lancet
The Lancet subsequently published these results in June 2023.

Final lot-to-lot consistency results were published in May 2022, twelve-month persistence data in December 2022, and adolescent data in November 2023.

Follow-up study underway to monitor 5-year immune response data (NCT04838444).

News!

November 2023

VLA1553 received U.S. FDA approval

under brand name IXCHIQ® (Valneva)

Indicated for prevention of disease caused by CHIKV in individuals **18 years of age and older who are at increased risk of exposure to CHIKV.**

Continued approval in US is contingent upon verification of clinical benefit in confirmatory studies.

VLA1553 is also under accelerated assessment by the European Medicines Agency (EMA) and a standard regulatory review is underway with Health Canada.

FDA Update on the Safety of Ixchiq (Chikungunya Vaccine, Live). FDA Suspends Biologics License: FDA Safety Communication

- FDA approval for IXCHIQ withdrawn in August of 2025 due to concerns for serious adverse events (severe or prolonged chikungunya-like illness with neurologic and cardiac complications)

- **Recombinant virus-like-particle (VLP) vaccine (VIMKUNYA) approved by FDA and EMA in 2025 for individuals 12 years and older**

NEMOURS CHILDREN'S HEALTH

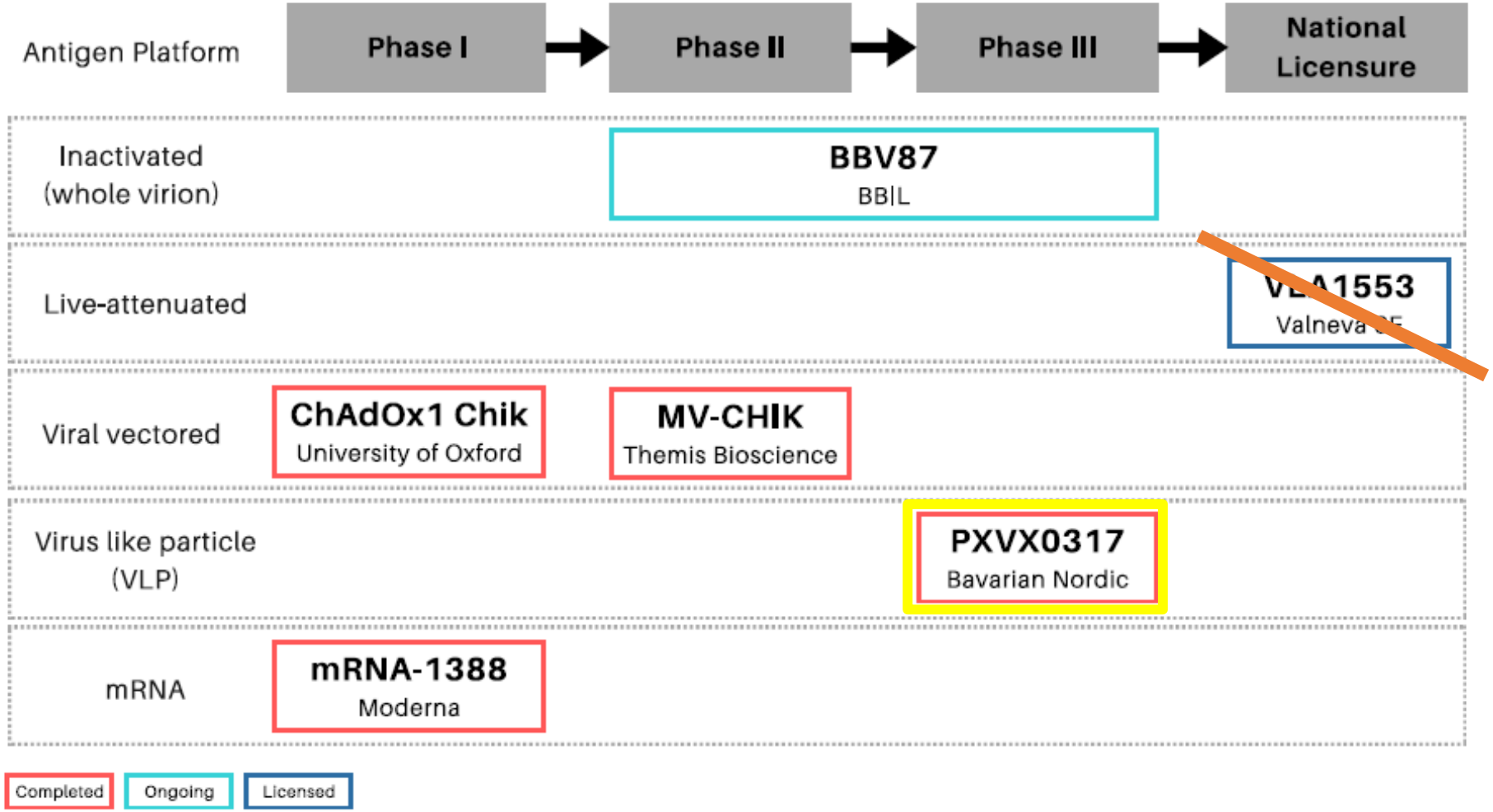


Fig. 1. Chikungunya vaccines. Licensed chikungunya vaccine (Ixchiq – VLA 1553) and new vaccines in the clinical development pipeline are illustrated by antigen platform, clinical trial phases, and licensure. BBIL - Bharat Biotech International Limited.

Maure C, et al. Vaccine, 2024.

NEMOURS CHILDREN'S HEALTH

Dengue

- RNA virus, 4 closely related viruses (DENV 1-4)
- *Vector: Aedes aegypti* and other species
- Diagnosis: PCR, serology
- Treatment: Supportive; no antiviral
- **Prevention: No US available travel vaccine**

Dengue without warning signs

Probable Dengue
Live in/travel to endemic area

Fever and 2 of the following criteria:

- Nausea/vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue:

- Molecular techniques
- IgM or IgG seroconversion

Dengue with warning signs

Presence of warning signs:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation (ascites, pleural effusion)
- Mucosal bleeding
- Lethargy, restlessness
- Postural hypotension
- Palpable hepatomegaly >2cm
- Progressive increase in hematrocrit

Severe dengue

One of the following manifestations:

- Shock or respiratory distress due to severe plasma leakage
- Severe bleeding, based on evaluation by attending physician
- Severe organ involvement (such as liver or heart)

From CDC Yellow Book: Dengue

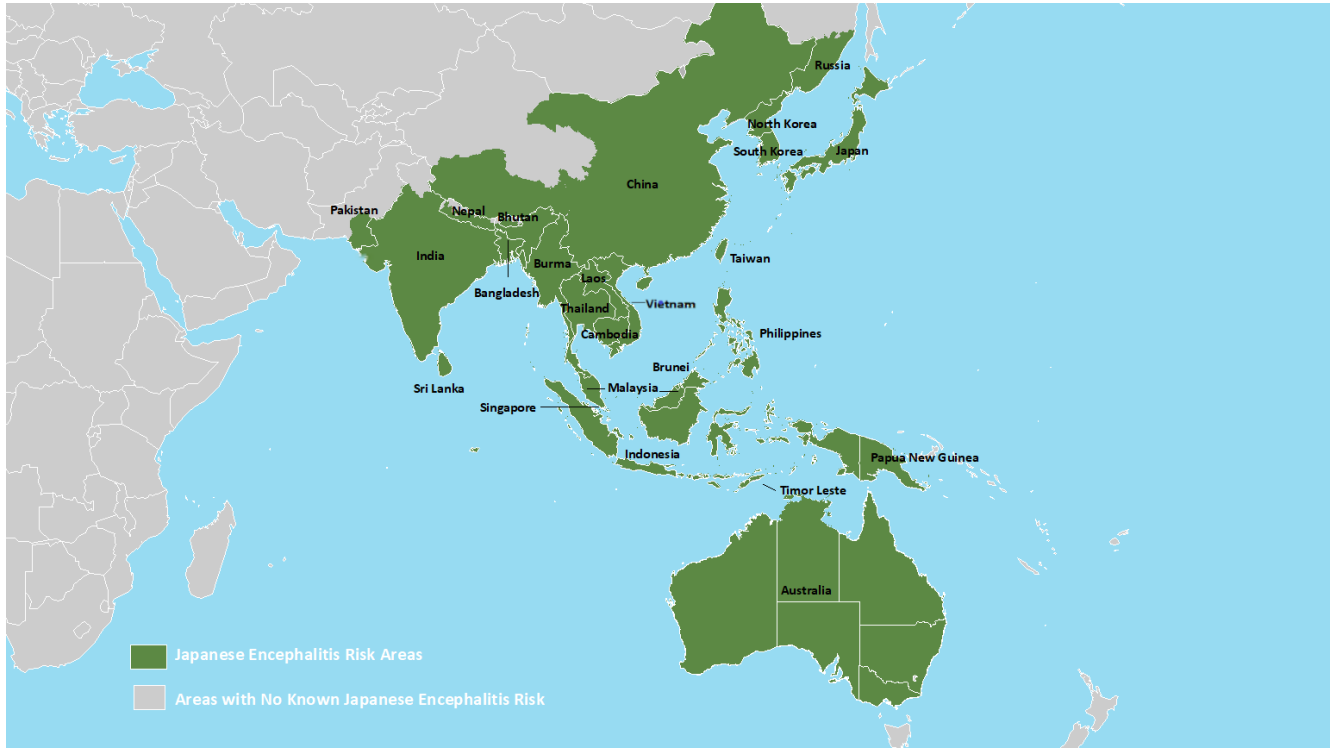
Dengue Vaccine

- Ideal vaccine would be efficacious for all four types
- Vaccines developed targeting all ages but specifically for children
- Dengvaxia (CYD-TDV) was approved in 2019 by US FDA for use in endemic areas. In 2021, recommended by ACIP for children aged 9 to 16 with serologic evidence of previous dengue infection & live in endemic US territories
- Worldwide, controversy over efficacy and safety; protective among children previously exposed but increased risk of hospitalization & severe illness who were not previously exposed
- Dengvaxia manufacturing discontinued because of low demand
- Odenga (TAK-003) approved in over 40 countries but not approved or available in US

Thomas SJ & Yoon I. Human Vaccines & Immunotherapies, 2019.
Kim KS, Curr Med Chem, 2019.
Adams AE, Waterman S, Paz-Bailey G. JAMA, 2022.

NEMOURS CHILDREN'S HEALTH

Japanese Encephalitis



- Japanese encephalitis virus- Flavivrus
- Vector: *Culex vishnui* mosquito subgroup, particularly *Culex tritaeniorhynchus*
- Most of Asia and Western Pacific region
- Typically affects children <15 years of age

- Fever, headache, mental status changes, seizures, focal neurologic deficits, aseptic meningitis
- Poliomyelitis-like acute flaccid paralysis due anterior horn cell damage
- Diagnosis: clinical, antibodies in serum and CSF, PCR
- Treatment: Supportive care; no effective antiviral therapy
- **Prevention: for frequent travelers or people moving to endemic areas ≥2 months or older**

NEMOURS CHILDREN'S HEALTH

Japanese Encephalitis Vaccine

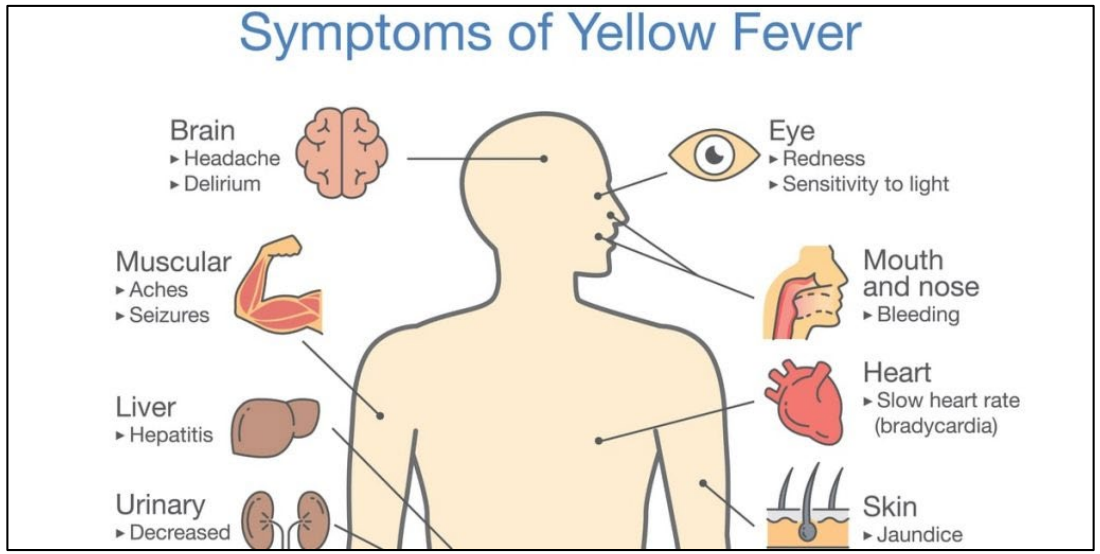
Vaccine type	Substrate	Trade name	Vaccine strain	Licensing year and country
Inactivated	Mouse brain	BIKEN®, JE-VAX, Sanofi Pasteur	Nakayama strain Beijing-1 strain	Japan in 1954
	Hamster kidney cells		Beijing-3 or P-3	China in 1968
	Vero cells	JEBIK®	Beijing-1	Japan in 2009
		ENCEVAC®	Beijing-1	Japan in 2011
		JEVACTM	Beijing P-3 strain	China in 2008
		IXIARO® (USA, EU); JESPECT® (AUS, NZ); JEEV®	SA-14-14-2	USA, Australia, and Europe in 2009
		JENVAC®	Kolar821564XY	India in 2014
Live attenuated	Hamster kidney cells	CD.JEVAX®	SA-14-14-2	China in 1988
Chimera	Vero cells	IMOJEV®	JE SA-14-14- 2/Yellow fever 17 D	Australia and Thailand in 2012

- Inactivated Vero cell culture-derived vaccine (IXIARO)
- Licensed in 2009 for use in individuals ≥17 yeas in 2013 for children 2 months through 16 years age
- Children immunization programs-> significant decrease in cases

Pavli A & Maltezou HC. Travel Med & Infect Dis. 2022.
Adunga T, et al. Frontiers in Immunology, 2024.
Hills SL, Netravathi M, Solomon T. Am J Trop Med Hyg. 2023.

NEMOURS CHILDREN'S HEALTH

Yellow Fever



- Single-stranded RNA Flavivirus
- Vector: infected female *Aedes aegypti* mosquitoes in Africa, *Haemagogus* species in South America
- Severe disease with fever, jaundice/hepatitis, renal failure, myocardial injury and hemorrhage
- Diagnosis: PCR, serology
- Treatment: Supportive care

From CDC Yellow Book: Yellow Fever
Monath TP & Vasconcelos PF. Journal of Verology, 2015.

NEMOURS CHILDREN'S HEALTH

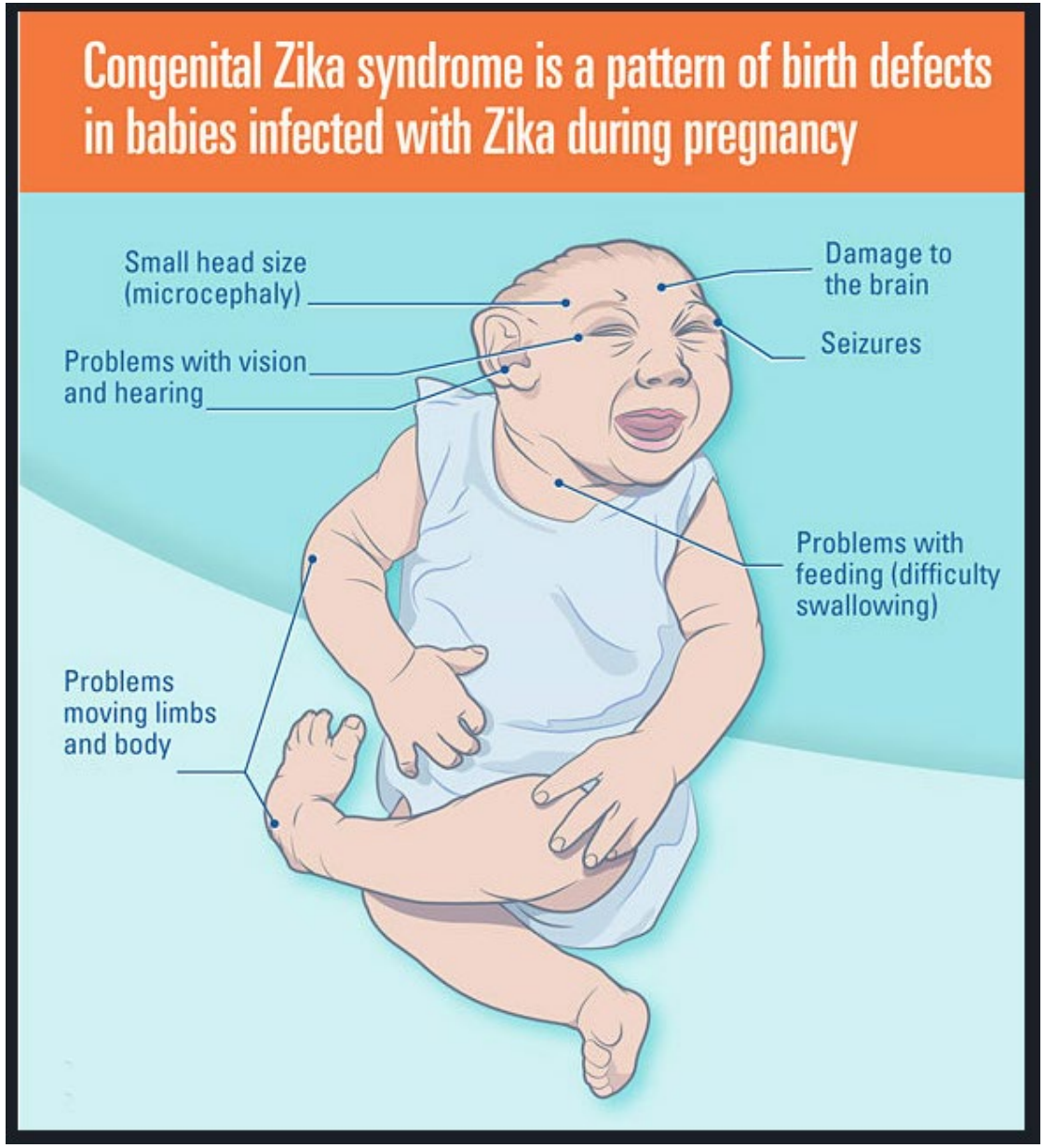
Yellow Fever Vaccine

- First developed in 1936
- Live-attenuated vaccine from 17D strain; multiple available worldwide but US YF-VAX
- Indicated/recommended in US for travelers to endemic areas in African and South America
- Some countries require vaccine for all travelers or only for those coming higher risk transmission areas
- Can be administered to individuals ≥9 months of age
- Routine immunization programs for immunization individuals living in endemic areas

Pavli A & Maltezou HC. Travel Med & Infect Dis. 2022.
Monath TP & Vasconcelos PF. Journal of Verology, 2015.

NEMOURS CHILDREN'S HEALTH

Zika



https://www.cdc.gov/zika/about/index.html

- Vector: *Aedes albopictus* & other species
- Most infections are asymptomatic or mild disease
- Fever, pruritic rash, arthralgia, conjunctival hyperemia, myalgia, headache, thrombocytopenia, leukopenia, elevated transaminases
- Diagnosis: PCR, serology but only really recommended for pregnant people & concern for congenital infected
- Treatment: Supportive; for congenital-early intervention, development referral

Zika Virus Vaccine

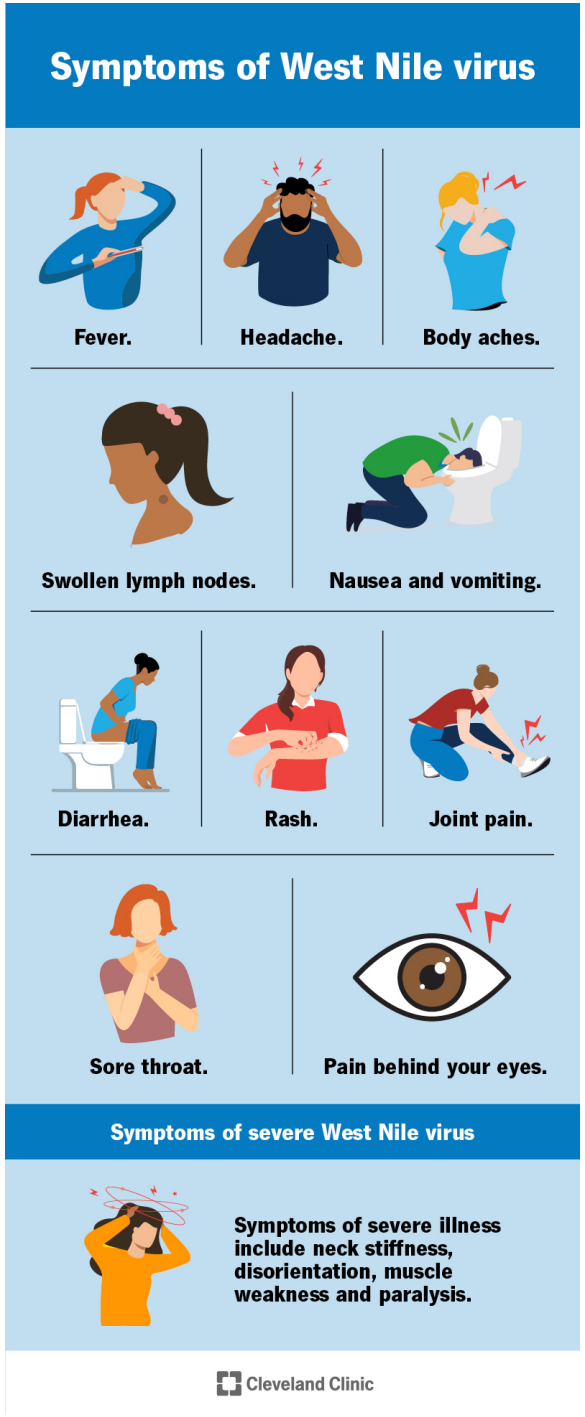
- Currently, no approved vaccine for clinical use but several in development
- Has 4 distinct serotypes similar to DENV which can be challenge for vaccine development due to cross-reactivity
- Challenges with long lasting immune response/protection that is cost effective
- GLS-5700, DNA vaccine which targets pre-membrane & envelope proteins (prM-E)
- ZPIV, an inactivated virus vaccine that targets whole Zika virus virions

Table 1
ZIKV vaccines in development.

Institute/company	Status	Vaccine platforms
Inovio Pharmaceuticals, Inc	In phase 1 clinical trials	DNA vaccine
NIH	In phase 1 clinical trials	DNA vaccine Live VSV recombinant (early R&D) Live attenuated ZIKV (early R&D)
WRAIR/Sanofi Pasteur Limited	In phase 1 clinical	trials Whole, purified, inactivated virus
Butantan Institute	In phase 1 clinical trials	Live, DENV-vectored vaccine expressing premembrane/ membrane and envelope proteins
	Early-stage research	Purified inactivated virus
Bharat Institute of Science and Technology	Preclinical/animal studies	Purified inactivated virus VLP-expressing polyprotein
NewLink Genetics Corporation	Preclinical/animal studies	Purified inactivated virus
PaxVax, Inc	Preclinical/animal studies	Purified inactivated virus
Novavax, Inc	Preclinical/animal studies	Protein nanoparticle vaccine
Replikins Ltd	Preclinical/animal studies	Synthetic peptide vaccine
Pharos Biologicals LLC	Preclinical/animal studies	DNA vaccine
Bio-Manguinhos	Early-stage research	Purified inactivated virus YF17DD chimera, VLP, DNA
US CDC	Early-stage research	VLP expressing ZIKV DNA Live adenovirus recombinant
CureVac AG	Early-stage research	Thermostabile mRNA-based vaccine
Geovax Labs, t Inc	Early-stage research	Live MVA recombinan
GlaxoSmithKline plc	Early-stage research	Self-amplifying mRNA platform Whole, inactivated virus
Hawaii Biotech Inc	Early-stage research	Aluminium hydroxide gel (Alhydrogel) þ recombinant protein
University of Oxford	Early-stage research	Live adenovirus recombinant
Protein Sciences Corporation	Early-stage research	Recombinant envelope protein
Sanofi	Early-stage research	YF17D chimera
Sementis	Early-stage research	Live poxvirus recombinant
Themis Bioscience	GmbH Early-stage research	Live measles recombinant
Valneva SE	Early-stage research	Purified inactivated virus
Mayo Clinic Vaccine Research Group	Early-stage research	Naturally processed and HLA-presented ZIKV peptides packaged with biodegradable nanoparticles
Moderna, Inc	Early-stage research	Lipid nanoparticleedelivered mRNA
Emergent BioSolutions Inc	Early-stage research	Inactivated, whole virus
Institut Pasteur of Shanghai	Early-stage research	Recombinant subunit VLP
Takeda Pharmaceutical Company Limited	Early-stage research	Alum adjuvanted, inactivated whole virus
Edward Jenner Institute for Vaccine Research	Early-stage research	Simian adenovirus vector
VBI Vaccines Inc	Early-stage research	VLP containing envelope and NS1 proteins
Vaxart, Inc	Early-stage research	Recombinant oral vaccine

CDC = Centers for Disease Control and Prevention; DENV = dengue virus; mRNA = messenger RNA; MVA = modified vaccinia virus Ankara; NIH = National Institutes of Health; R&D = research and development; VLP = virus-like particles; VSV = vesicular stomatitis virus; WRAIR = Walter Reed Army Institute of Research; ZIKV = Zika virus

Kim K. Current Medical Chemistry, 2019.
Pielnaa P, et al. Virology.2020.



West Nile Virus

- RNA single-stranded Flavivirus
- Vector: Culex spp. Mosquitoes
- 80% of case are asymptomatic; 1 in 5 cases flu-like illness
- 1 in every 150 cases progress to potentially fatal neurologic disease (encephalitis, meningitis, acute flaccid paralysis)
- Treatment: Supportive care

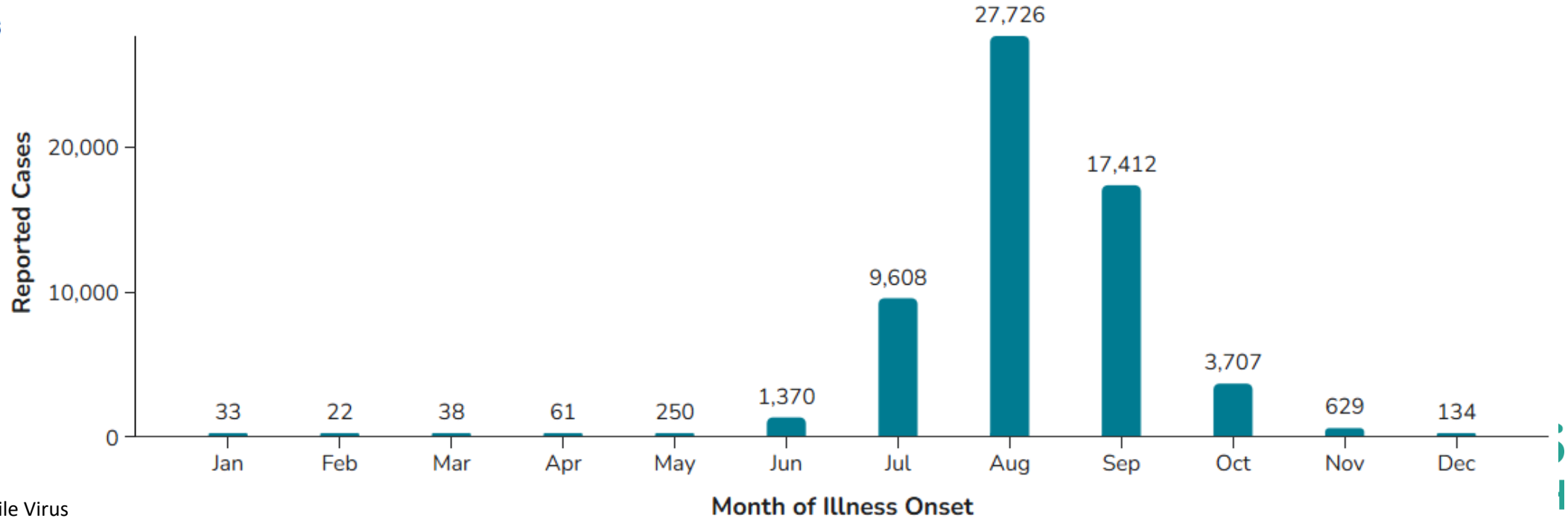
Kasier JA & Barrett. Viruses. 2019.
Singh P, et al. Emerging Microbes & Infections. 2025.

NEMOURS CHILDREN'S HEALTH

Data are current as of *December 2, 2025.*

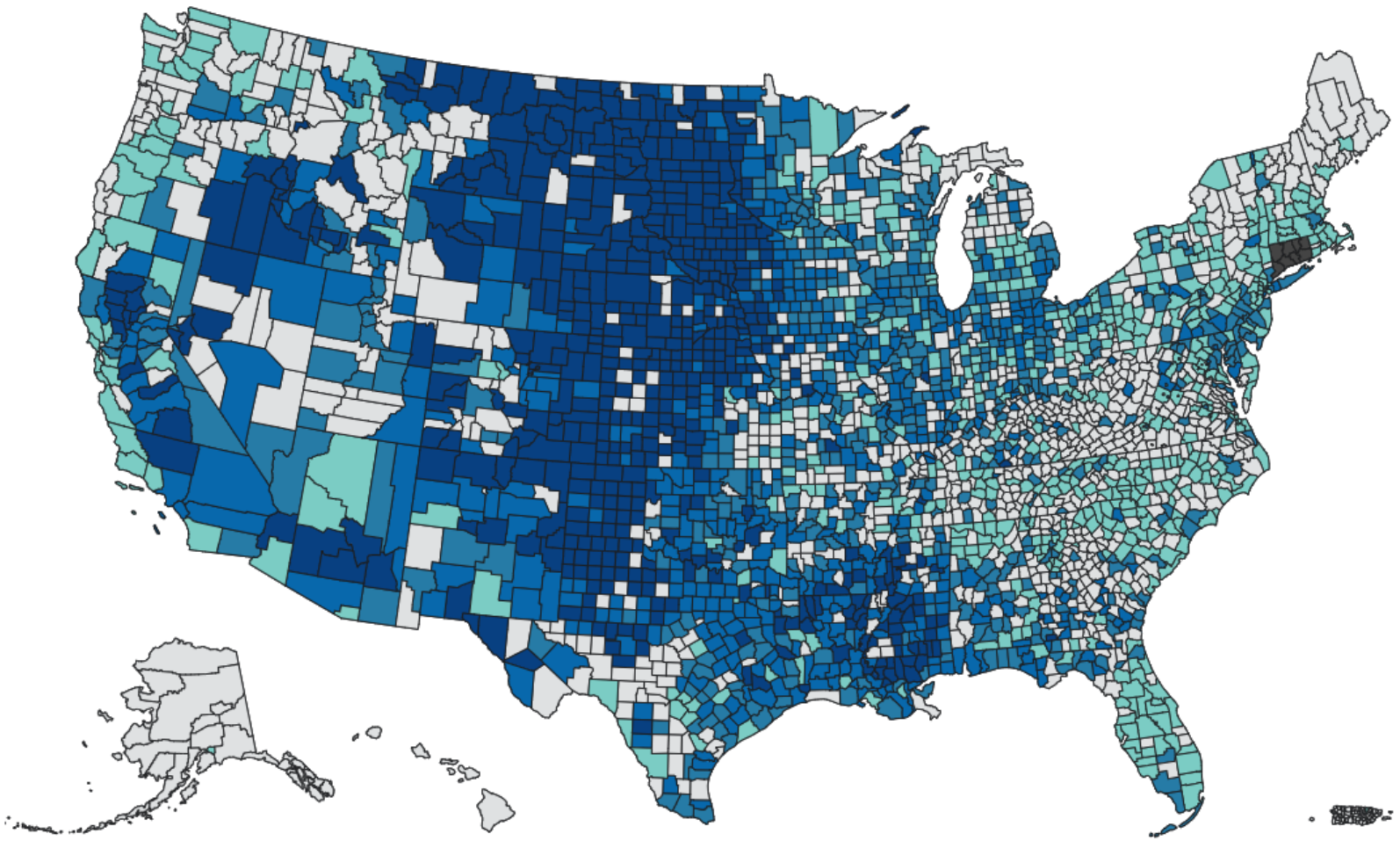
Total Human Disease Cases in 2025*	Neuroinvasive Human Disease Cases in 2025	States Reporting Human Disease Cases in 2025
1,981 *West Nile virus disease cases in 2025*	**1,359** *West Nile virus neuroinvasive disease cases in 2025*	**46** *States reporting West Nile virus disease cases in 2025*

*Total human dis



From CDC website: West Nile Virus

West Nile virus human neuroinvasive disease average annual incidence per 100,000 population by county of residence, 1999-2024*



Incidence per 100,000 Population

0.01 to 0.16 | 0.17 to 0.37 | 0.38 to 1.09 | >1.10 | Cumulative data unavailable

Human Disease Cases

60,992

Cases from year(s) and type of case selected above

Deaths

3,134

Deaths from year(s) and type of case selected above

From CDC website: West Nile Virus

NEMOURS CHILDREN'S HEALTH

West Nile Virus Vaccine

Table 1. Overview of clinical trials and observations for West Nile Virus vaccines: safety, adverse effects, and immunogenicity.

Vaccine Name	Vaccine Type	Clinical Trial ID	Age Group	Dose	Adverse Effects	Immunogenicity Observations
ChimeriVax-WN02	Live attenuated chimeric	NCT00442169	Part1 18–40 Part2 41–64 and ≥ 65 years	Part1 3.7 × – 10(5) PFU, 3.7 ×10 (4) PFU, 3.7× 10(3) PFU Part2 3.7 × 10(5) PFU	Similar adverse event profile across all dose groups; more events in 41–64 years cohort.	High seroconversion rates; higher antibody titers and lower viremia levels with the highest dose.
WN/DEN4delta30	Live attenuated	NCT00537147	Adults (18–50 years old)	Experiment1 10^4 PFU (0.5 ml) Experiment2 10^5 PFU (0.5 ml)	Vaccine-related adverse events classified by both intensity and severity.	Immunogenicity assessed by anti-WN/DEN4 neutralizing antibody titer.
WN-80E	Protein-based	NCT00707642	Adults (18–45 years old)	Experiment1 5 µg + Alhydrogel (3.5 mg) Experiment 2 15 µg + Alhydrogel (3.5 mg) Experiment 3 50 µg + Alhydrogel (3.5 mg) Experiment4 50 µg + no adjuvant	No serious adverse biological effects reported.	Immunogenic in None; high antibody titers indicating good immunogenidty.
HydroVax-001 WNV	Inactivated, whole virion	NCT02337868	Adults 18–50 years	1 and 4 mcg	Well-tolerated; no serious adverse events. Increased reactogenidty with complement.	Modest immunogenidty at 4 mcg dose; higher PRNT (50) seroconversion rates with added complement.
VRC-WNVDNA020-00-VP	DNA vaccine	NCT00300417	Adults (18–65 year old)	Not specified	Participants reported symptoms like fever, headache, neck stiffness, muscle weakness, vision loss, numbness, and paralysis, monitored via diary cards.	Vaccine-induced immunity assessed via blood tests for immune response; details not specified.
VRC-WNVDNA017-00-VP	DNA vaccine	NCT00106769	Adults 18–50 years	Not specified	Participants reported experiencing fever, headache, and muscle weakness via diary cards after vaccination.	Generated neutralizing antibody and T cell responses; protective in studies of incidental natural host for WNV

- 4 equine vaccines are licensed in US but no human vaccines
- Live attenuated chimeric, recombinant E protein-based, plasma DNA vaccine, hydrogen-peroxide-inactivated

NEMOURS CHILDREN'S HEALTH

Singh P, et al. Emerging Microbes & Infections. 2025.