EMERGING AND RE-EMERGING INFECTIONS - MOSQUITO BORNE

AOHC FALL CONFERENCE 2024

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Disclosures : None

EMERGING AND RE-EMERGING INFECTIONS

Emerging infectious disease (EID) is defined as a disease caused by a pathogen that has not before been observed within a population or geographic location

Re-emerging infectious disease is caused by an established pathogen that appears in a new geographical location or was once controlled but begins appearing at a higher incidence

A significant number of emerging and reemerging infections are viral in nature, and they are becoming more frequent

Three-quarters of emerging or reemerging infectious diseases are **zoonoses**

Zoonoses : infectious diseases of animals that are transmitted to humans arise from wildlife or from domesticated animals

ARBOVIRUSES

Arboviruses (**ar**thropod-**bo**rne **viruses**) are viruses that are transmitted to humans or other mammals by arthropods, invertebrate animals possessing an exoskeleton

The major arthropod **vectors** for the transmission of viruses are **mosquitoes** and **ticks**

CDC arbovirus catalog lists 537 known arboviruses, approximately a quarter of which can cause disease in humans

Most arboviruses are RNA viruses and with inherent ability of the RNA viruses to recombine and reassort can lead to genetic mutations and change in host range

A large proportion of the arboviral diseases of humans are **zoonotic**

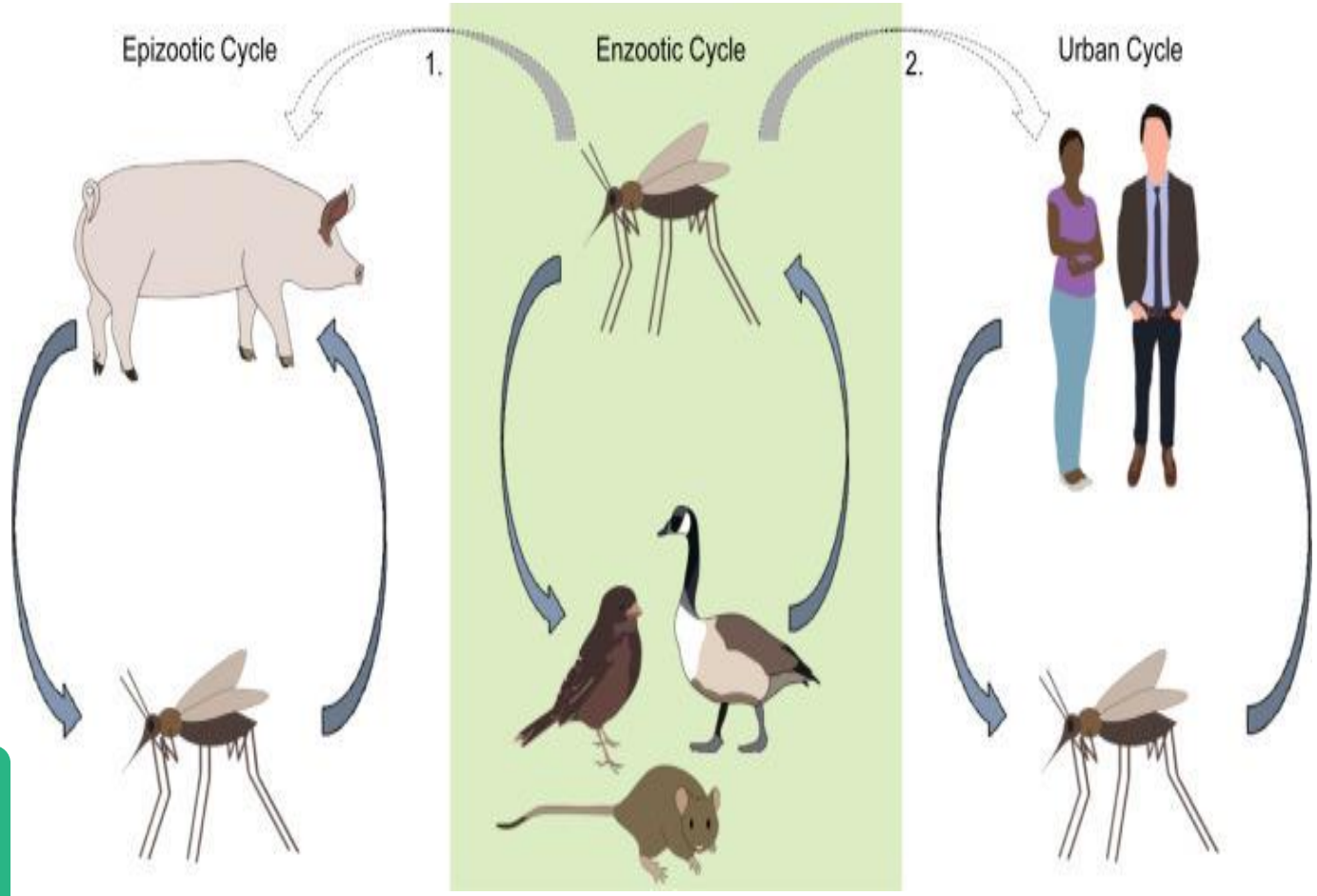
ARBOVIRUS TRANSMISSION MODEL

Enzootic cycle : occurs when the virus is transmitted between its arthropod vector and its natural reservoir, a wild animal

Epizootic cycle : occurs when vector infects and cause an epidemic within domestic animals & further amplify the virus

Urban cycle : occurs when the virus cycles directly between the vector & a human host

Humans may also become infected tangentially from enzootic cycles



Ref : Essential Human Virology. 2016 : 291–310

MOSQUITO BORNE INFECTIONS

Include such as Malaria, Dengue, Zika virus fever, West Nile fever, Chikungunya viral disease, Yellow fever, Japanese encephalitis, Eastern Equine Encephalitis

Studies emphasize the ongoing evolution of pathogens, proliferation of reservoir populations, and antimicrobial drug use to be the principal exacerbating forces for emergence and re-emergence of vector-borne infectious diseases

Studies equivocally claim that climate change has been associated with appearance and resurgence of vector-borne infectious diseases

Social and demographic factors such as human population growth, urbanization, globalization, trade, travel and close interactions with livestock have significantly been linked with the emergence and/or re-emergence of vector-borne diseases

Ecological, environmental, or demographic may contribute to this adaptation and consequent of disease emergence

FACTORS INVOLVED IN THE EMERGENCE/REEMERGENCE OF VIRAL DISEASES

Human (including economical, societal)	
Population growth	Inadequate public health infrastructures
Urbanization	Lack of access to health care
International travel	Reduced immunization policies
Human susceptibility to virus	Human invasion of wild animal habitats
Environmental and ecological	
Rainfall accumulation	Wildlife host species richness
Temporary weather patterns	Human encroachment into pristine lands
Long-term climate change	Building of dams, land development
Dew point	Deforestation for farming
Soil moisture	
Viral	
Genomic changes through reassortment, recombination, or mutation	**Ref :** Essential Human Virology. 2016 : 291–310.

CLIMATE AND NON-CLIMATE FACTORS

Climate factors : affect pathogens directly, through influencing the survival, reproduction, and life cycle or indirectly, by affecting habitat, environment and altering the contact patterns of human-vector

Non-climatic factors : global human populations and urbanization, international trade and travel, modernization of agricultural practices

Globalization : factors relating to human behavior and activities, pathogen evolution, poverty,

Urbanization : High influx of rural-to-urban migration has been linked to high-density peri-urban poor housing status

which create conducive atmosphere breeding of vectors, associated with improper

water & waste management, which creates ideal habitats for expansion of vector population

MALARIA

Caused by five genera of *Plasmodium* namely *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*

Transmitted by the **female** *Anopheles* mosquitoes

Globally in 2022, there were an estimated 249 million malaria cases and 608,000 malaria deaths in 85 countries

African region was home to 94% of malaria cases (233 million) and 95% (580,000) of malaria deaths

Children under 5 accounted for about 80% of all malaria deaths in the region

Tropical regions with warm temperature, heavy rainfall, high humidity and low altitudes are conducive for mosquito breeding, longevity and parasite sporogony

MALARIA VACCINE (MOSQUIRIX)

2021, the World Health Organization (WHO) recommended the RTS,S/AS01 vaccine for use in children under 5

Four doses of the vaccine had 36% efficacy against malaria over a 4-year period among children 5 to 17 months of age

RTS,S/AS01 malaria vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high malaria transmission, as defined by WHO

RTS,S/AS01 vaccine should be provided in a 4-dose schedule in children with the first dose starting at 5 months of age

There should be a minimum interval of 4 weeks between doses

The vaccine should be administered in a 3-dose primary schedule, with a fourth dose provided approximately 12–18 months after the third dose to prolong the duration of protection

MALARIA VACCINE (MOSQUIRIX)

RTS,S/AS01 vaccine may be administered simultaneously with other vaccines of the childhood immunization schedule

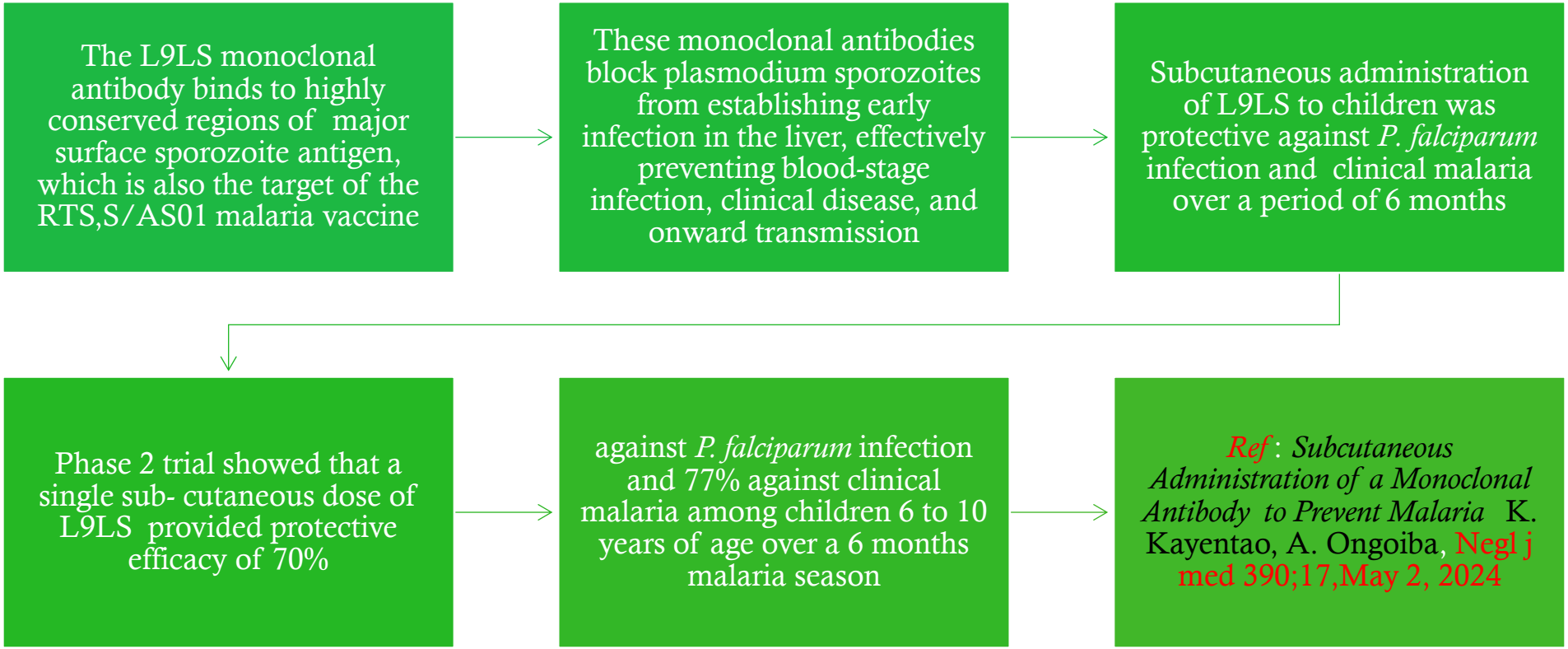
WHO also recently endorsed the R21/Matrix-M vaccine for use in children in 2023

Where monthly seasonal malaria chemoprevention is the standard care during the 4 to 6 months malaria season, a **three-dose regimen** of the R21/Matrix-M vaccine had 75% efficacy over a 12-month period among children 5 to 36 months of age

A booster after 12 months was necessary to maintain efficacy

Both vaccines are not a part of Essential Programme on Immunization of WHO

MALARIA MONOCLONAL ANTIBODY



CHIKUNGUNYA

The name “chikungunya” derives from a word in the Kimakonde language meaning “to become contorted” or “to walk bent over,” in the Tanzanian Makonde dialect

An apt description of the appearance of some infected people with arthralgias

Is a mosquito-borne (Ades *aegypti* or Ades *albopictus*) viral disease caused by an *alphavirus* from the *Togaviridae* family

Chikungunya is an arbovirus first described during a 1952 outbreak in southern Tanzania

Evolved rapidly after its successful introduction to new localities and getting new anthropophilic vectors

Virus has been associated with several episodes of epidemics in Africa, Asia, and India

Acute onset of fever and prostration, muscle and joint pains, lymphopenia (as in many arboviral diseases), and frequently a nonspecific maculopapular rash

CHICKUNGUNYA VACCINE

Symmetric arthralgias are usually prominent in phalanges, wrists, and ankles

After 1 year, at least 20% of patients still have severe recurrent joint pains

DDx : Chikungunya includes Dengue and other Arboviral infections, as well as influenza

Distinguished from dengue clinically by persistent or recurring poly arthralgias

One chikungunya vaccine live attenuated (called IXCHIQ) is available in the United States

The vaccine is licensed for adults aged 18 years and older

The U.S. Advisory Committee on Immunization Practices (ACIP) approved for use of the vaccine in travelers and laboratory workers in February 2024

JAPANESE ENCEPHALITIS (JE)

Major cause of viral meningo-encephalitis in the world

Single-stranded RNA virus belonging to the genus *Flavivirus*

First described in Japan in 1870s and spread throughout huge parts of Asia

JE is endemic in different parts of the world mainly Asia extending from Japan to India & Pakistan

Transmission of JE virus between animals occurs by ***Culex* mosquitoes**

Natural transmission is maintained among wild and domestic **birds**, and **pigs**

The widespread expansion of JEV attributed to the growth in human populations, land use for irrigated rice agricultural activity and in pig farming

One JE vaccine (called IXIARO) is available in the United States for high risk travelers

WEST NILE VIRUS (WNV)

WNV infection is caused by West Nile virus of the genera *Flavivirus*

Transmitted principally by ***Culex*** species of mosquitoes

WNV is known to have wide range of mosquito vectors and hosts including birds, horses & other mammals

WNV first isolated from a febrile patient from the West Nile district of Northern Uganda in 1937

First episode in the Americas in 1999, an estimated 7 million cases have been recorded in United States

WNV is regarded among the most important **zoonotic** diseases of concern to the US population

WNV has become the leading cause of domestic arthropod-borne viral **(arboviral)** disease in US

Symptoms include fever, headache, body aches, vomiting, diarrhea, or rash

West Nile virus causes potentially fatal neuroinvasive disease in humans and animals world- wide

Human infections are mostly asymptomatic but can cause life-threatening illness in rare cases, predominantly in older adults and in immunocompromised persons

Normally humans are dead end hosts for WNV, the risk of infection is greatly increased by the zoonotic viral amplification and its persistence in the environment

659 *West Nile virus disease cases in 2024 - CDC DATA sheet*

43 *States reporting West Nile virus disease cases in 2024 CDC Data Sheet*

OH – 3 cases

Rituximab/other B cell depleting therapy severe disease

WEST NILE VIRUS (WNV)

YELLOW FEVER

Caused by a Yellow fever virus belonging to the genus of *Flavivirus* in the family of *Flaviviridae*

Transmitted by the bite of infected Aedes species of mosquito

Yellow fever is among viral hemorrhagic fevers and the most devastating disease in history

First outbreak was reported in 1648 in the Yucatan Peninsula

Yellow fever epidemics have been persistent in South America and Africa

Rise in international travel and population movements led to spread of the disease into metropolitan parts of tropical and subtropical areas

Yellow fever virus is maintained in the environment between mosquitoes and non-human primates, like monkeys

A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity

It is recommended that YF vaccine be given to children at age 9-12 months at the same time as the measles vaccine

Vaccine is contraindicated in children aged <6 months and is not recommended for those aged 6-8 months, except during epidemics when the risk of infection with the YF virus is very high

Other contraindications for YF vaccination are severe hyper-sensitivity to egg antigens and severe immunodeficiency

YF vaccines are live attenuated viral vaccines from the 17D lineage, developed by empirical passage in tissue culture, principally chicken embryo

YELLOW FEVER VACCINE

ZIKA VIRUS FEVER

Zika virus (ZIKV) was first isolated in the **Zika forest** in Uganda from a rhesus macaque in 1947

It is one of the member of *Flaviviridae* responsible for important human diseases

A. aegypti and *A. albopictus* primary vectors bite during the daytime and are widely distributed throughout the tropical and subtropical world

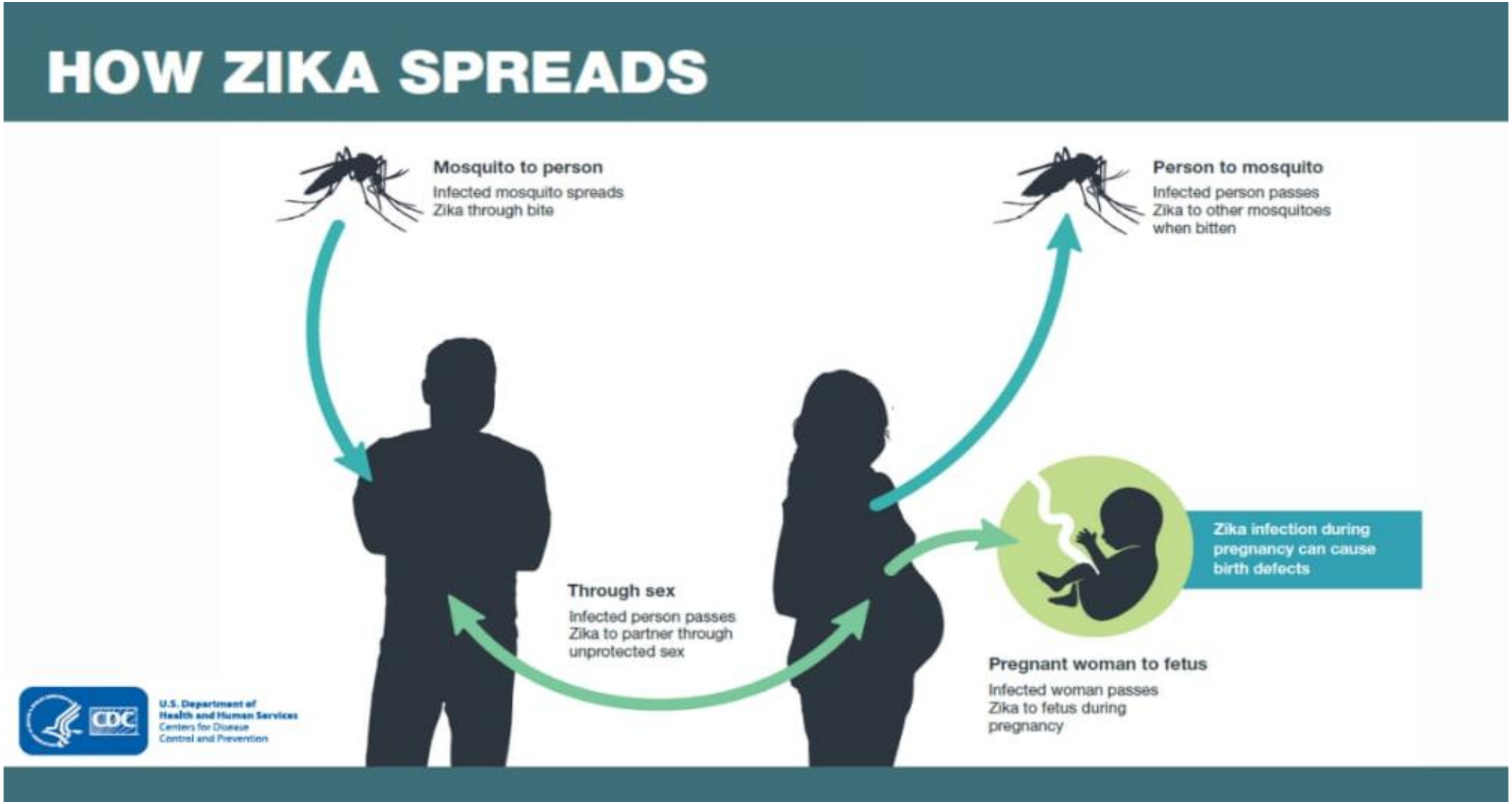
Zika virus was emerged in South and Central America in Southern Florida and at the Texas/Mexico border in the USA in 2015

With in the span of just 1 year, Zika virus was introduced into Brazil from the Pacific Islands and spread rapidly throughout the Americas

First major infectious disease linked to human birth defects to be discovered in more than half a century

Sexual transmission to partners of returning male travelers who acquired Zika virus has been reported

HOW ZIKA SPREADS



ZIKA VIRUS FEVER

- ZIKV infection can be diagnosed through detection of ZIKV RNA in blood, urine, and other body fluids by (RT-PCR) assay or by detection of serum IgM antibodies
- Viral RNA was detected in serum approximately 10 weeks after infection in a pregnant woman whose fetus had evidence of congenital infection
- ZIKV is now recognized as a cause of congenital neurologic birth defects, notably microcephaly and has been associated with potentially fatal complications
- Congenital Zika virus infection can cause serious defects of the brain and eye, neurodevelopmental abnormalities, such as seizures, joint contractures, swallowing difficulties, and hearing loss in infants
- Multiple Vaccines are in developmental phase

DENGUE

Most important human arbovirus, has increased in incidence by 30-fold in the last decade with an estimated **50-100 million** annual cases

Most common **mosquito-borne viral disease** worldwide

Southeast Asia region around 1.3 billion people are at-risk of dengue, which is the leading cause of hospitalization and death among children

More than 3.9 billion people in over 129 countries are at risk of contracting dengue

Dengue is caused by a virus of family Flaviviridae, genus *Flavivirus*

Transmitted between humans — **the primary reservoir host** — by infected **female mosquitoes**, most commonly ***Aedes aegypti* and *Aedes albopictus***

Dengue is also known as "**breakbone fever**," eluding to the extreme bone pain that can be experienced

Prime example of **arboviral** disease for which the urbanization factor is strongly associated with its emergence

DENGUE

The **vector (*Aedes aegypti*)** prefer artificial water containers as its larval habitat thus human habitations became its choice

Water-storage containers, or rainwater-filled containers (e.g., tires, pots, and tree holes) can become mosquito breeding sites and can thus drive epidemics

Globalization of trade, in particular the trade of tires from used vehicles, is thought to explain the dispersal of eggs and immature forms of these arboviral vectors into new territories

Although they cause similar clinical symptoms, the four serotypes of DENV (DENV-1, DENV-2, DENV-3, and DENV-4) are genetically distinct

Immunity against one serotype **does not** provide long-term protection against another serotype, although some short-term protection may occur

5–7 days of being bit by an infected mosquito, a person develops a viremia that lasts 5–12 days

human to human through blood transfusions or organ transplants, and perinatal transmission reported

Virus can be transmitted back to a mosquito host if the insect feeds on an infected person during the viremia

DENGUE

75% DENV infections are **asymptomatic**

25% Symptomatic illness is divided into **Non severe dengue** and **Severe dengue (5%)**

Non severe dengue is further divided into dengue **without warning signs** or **dengue with warning signs**

Dengue without warning signs is the less severe form of disease, characterized by fever and at least two of the following symptoms: nausea/vomiting, rash, **retro orbital pain**, joint aches and pain **leukopenia** or a positive tourniquet test

Dengue rash : "**islands of white in a sea of red** "

The **tourniquet test** is performed by applying a blood pressure cuff on the individual for 5 min at a pressure between the person's systolic and diastolic pressures and then counting the number of **petechiae**

DENGUE

Dengue with warning signs, individuals display any of the symptoms with out warning in addition of abdominal pain, mucosal bleeding, lethargy, liver enlargement >2 cm, persistent vomiting, Ascites, Pleural effusions

They may also have an increase in hematocrit indicating that plasma is leaving the bloodstream

Severe dengue, which is characterized by **hemorrhagic fever**. This is a severe multiorgan syndrome that results from increased permeability of the vascular system, leading to petechiae and bleeding within the internal organs or from orifices like the mouth, nose, and eyes

Severe dengue usually occurs after **defervescence**, the abatement of fever

During this 1–2-day "critical period," plasma leakage can also result in **shock**

TRAVEL ASSOCIATED DENGUE

In the United States, public health authorities in Puerto Rico declared an outbreak in March 2024 current cases reported (3178)

Dengue is endemic in 6 U.S territories and freely associated states

5027 Dengue cases reported in 2024 – CDC Data

Ohio Reporting 22 cases in 2024 - CDC Data

Dengue continues to expand outside the tropics, more frequent importation and local transmission of DENV in the United States is expected

Southern United States is an ideal setting for the introduction and spread of DENV, given the wide-spread presence of *A. aegypti* mosquitoes, and appropriate environmental conditions for transmission

The diagnosis should be considered in any patient presenting with fever that has developed within 14 days after even a brief trip to the tropics or subtropics, including those regions where dengue has not traditionally been considered an endemic disease

Infectious virus and the virus-encoded Non Structural Protein S1 are present in blood during the acute phase

High-level early viremia and Non Structural Protein S1 antigenemia have been associated with more severe clinical presentations

Dengue viruses exist in two environments: Urban or endemic setting, where humans and mosquitoes are the only known hosts

Forested areas, where transmission of mosquito- borne viruses occurs between nonhuman primates and, rarely, from these primates to humans

Young age, Female sex, High body-mass index, Virus strain DENV -2, risk factors for severe dengue

DENGUE VIRUS

LABORATORY DIAGNOSIS OF DENGUE

(RT-PCR) assay or detection of the virus- expressed soluble Nonstructural Protein 1 (NS1) by means of (ELISA) is sufficient for a confirmatory diagnosis

The presence of the dengue virus non-structural protein 1 (NS1) in blood (serum) during the first 7 days of illness is indicative of a current or recent dengue virus infection

Persons who have not been infected previously (which is typical in the case of most travelers), the diagnostic sensitivity of NS1 detection – Antigen in the febrile phase can exceed 90%

Antigenemia may persist for several days after the resolution of fever

Serologic diagnosis relies on the detection of serum IgM ESLISA that bind dengue virus antigens

DENGUE TREATMENT

Currently, **No effective antiviral agents** to treat Dengue infection

Treatment remains supportive, with particular emphasis on careful fluid management

AVOID ASPIRIN, NSAID, STEROIDS

Patients who have no complications and may remain at home with instructions to return to the hospital immediately if bleeding or warning signs suggestive of vascular leakage develop

Practice is to evaluate these patients **daily in a medical clinic** with a **complete blood count** to monitor hematocrit and platelets

Development of any **warning sign** indicates the need for hospitalization and close observation, with judicious use of parenteral fluids in patients with inadequate oral intake or a rapidly increasing hematocrit

Dengue shock syndrome, prompt fluid resuscitation to restore plasma volume is imperative

DENGUE VACCINE AND SEROSTATUS

Currently, there are Two Dengue vaccines approved for use and recommended by the World Health Organization: **Dengvaxia** (3 doses) and **TAK-003** (2 doses)

Dengvaxia: (CYD –TDV) derived from yellow fever virus is recommended only for use in ages 9 to 45 with at least one documented case of dengue

Check for seropositivity as dengue-naive recipients can suffer antibody dependent enhancement if they receive a vaccine prior to a natural infection

CYD-TDV is recommended as a 3-dose series given 6 months apart

Excessive T-cell responses in the context of inadequate neutralizing antibodies may explain increased DENV-associated adverse events among Dengvaxia recipients

There are NO dengue vaccines currently approved for use in U.S. travelers who are visiting but not living in dengue-endemic areas

DENGUE VACCINE

TAK-003, also known as Qdenga (Takeda), a **two-dose** dengue vaccine derived from **live-attenuated vaccine** containing weakened versions of the four serotypes

Not currently available in USA

WHO recommends the use of TAK-003 in children aged 6–16 years in settings with high dengue burden and transmission intensity

The vaccine should be administered in a 2-dose schedule with a 3-month interval between doses

Received approval in Indonesia for persons 6 to 45 years of age, in the European Union for persons 4 years of age or older, and in Brazil for persons 4 to 60 years of age

DENGUE VACCINE – IN PHASE 3 TRIAL

LIVE, ATTENUATED, TETRAVALENT BUTANTAN–DENGUE VACCINE IN CHILDREN AND ADULTS

E.G. KALLÁS, M.A.T. CINTRA, J.A. MOREIRA, E.G. PATIÑO, *N ENGL J MED* 2024;390:397-408

Butantan–Dengue Vaccine is an investigational, single-dose, live, attenuated, tetravalent vaccine against dengue

Ongoing phase 3, randomized, double-blind, placebo-controlled trial, with 5 years of planned follow-up, being conducted at 16 sites in Brazil

Vaccine efficacy of approximately 80% for protection against symptomatic, virologically confirmed dengue through 2 years of follow-up

Was efficacious in children, adolescents, and adults across an age range of 2 to 59 years

A single administration of Butantan-DV was shown to have a favorable safety profile

Efficacious in preventing symptomatic, virologically confirmed dengue caused by DENV-1 and DENV-2, irrespective of previous dengue exposure, throughout a 2-year follow-up

MOSQUITO CONTROL MEASURES

Include larvicidal strategies, insecticide spraying, mosquito traps, toxic sugar baits, repellents, insecticide treated materials, reduction of mosquito-breeding sites, and vaccines

Three new strategies for the control of *A. aegypti* vector populations have been developed and evaluated

1. Sterile Insect technique 2.Release of insects with dominant lethality 3. Introgression with *wolbachia*

Wolbachia pipientis — a common, maternally inherited, obligate intracellular type of bacteria

infects many species of insects but does not occur naturally in *A. aegypti*

Aedes aegypti mosquitoes infected with the *w*Mel strain of *Wolbachia pipientis* are less susceptible than wild-type *A. aegypti* to dengue virus infection

MOSQUITO CONTROL MEASURES

Trans infection of *A. aegypti* with some strains of *wolbachia* confers resistance to disseminated infection by **DENV** and other **arboviruses**

Introgression of "**virus-blocking**" strains of *wolbachia* into field populations of *A. aegypti* is an emerging dengue-control method

Stable *w*Mel transinfection imparts a viral- resistant state in *A. aegypti* mosquitoes that attenuates superinfection by several medically important flaviviruses and alphaviruses

With the use of *A. aegypti* infected with the *w*Mel strain of *Wolbachia pipientis*, Trial conducted in Indonesia the incidence of virologically confirmed dengue was 77% lower among participants who lived in intervention clusters than among those who lived in control clusters

EASTERN EQUINE ENCEPHALITIS VIRUS(EEE)

Virus is spread to people by the bite of an infected mosquito (*Aedes, Coquillettidia, & Culex*)	Only a few cases are reported in the United States each year	Most severe of Arbovirus infection	30% case fatality
50% long term disability	Mostly along Easter/Gulf coast/Greatlakes region	Peak in August/ September	No vaccines to prevent or No specific medications available

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