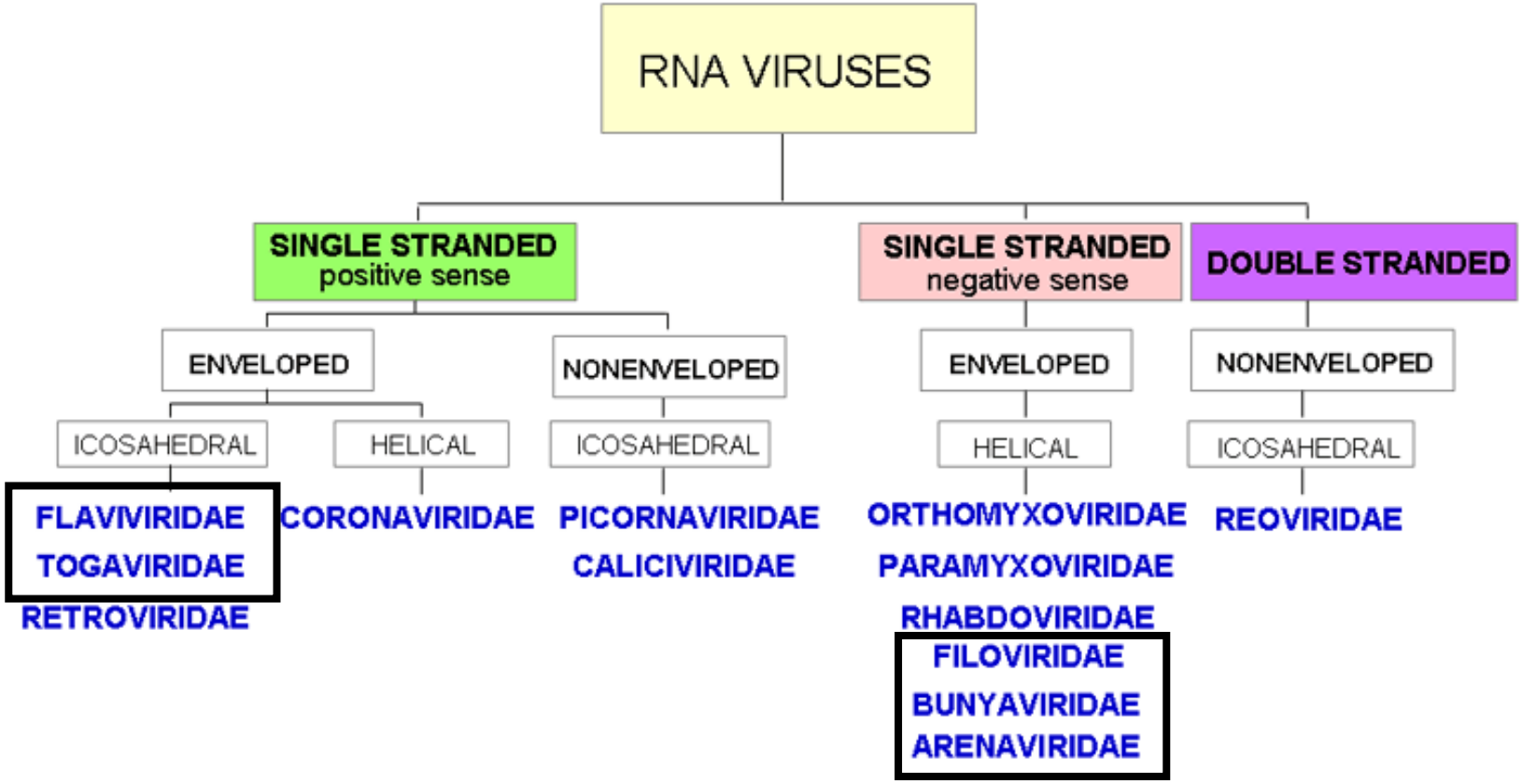
Arboviruses and Roboviruses



Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991

ARBOVIRUSES =

ARTHROPOD-BORNE VIRUSES

Togaviridae

Flaviviridae

Bunyaviridae

ROBOVIRUSES =

RODENT-BORNE VIRUSES

Filoviridae

Arenaviridae

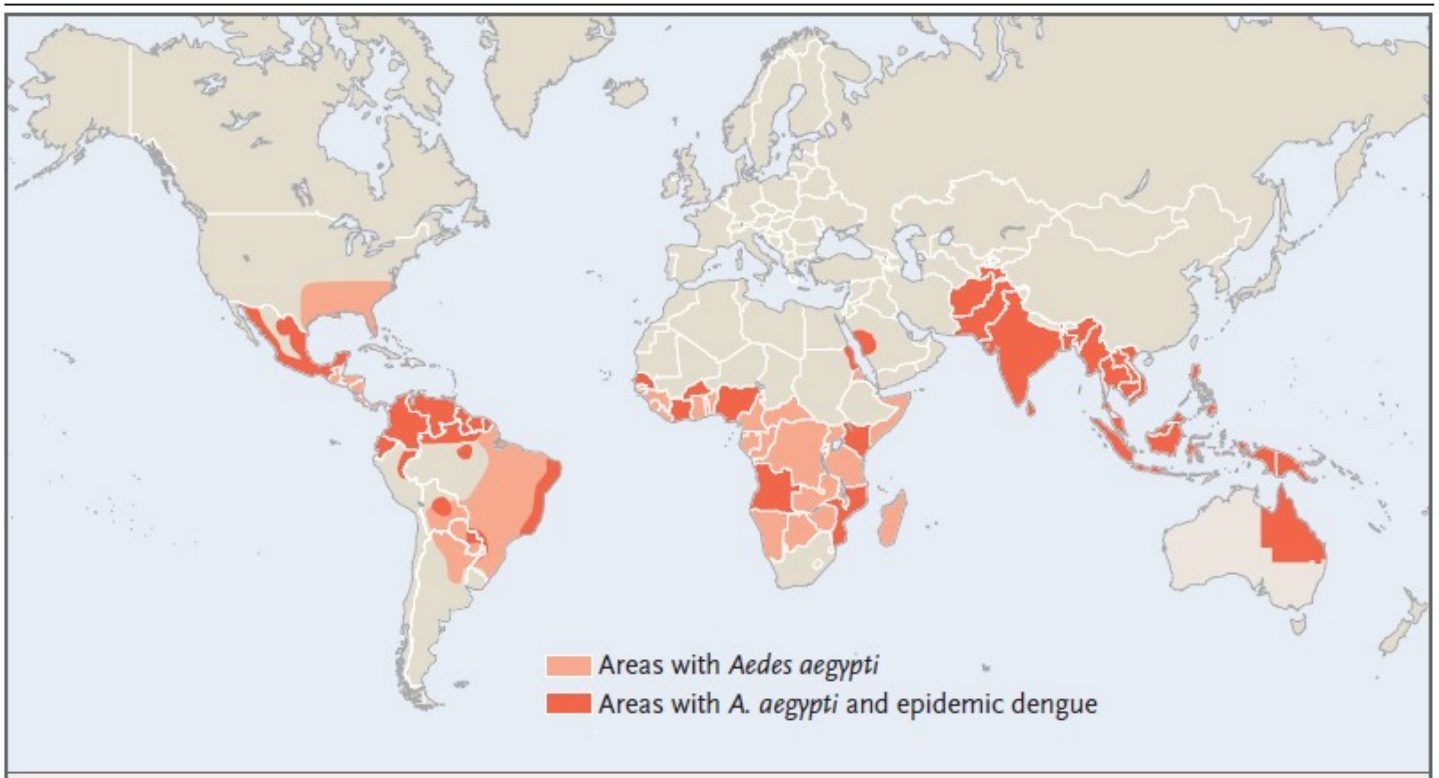


Figure 1. World Distribution of Dengue, 2002.
Adapted from the Centers for Disease Control and Prevention.[8]

- Dengue virus is now the most common cause of arboviral disease in the world, with an estimated annual occurrence of 100 million cases of dengue fever and
- 250,000 cases of dengue hemorrhagic fever and
- a mortality rate of 25,000 per year.
- Dengue virus infection has been reported in more than 100 countries, with 2.5 billion people living in areas where dengue is endemic

VIRUS ZAPADNOG NILA U REGIJI U Banja Luci umro dječak (6): 'Vjerujemo da se zarazio na moru'

Thinkstock

Autor: Portal Jutarnji.hr Objavljeno: prije 47 min

BANJA LUKA - Šestogodišnji dječak iz Banja Luke preminuo je u nedjelju navečer od posljedica zaraze virusom zapadnog Nila, objavile su **Nezavisne novine** pozivajući se na priopćenje Kliničkog centra Banja Luka. Kako se navodi u priopćenju, dječak je 7. kolovoza primljen na odjel intenzivne njege Klinike za dječje bolesti zbog povišene temperature, povraćanja, poremećenog stanja svijesti i ponašanja.

Njemački turist u Hrvatskoj 'zakačio' tropski virus

Odmah nakon povratka kući s dvotjednog ljetovanja u kolovozu na Pelješcu u Hrvatskoj, kod njemačkog je turista utvrđena bolest dengue, koju prenose tzv. tigrasti komarci, koji su se zadnjih godina pojavili u Hrvatskoj, osobito u priobalju.

Aedes aegypti

VIROLOGY DIAGNOSIS OF RE-EMERGENT INFECTIONS: DENGUE VIRUS

TATJANA VILIBIĆ-ČAVLEK, SUNČANICA LJUBIN-STERNAK, ANDREA BABIĆ-ERCEG, MARIO SVIBEN, GORDANA MLINARIĆ-GALINOVIĆ

Deskriptori: Dengue – dijagnoza, virologija, imunologija; Dengue virus – izolacija, genetika, imunologija; Antitijela, virusna – u krvi nestrukturne virusne bjelančevine – u krvi; Virusna RNK – analiza; Virologija – metode

Sažetak. Dengue je akutna virusna bolest koju na čovjeka prenose komarci roda Aedes (Ae. aegypti, Ae. albopictus). Uzročnik je virus porodice Flaviviridae, roda Flavivirus. Postoje četiri različita serotipa virusa dengue (1-4) koji se mogu održavati u endemskim područjima svijeta. Bolest se većinom pojavljuje u tropskim i suptropskim krajevima između 35° sjeverne i 35° južne geografske širine. Infekcija može biti asimptomatska ili se očitovati kao nespecifična febrilna bolest, dengue groznica, dengue hemoragijska groznica te dengue šok sindrom. Prisutnost komarca Ae. albopictus dokazana je i u Hrvatskoj. Prvi nalaz ovog komarca zabilježen je na području Zagreba u listopadu 2004. godine, a u jesen 2005. godine i u brojnim mjestima duž jadranske obale. Tijekom 2007. godine u nas su dokazana dva importirana slučaja dengue groznice, nakon čega su importirani slučajevi kontinuirano bilježeni. U kolovozu 2010. godine zabilježen je prvi slučaj autohtone dengue groznice u Hrvatskoj, na poluotoku Pelješcu. Iako Hrvatska nije endemsko područje za dengu, prisutnost odgovarajućeg vektora, kao i moguća opasnost od importiranih slučajeva dengue zahtijevaju suvremenu i pravodobnu dijagnostiku ove bolesti. Dijagnostika virusa dengue najčešće se provodi detekcijom virusne RNK, detekcijom antigena te serološkom dijagnostikom (dokaz specifičnih protutijela).

Aedes albopictus

SMRTONOSNI VIRUS U HRVATSKOJ Pacijent u Sl. Brodu zaražen virusom zapadnog Nila!

ARBO*VIRUSES*

- *Ecological description*
- *Today >500 viruses*
- *Heterogeneous group of animal viruses*
  - *Similar epidemiological characteristics*
  - *Similar clinical syndromes*

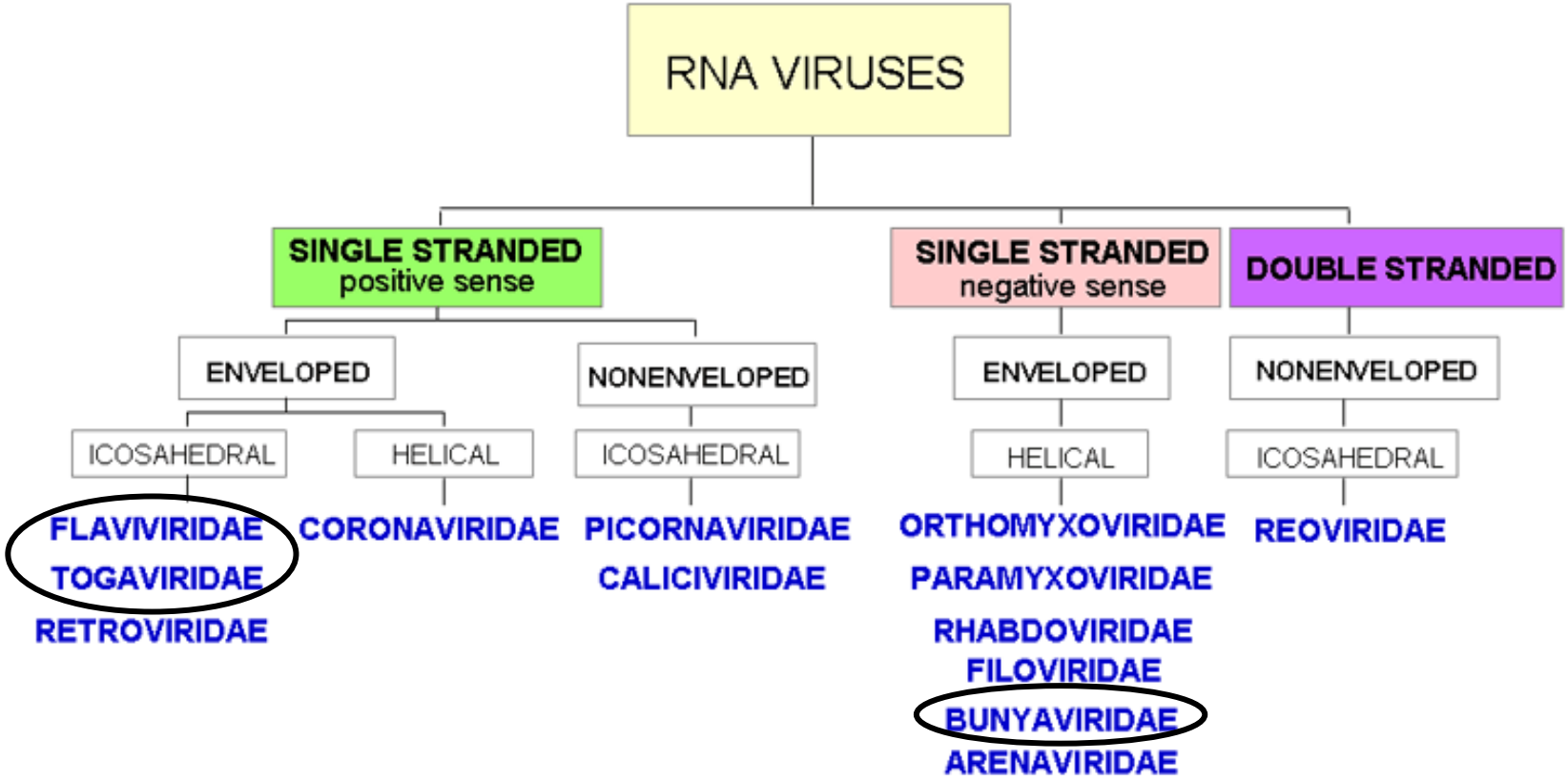
Arthropod-borne Viruses

Arthropod-borne viruses (arboviruses) are viruses that can be transmitted to man by arthropod vectors. The WHO definition is as follows

"Viruses maintained in nature principally, or to an important extent, through biological transmission between susceptible vertebrate hosts by haematophagus arthropods or through transovarian and possibly venereal transmission in arthropods."

Arboviruses belong to three families

1. ***Togaviruses*** *e.g. EEE, WEE, and VEE*
2. ***Bunyaviruses*** *e.g. Sandfly Fever, Rift Valley Fever, Crimean-Congo Haemorrhagic Fever*
3. ***Flaviviruses*** *e.g. Yellow Fever, dengue, Japanese Encephalitis*



Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991

Arboviruses

Togaviridae	ss (+) RNA nonsegmented							
	Alphavirus					***Rubivirus***		
	Encephalitis		Fever and Arthritis			Rubellavirus		
	Eastern Equine		Chikungunya					
	Western Equine		O'nyong-nyong					
	Venezuelan Equine		Maryaro					
			Ross River					
			Sindbis					
Flaviviridae	ss (+) RNA nonsegemented							
	Hepacivirus							
	Pestivirus							
	Flavivirus							
	Mosquito-Borne		Tick-Borne					
	Yellow fever		TBE	CEEV	RSSEV			
	Dengue		Louping ill					
	West Nile		Powassan					
			Kyasanur forest disease					
			Omsk hemorrhagic fever					
Bunyaviridae	ss (-) RNA segmented (3 segments)							
	Bunyavirus		***Phlebovirus***		***Nairovirus***		***Hantavirus***	
	Bunyamwera Group		SFNV		Crimean-Congo hemorrhagic fever		Hantaan	
	Čalovo		SFSV		(C-CHFV)		Dobrava	
	California Group		TOSV		(Tick-Borne)		Seoul	
	La Crosse		(Phleobotmus papatasi)				Pumala	
	Tahyna		Rift Valley (RVFV)				Sin Nombre	
	(Mosquito-Borne)		(Mosquito-Borne)				(Rodent-Borne)	
			Uukuniemi virus group					
			(Ticks)					

Roboviruses

Arenaviridae	ss (-) RNA segmented (2 segments)				
	Rodent-Borne			Rodent-Borne	
	Old World viruses			**New World viruses**	
	LCMV			South American HF viruses	
	Lassa Fever virus			Junin	
				Machupo	
				Guannarito	
				Sabia	
Filoviridae	ss (-) RNA nonsegemented				
	Ebolavirus		***Marburgvirus***		
	Zaire ebolavirus		Marburg marburgvirus		
	Sudan ebolavirus				
	Tai Forest ebolavirus				
	Bundibugyo ebolavirus				
	Reston ebolavirus				

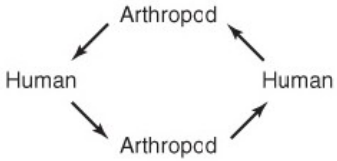
TRANSMISSION

Arboviruses are a large group of RNA viruses that are *transmitted* primarily by arthropods, such as mosquitoes and ticks.

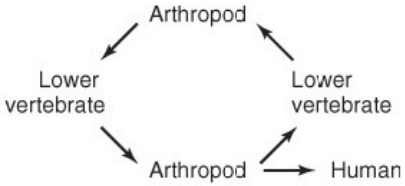
TRANSMISSION

At least three different transmission patterns have been recognized among the arthropod-borne viruses:

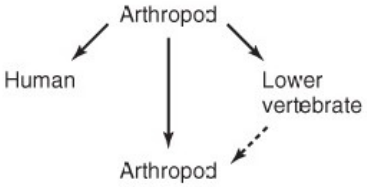
1. **Human–arthropod cycle:** ***Examples***—Urban yellow fever, dengue.



2. **Lower vertebrate–arthropod cycle with tangential infection of humans**: ***Examples***—Jungle yellow fever, St. Louis encephalitis. The infected human is a "dead end" host. This is a more common transmission mechanism.

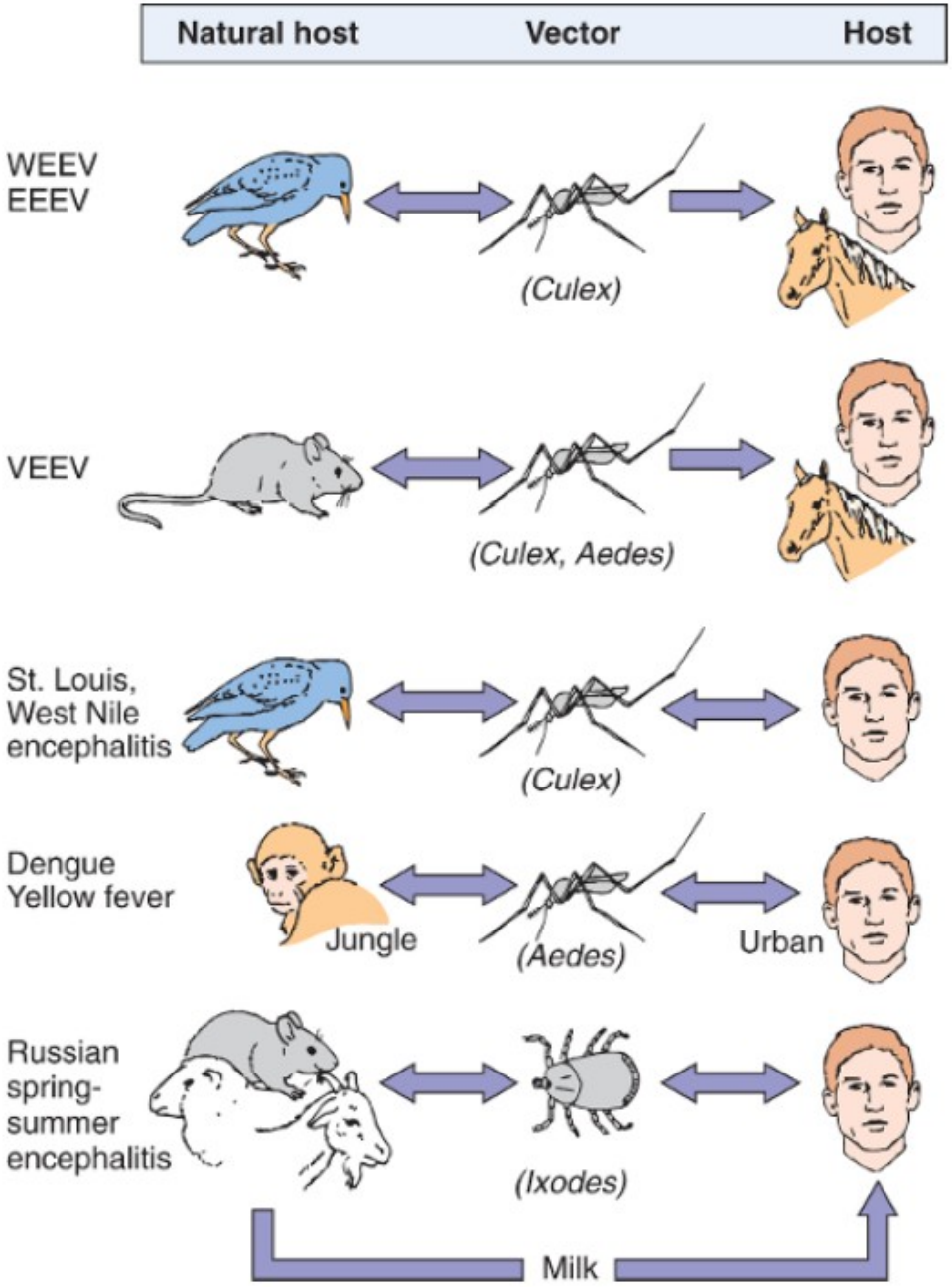


3. **Arthropod–arthropod cycle with occasional infection of humans and lower vertebrates:** ***Examples***—Colorado tick fever, LaCrosse encephalitis.

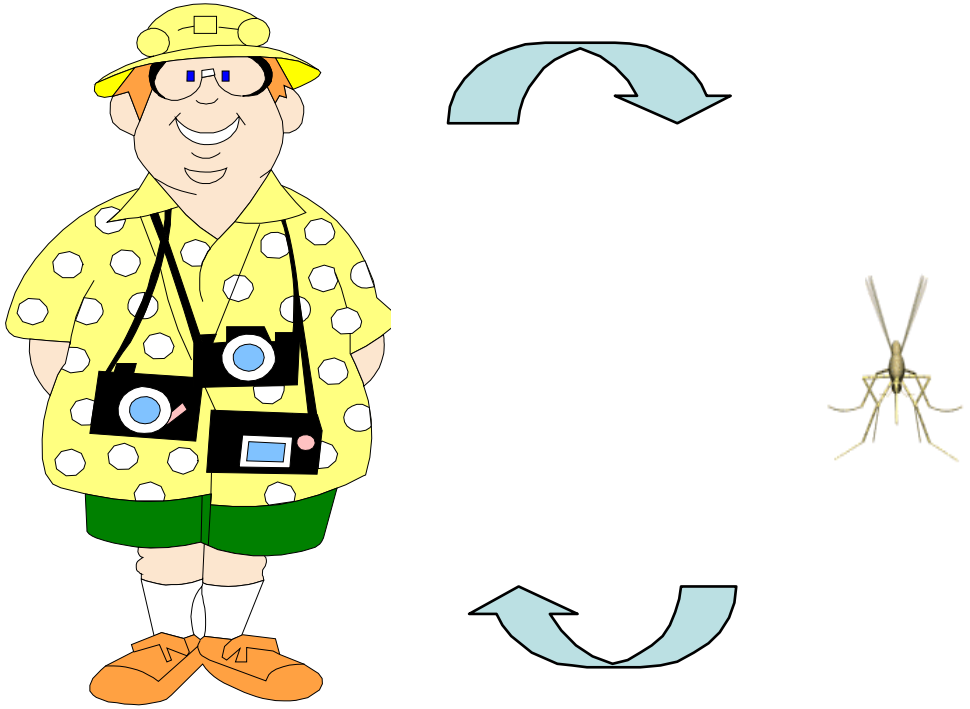


Transmission Cycles

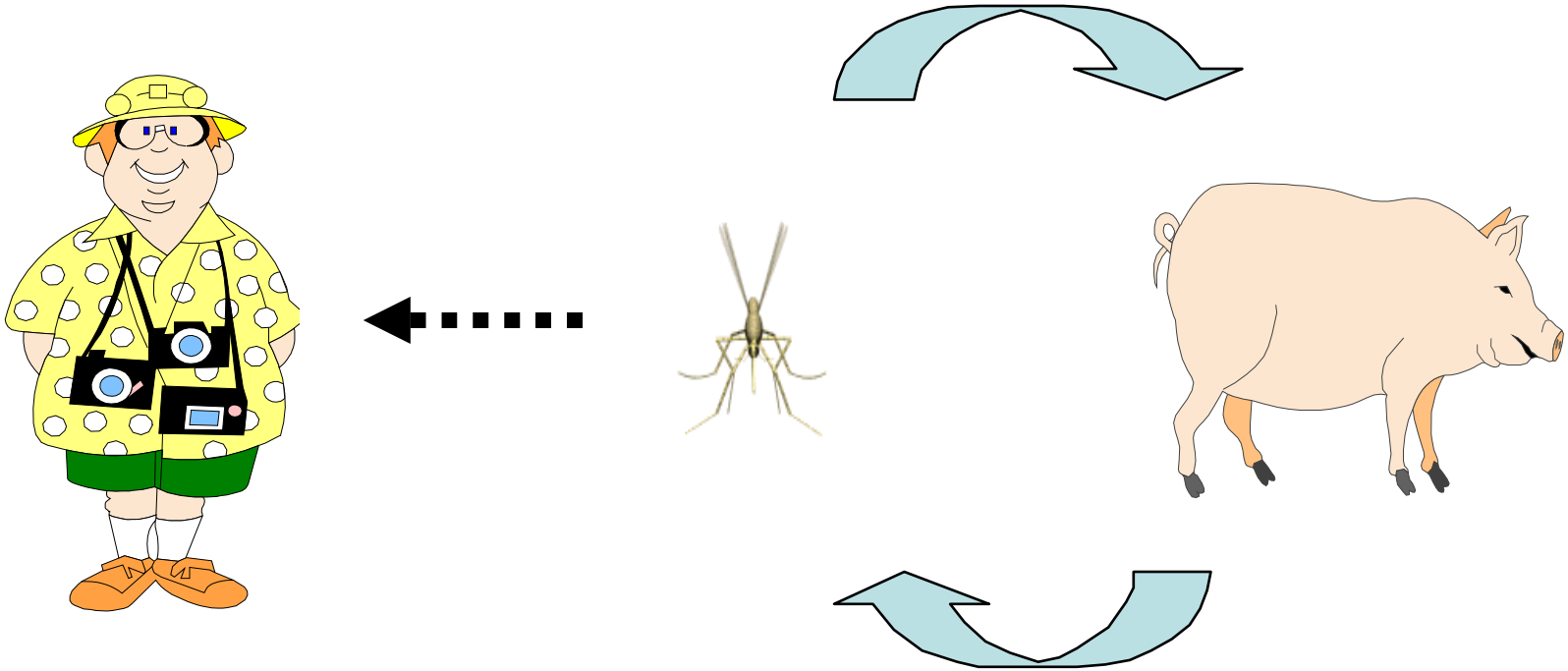
- *Man - arthropod -man*
  - *e.g. dengue, urban yellow fever.*
  - *Reservoir may be in either man or arthropod vector.*
  - *In the latter transovarial transmission may take place.*
- *Animal - arthropod vector - man*
  - *e.g. Japanese encephalitis, EEE, WEE, jungle yellow fever.*
  - *The reservoir is in an animal.*
  - *The virus is maintained in nature in a transmission cycle involving the arthropod vector and animal. Man becomes infected incidentally.*
- *Both cycles may be seen with some arboviruses such as yellow fever.*


Natural host
Vector
Host
WEEV
EEEV
(Culex)
VEEV
(Culex, Aedes)
St. Louis,
West Nile
encephalitis
(Culex)
Dengue
Yellow fever
Jungle
(Aedes)
Urban
Russian
spring-
summer
encephalitis
(Ixodes)
Milk

Man-Arthropod-Man Cycle



Animal-Arthropod-Man Cycle



Arthropod Vectors

Mosquitoes

Japanese encephalitis, dengue, yellow fever, St. Louis encephalitis, EEE, WEE, VEE etc.

Ticks

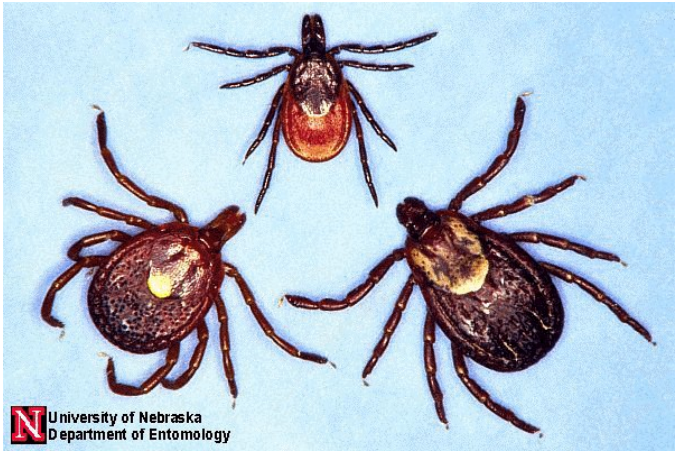
Crimean-Congo haemorrhagic fever, various tick-borne encephalitides etc.

Sandflies

Sicilian sandfly fever, Rift valley fever.

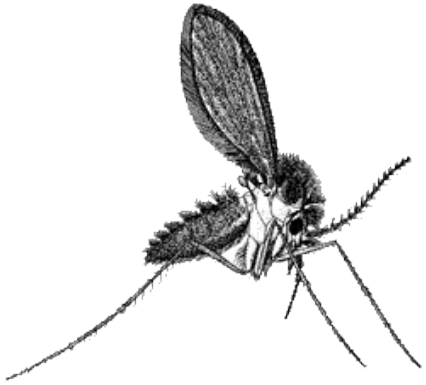
Examples of Arthropod Vectors

Aedes Aegypti



Assorted Ticks

Culex Mosquito



Phlebotmine Sandfly

Animal Reservoirs

In many cases, the actual reservoir is not known. The following animals are implicated as reservoirs

Birds	Japanese encephalitis, St Louis encephalitis, EEE, WEE
Pigs	Japanese encephalitis
Monkeys	Yellow Fever
Rodents	VEE, Russian Spring-Summer encephalitis

Diseases Caused

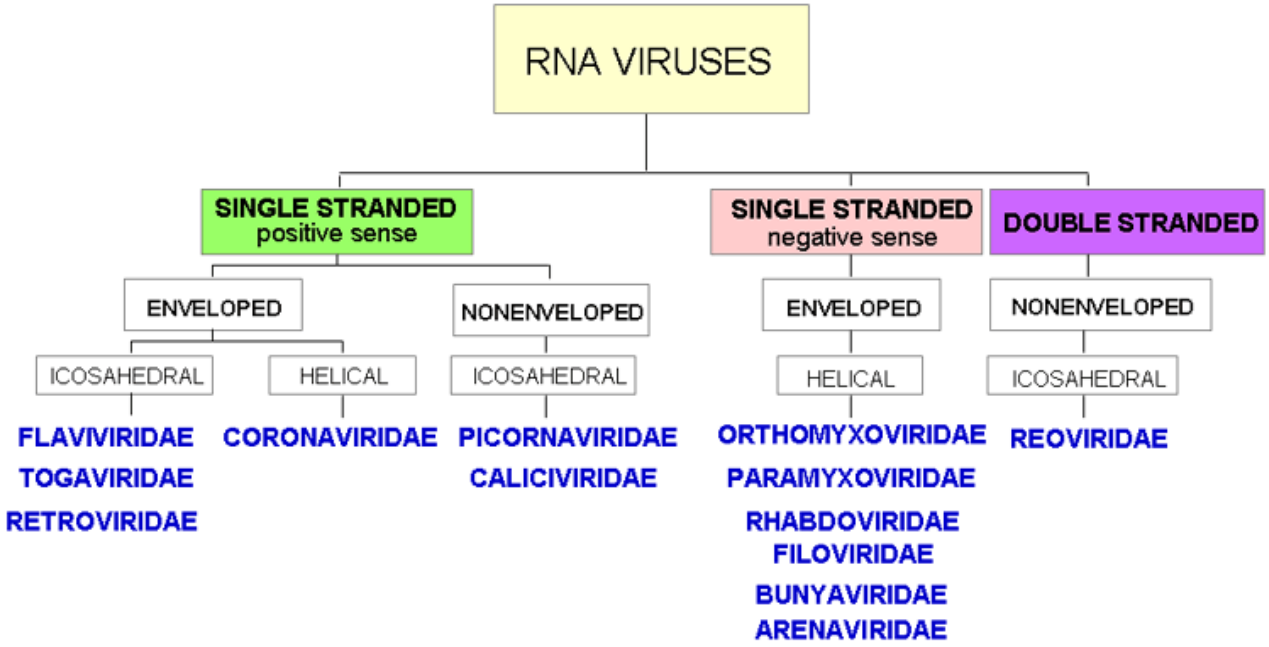
- ***Fever and rash*** *- this is usually a non-specific illness resembling a number of other viral illnesses such as influenza, rubella, and enterovirus infections. The patients may go on to develop encephalitis or haemorrhagic fever.*
- ***Encephalitis*** *- e.g. EEE, WEE, St Louis encephalitis, Japanese encephalitis.*
- ***Haemorrhagic fever*** *- e.g. yellow fever, dengue, Crimean-Congo haemorrhagic fever.*

ARBOVIRUSES

Family	Broj uzroč bolesti/ ukupni broj virusa	Genome	Genome segments	Size nm	Morphology
TOGAVIRIDAE **Alphavirus**	16/31	ss (+) RNA	1	60	Spherical, icosahedral, enveloped
FLAVIVIRIDAE **Flavivirus**	31/62	ss (+) RNA	1	40-50	Spherical, pleomorph, enveloped
BUNYAVIRIDAE **Bunyavirus** **Phlebovirus** **Nairovirus** Hantavirus	71/263	ss (-) RNA	3	80-120	Spherical, spiral. symm. pleomorph, enveloped

>60% of all arboviruses are members of these 3 families

Togaviridae



Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991

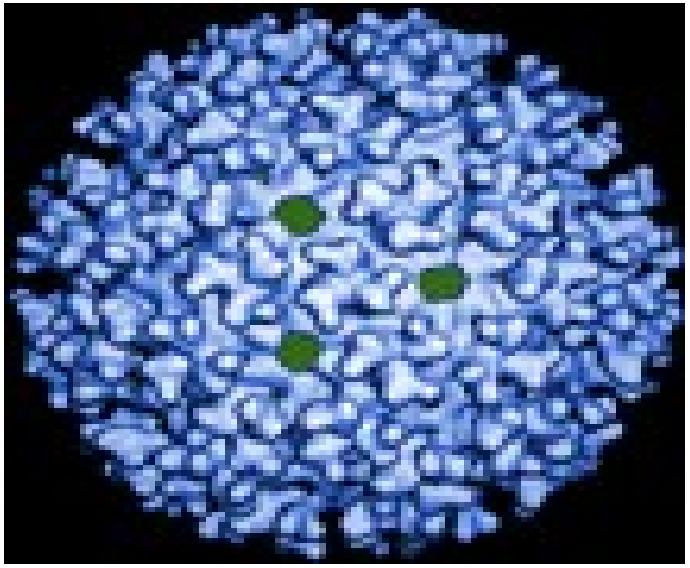
Togaviridae

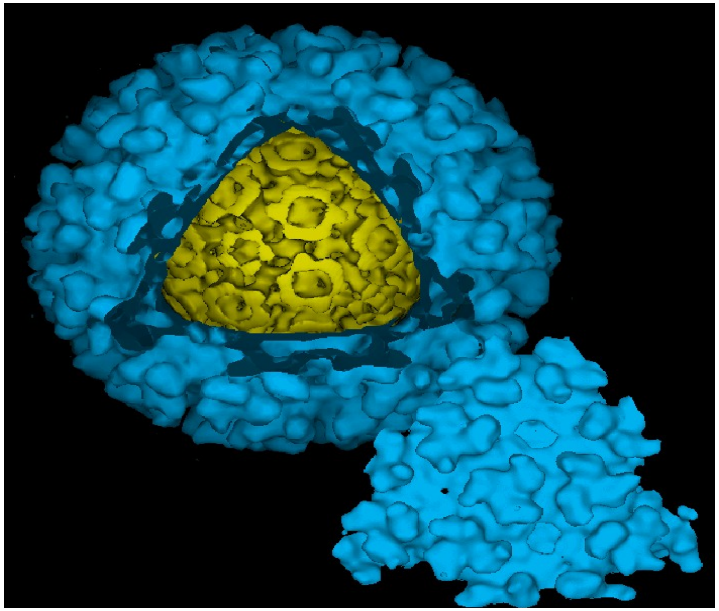
Genera

Alphavirus
31 arbovirus

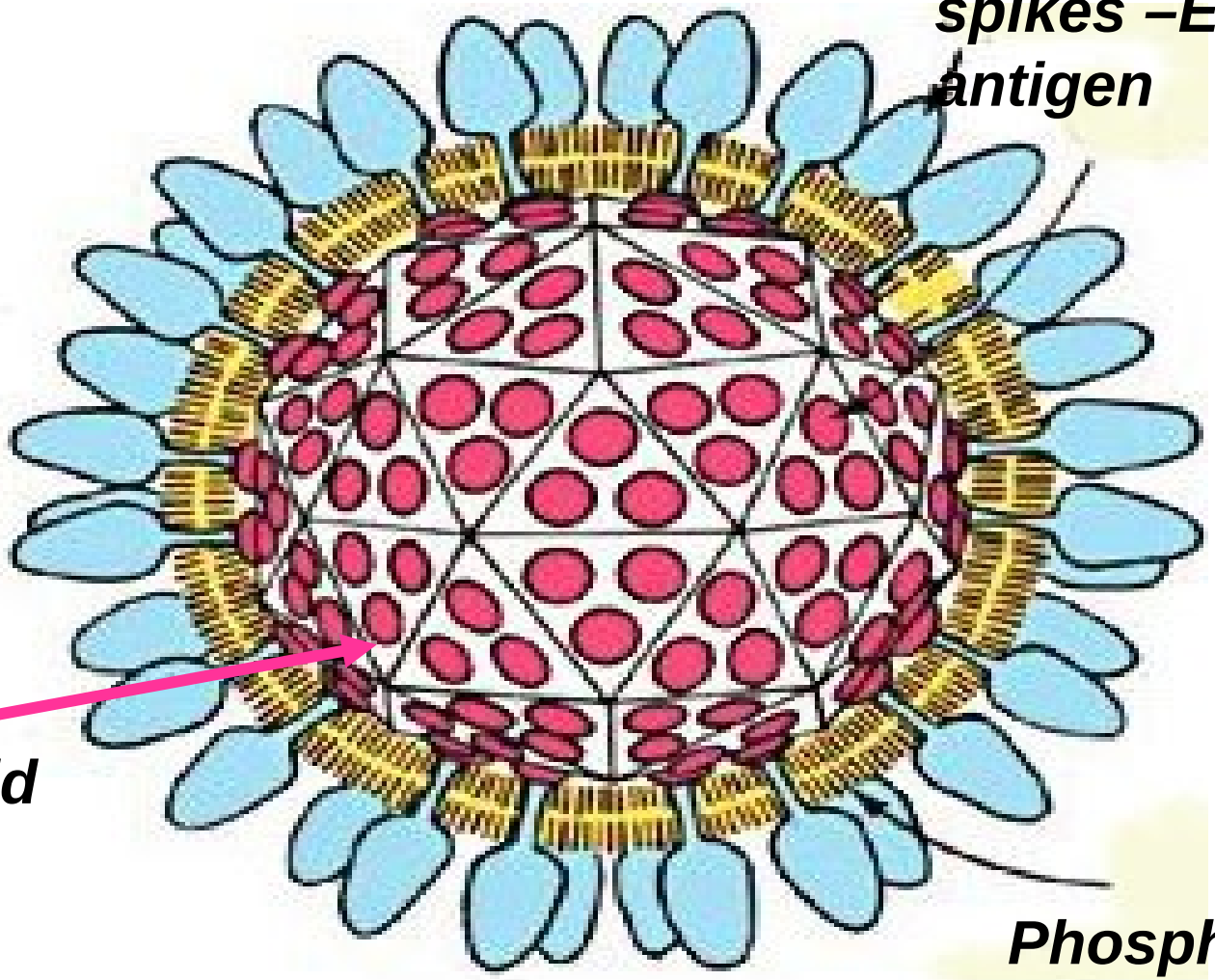
Rubivirus
Rubella v.

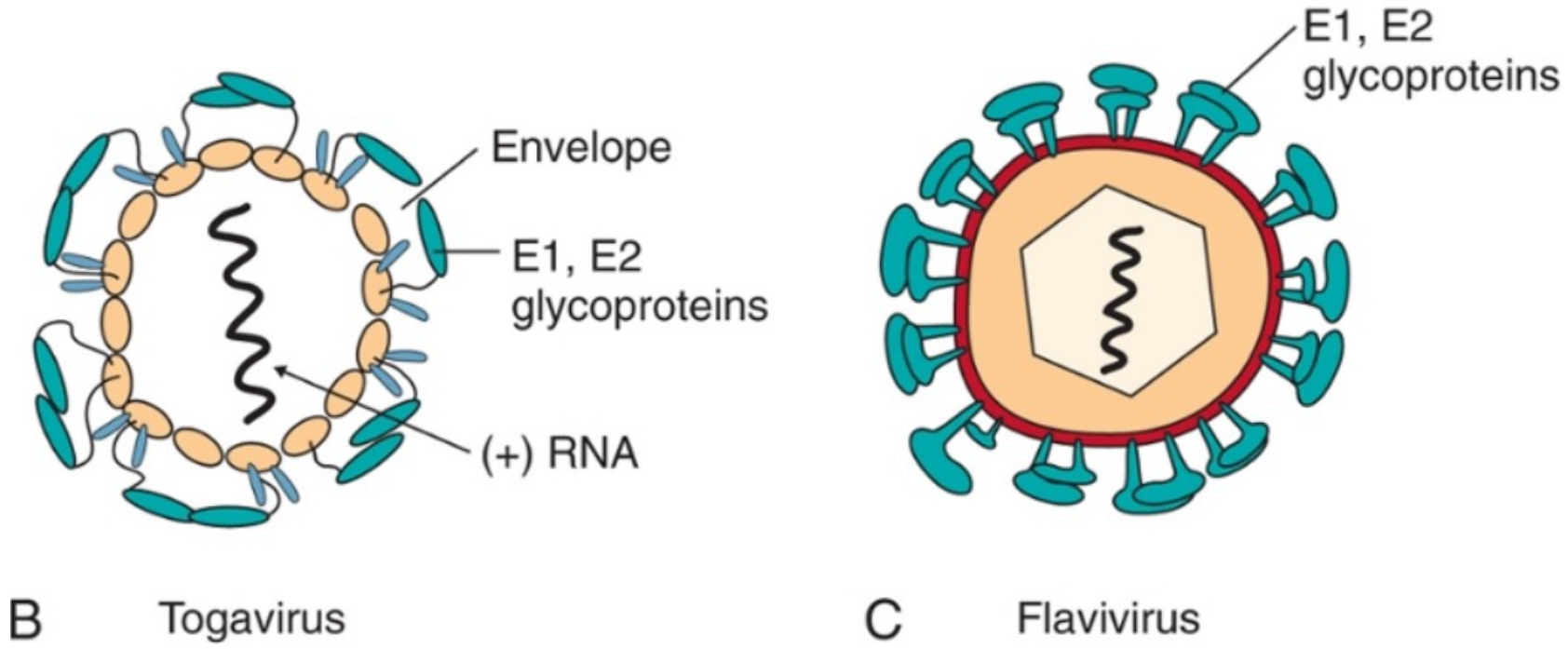
Togaviridae





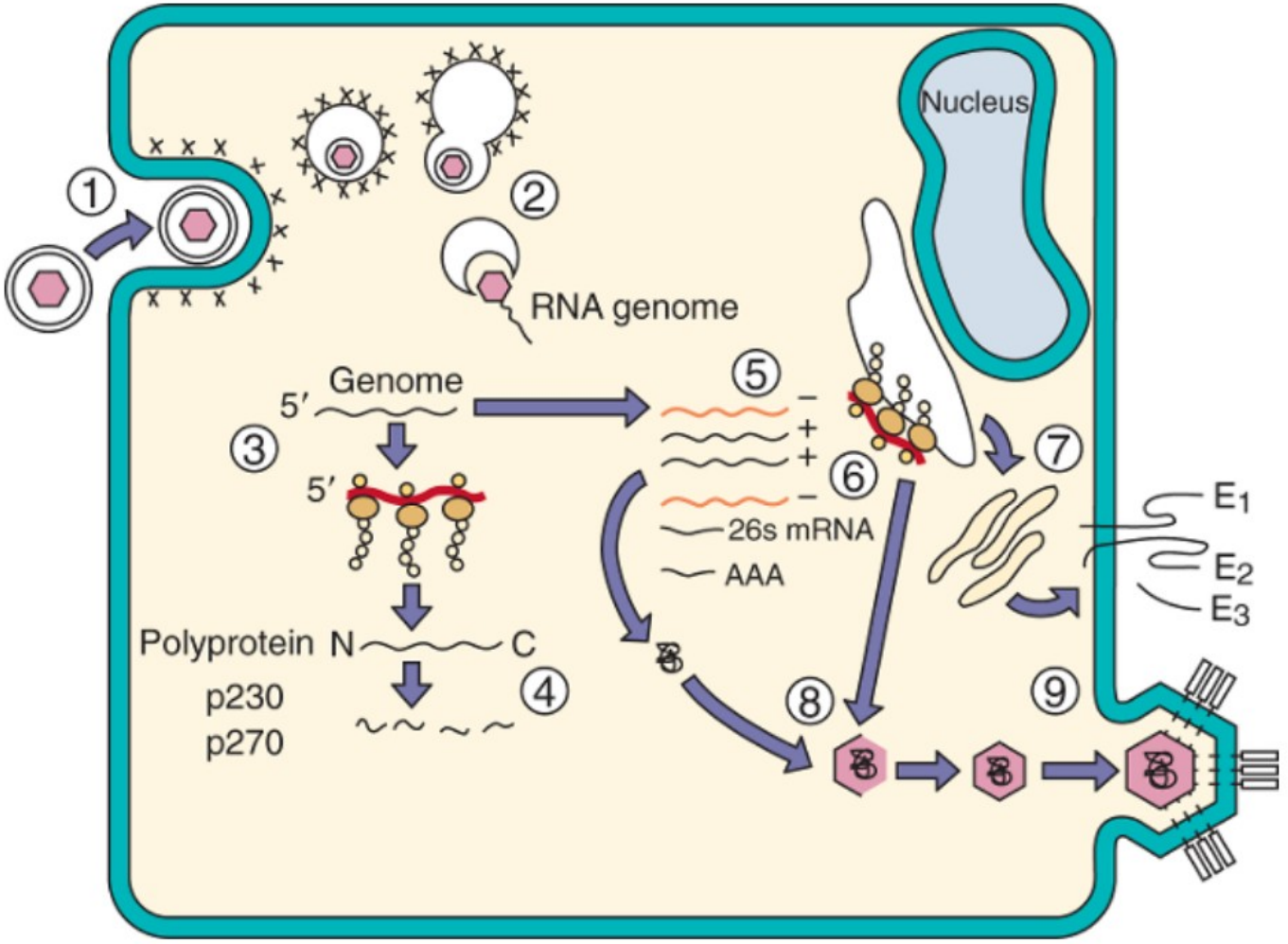
- *Enveloped viruses with glycoprotein spikes on the surface*
-
- *Infectious ss (+) RNA*


Glikoprotein spikes –E antigen
Nucleocapsid protein C
Phospholipid layer



- The alphaviruses have an **icosahedral capsid** and a positive-sense, single-strand RNA genome that resembles messenger RNA (mRNA). They are surrounded by an **envelope** (Latin **toga,** “cloak”).
- Alphaviruses have two or three glycoproteins that associate to form **a single spike**.
- The capsid proteins of all the alphaviruses are similar in structure and are antigenically cross-reactive. The envelope glycoproteins express unique antigenic determinants that distinguish the different viruses and also express antigenic determinants that are shared by a group, or “complex,” of viruses.

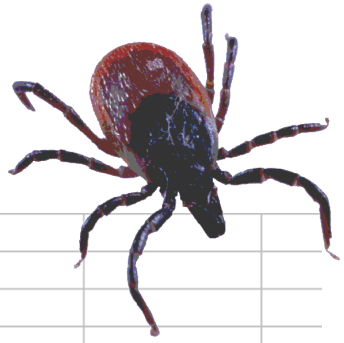
Replication of a Togaviruses



Genus Alphavirus

- *6 antigenic groups*
- ***All are arboviruses***
- *All are transmitted by mosquitoes*

Arboviruses



Togaviridae	ss (+) RNA nonsegmented										
	Alphavirus							***Rubivirus***			
	Encephalitis		Fever and Arthritis					Rubellavirus			
	Eastern Equine		Chikungunya								
	Western Equine		O'nyong-nyong								
	Venezuelan Equine		Maryaro								
			Ross River								
			Sindbis								
Flaviviridae	ss (+) RNA nonsegemented										
	Hepacivirus										
	Pestivirus										
	Flavivirus										
	Mosquito-Borne		Tick-Borne								
	Yellow fever		TBE	CEEV	RSSEV						
	Dengue		Louping ill								
	West Nile		Powassan								
			Kyasanur forest disease								
			Omsk hemorrhagic fever								
Bunyaviridae	ss (-) RNA segmented (3 segments)										
	Bunyavirus		***Phlebovirus***		***Nairovirus***					***Hantavirus***	
	Bunyamwera Group		SFNV		Crimean-Congo hemorrhagic fever					Hantaan	
	Čalovo		SFSV		(C-CHFV)					Dobrava	
	California Group		TOSV		(Tick-Borne)					Seoul	
	La Crosse		(Phleobotmus papatasi)							Pumala	
	Tahyna		Rift Valley (RVFV)							Sin Nombre	
	(Mosquito-Borne)		(Mosquito-Borne)							(Rodent-Borne)	
			Uukuniemi virus group								
			(Ticks)								

New World Alphaviruses

3 viruses – EEEV, WEEV i VEEV

- ***All cause encephalitis***
- ***All are transmitted by mosquitoes***
- ***Major vertebrate hosts are usually birds***

Old World Alphaviruses *– cause* ***acute febrile illnesses with arthritis, arthralgia and rash***

- *Vectors mosquitoes*

- ***Humans are reservoirs for***
  - ***Chikungunya (*****in the Makonde language "that which bends up„)**
  - *O‘nyong-nyong*
  - *Igbo Ora*

- *Mainly in Africa and Asia*
-
- *In Australia - Ross River virus – epidemic polyarthritis)*

News Front Page

Africa
Americas
Asia-Pacific
Europe
Middle East
South Asia
UK
Business
Health
Medical notes
Science/Nature
Technology
Entertainment
Also in the news

Video and Audio

Have Your Say
In Pictures
Country Profiles
Special Reports

RELATED BBC SITES
SPORT
WEATHER
ON THIS DAY

Last Updated: Thursday, 6 September 2007, 10:47 GMT 11:47 UK

E-mail this to a friend Printable version

Mosquito virus arrives in Europe

A debilitating tropical virus carried by mosquitoes has become established in Europe for the first time.

The virus is transmitted by the mosquito Aedes albopictus

The Ministry of Health in Italy has confirmed about 160 cases of chikungunya in the Ravenna region in northern Italy.

Travellers have been advised to protect themselves against mosquito bites.

The European Centre for Disease Control urged pregnant women and those with chronic illnesses to seek medical advice before visiting the area.

The villages of Castiglione di Ravenna and Castiglione di Cervia have reported most of the cases.

The main symptoms of the patients were high fever and joint pain, as well as headache, muscle pain, rash and less frequently gastrointestinal symptoms.

One death was reported in a 83-year old individual with underlying medical conditions.

Primary vector CHIKV

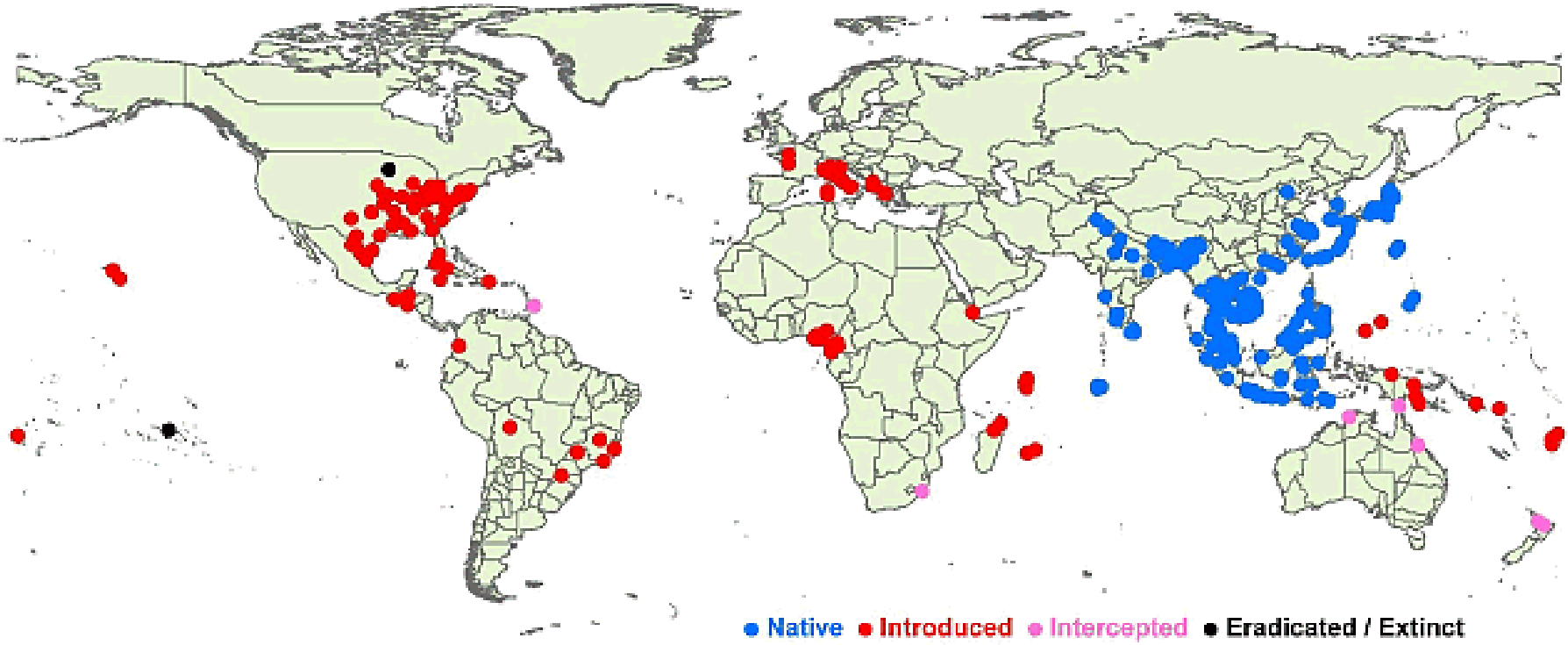
- ***Aedes aegypti and Aedes albopictus*** *– antropofilni komarci – zadržavaju se u kući i oko kuće*

- *Agresivno* ***bodu danju****;*

- *Jednom inficirani – sadrže virus doživotno (30 d)*

- *Množe se u vodi koja se zadržava u kontejnerima (metalnim, plastičnim, gumenim, cementnim itd.) koji se napune s vodom*

Worldwide distribution of Aedes albopictus



http://www.landcareresearch.co.nz/research/biocons/invertebrates/mosquitoes/Mosquitoes%20of%20New%20Zealand/images/albopictusDmap0.gif

CHIKV in Italy, 2007

Lancet, 2007; 370:1840-46.

Aedes albopictus imported to Italy in 1990

A. albopictus colonized Italy

CHIKV Imported from Keral, India 21.06. 2007

Epidemic!

***270** people ill in*
~ 3 months
Castiglione di Cervia
& Castiglione di Ravenna

The perfect microbial storm: *Ravenna, Italy*

- *Virus from Africa (alphavirus – Chikungunya)*
- *Mosquito from Asia (Aedes albopictus)*
- *Tourist from India (1,25 million o oboljelih u 2006.)*

- ***Globalisation***
- *Global tire trading*
- ***Climate changing***

Bloomberg Report 25.9.07.

ECDC - Chikungunya risk assessment for Europe

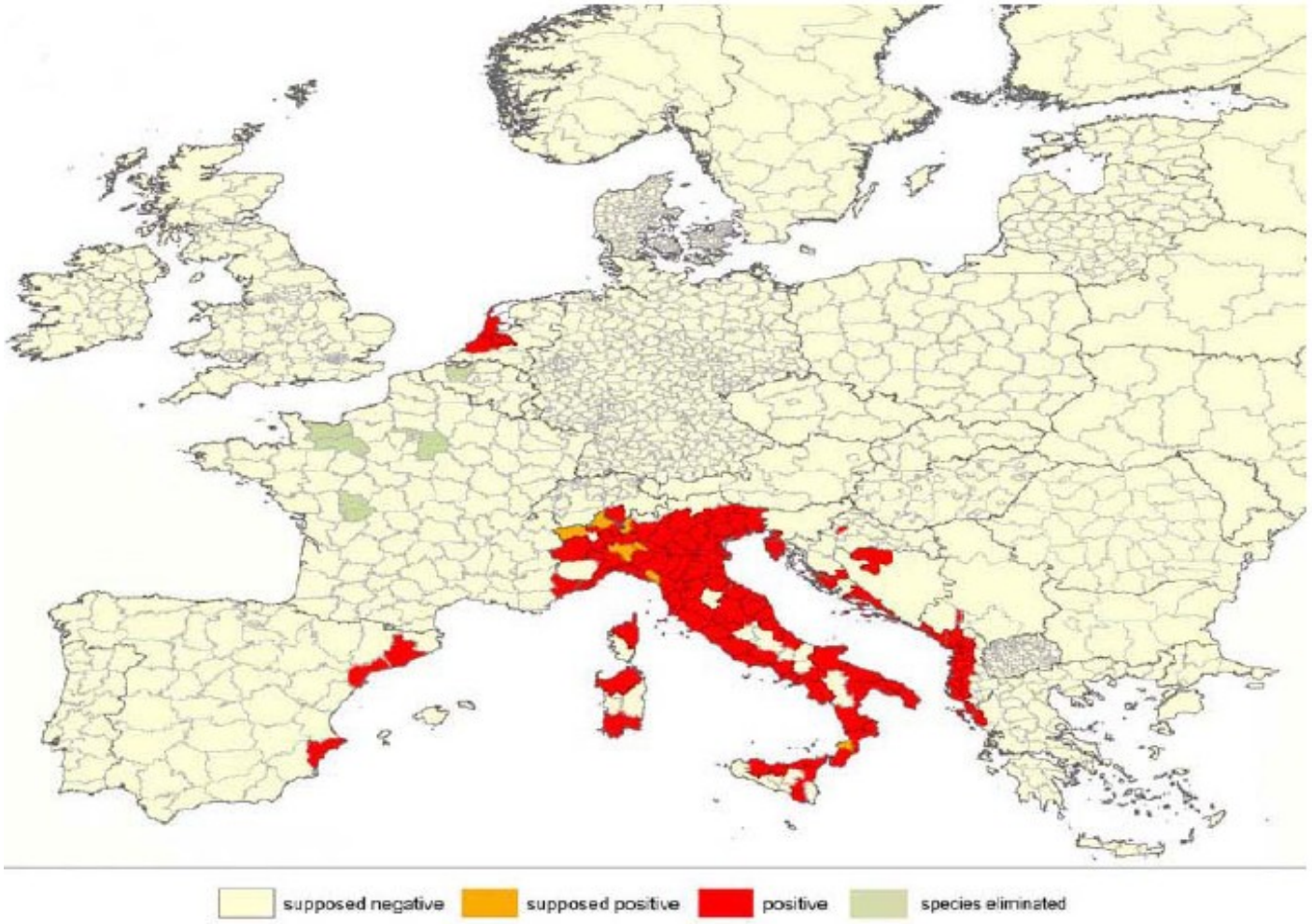


Figure 3: Presence of *Aedes albopictus* in Europe, per province, as of January 2007.[2]

As chikungunya is transmitted by mosquitoes, mosquito control is essential in its prevention.

Old World Alphaviruses

Clinical picture	***Viruses***
Fever, rash (exanthem)	*Sindbis, Ockelbo*
Fever, rash, polyarthritis	*Ross River, Barmah Forest*
Fever, rash, myalgia, arthralgia	***Chikungunya**, O'nyong-nyong, Mayaro, Sindbis, Ockelbo, Ross River, Barmah Forest, Igbo Ora*

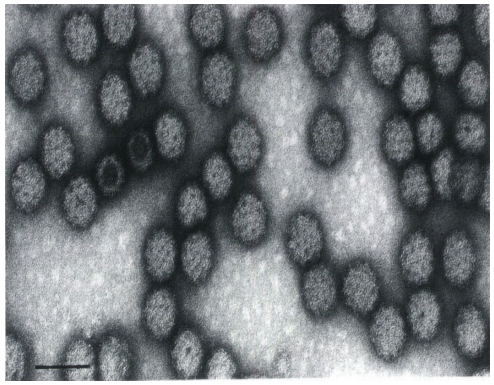
Togaviridae

Genus:

Alphavirus

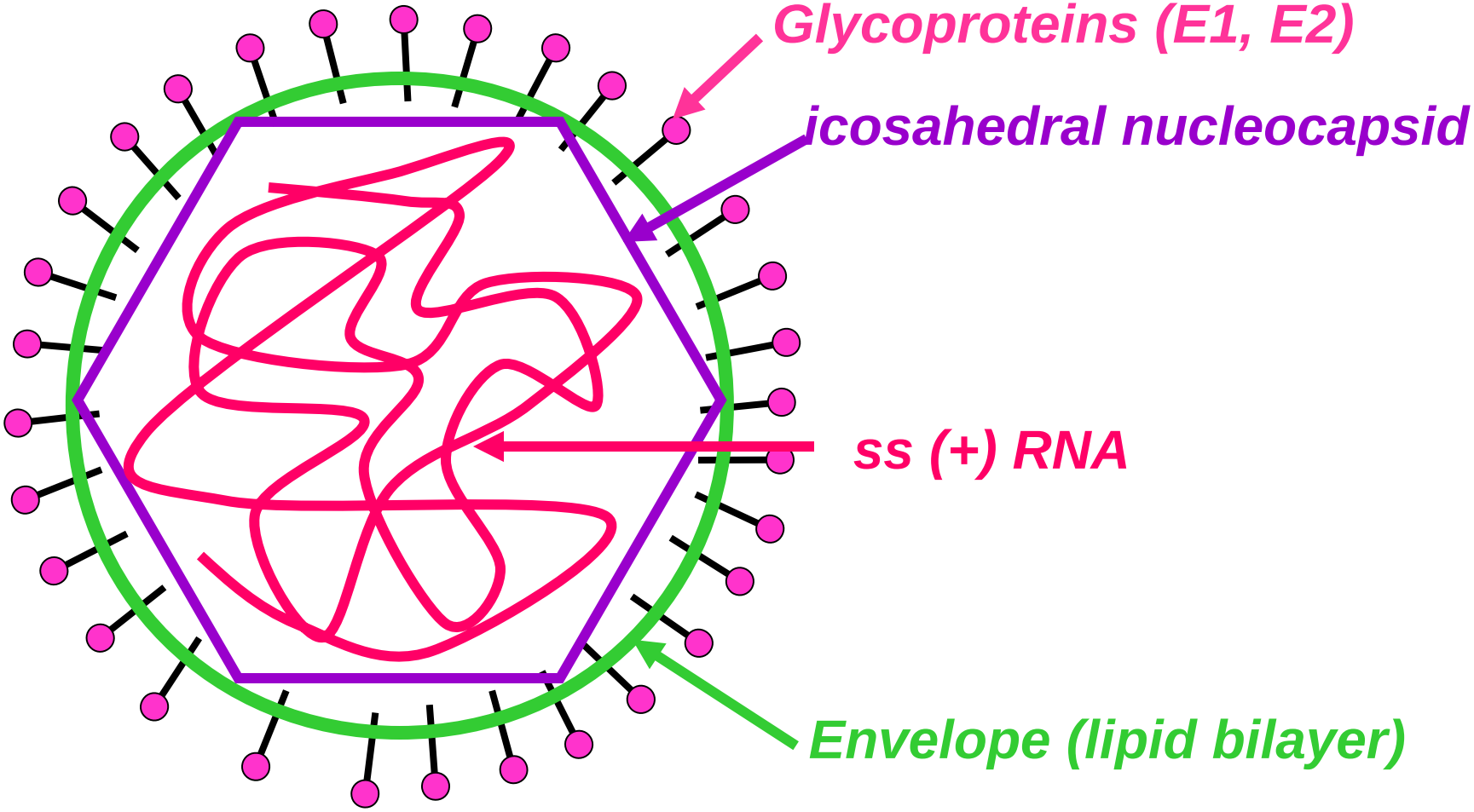
Rubivirus

Genus Rubivirus

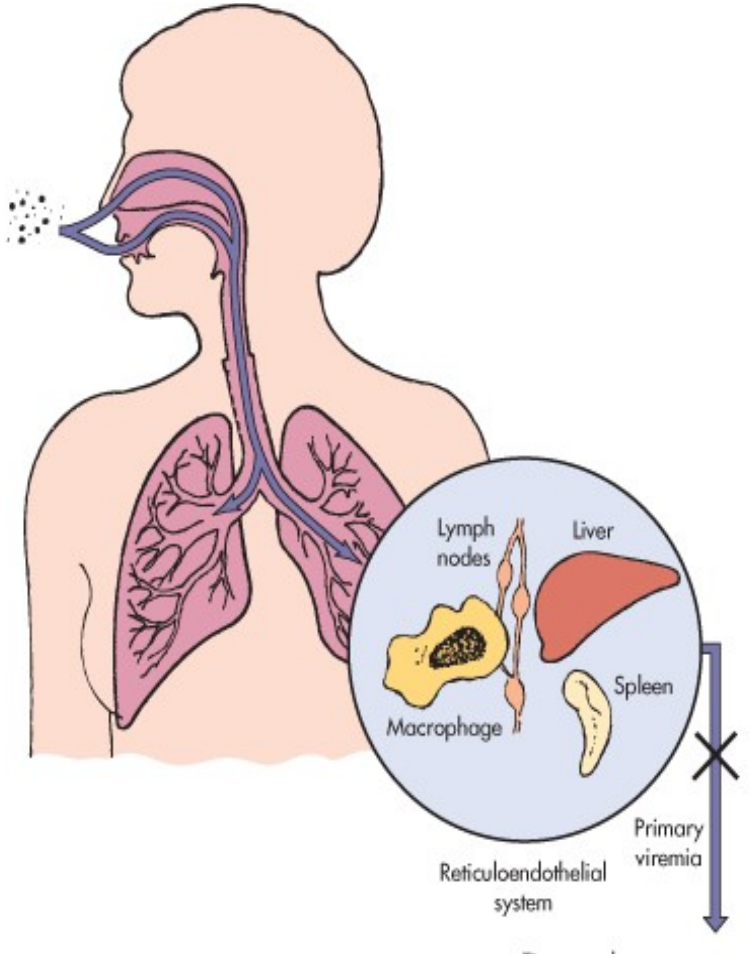


- ***Rubella virus***
- ***Humans are the only known host***
- *One antigenic type*
- *Very sensitive:*
  - *Lipid solvents,*
  - *Low pH,*
  - *Higher tempartures*
  - *UV light*

RUBELLA VIRUS

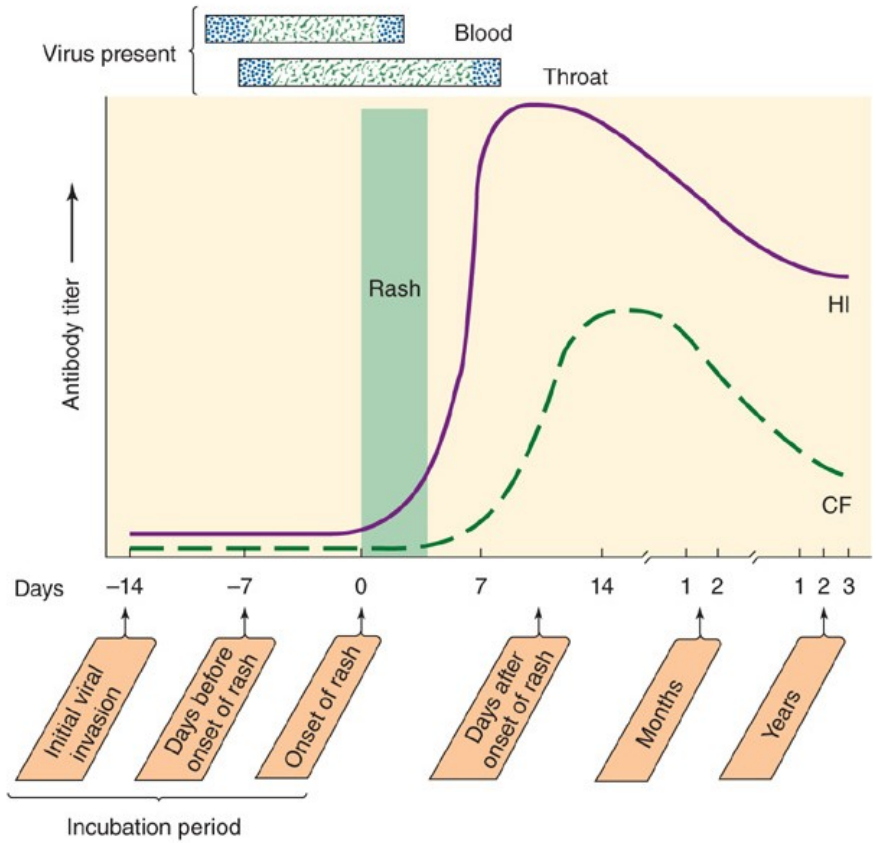


Postnatal Rubella- Pathogenesis and Pathology



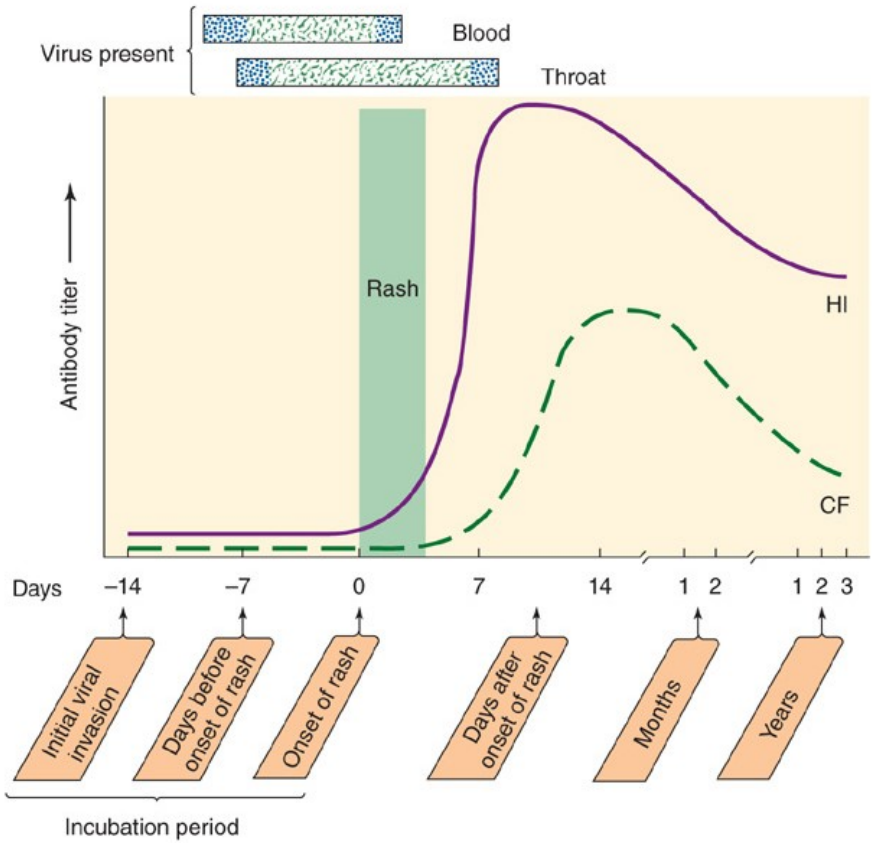
- *Neonatal, childhood, and adult infections occur through the mucosa of the upper respiratory tract.*
- *Rubella has an incubation period of about 12 days or longer.*
- *Initial viral replication probably occurs in the respiratory tract followed by multiplication in the cervical lymph nodes.*

Postnatal Rubella- Pathogenesis and Pathology



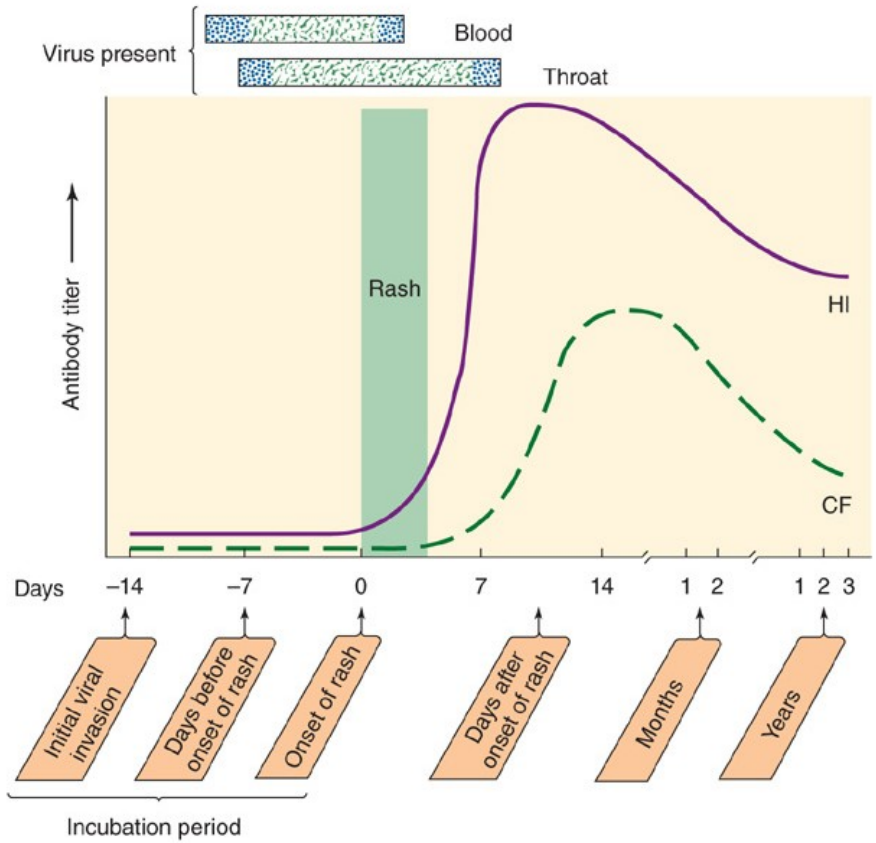
- *Viremia develops after 7–9 days and lasts until the appearance of antibody on about day 13–15.*

- *The development of antibody coincides with the appearance of the rash, suggesting an immunologic basis for the rash.*



- *After the rash appears, the virus remains detectable only in the nasopharynx, where it may persist for several weeks.*
- *In 20-50% of cases, primary infection is subclinical.*

Immunity



- *Rubella antibodies appear in the serum of patients as the rash fades and the antibody titer rises rapidly over the next 1–3 weeks.*
- *IgM rubella antibodies found in a single serum sample obtained 2 weeks after the rash give evidence of recent rubella infection.*
- *IgG rubella antibodies usually persist for life.*
- *One attack of the disease confers lifelong immunity because only one antigenic type of the virus exists.*

- *Immune mothers transfer antibodies to their offspring, who are then protected for 4–6 months*

Laboratory Diagnosis

- *Nucleic acid detection*
- *Isolation and identification of virus*
- *Serology*

Treatment, Prevention, and Control

- *Rubella is a mild, self-limited illness, and no specific treatment is indicated.*
- *Attenuated live rubella vaccines have been available since 1969.*
- *The vaccine is safe and causes few side effects*

Congenital Rubella Syndrome

- *Laboratory-proved rubella in the first 3–4 months of pregnancy is almost uniformly associated with fetal infection*

Pathogenesis and Pathology

- Maternal viremia associated with rubella infection during pregnancy may result in infection of the placenta and fetus. Only a limited number of fetal cells become infected.
- The growth rate of infected cells is reduced, resulting in fewer numbers of cells in affected organs at birth.
- The infection may lead to deranged and hypoplastic organ development, resulting in structural anomalies in the newborn.

Pathogenesis and Pathology

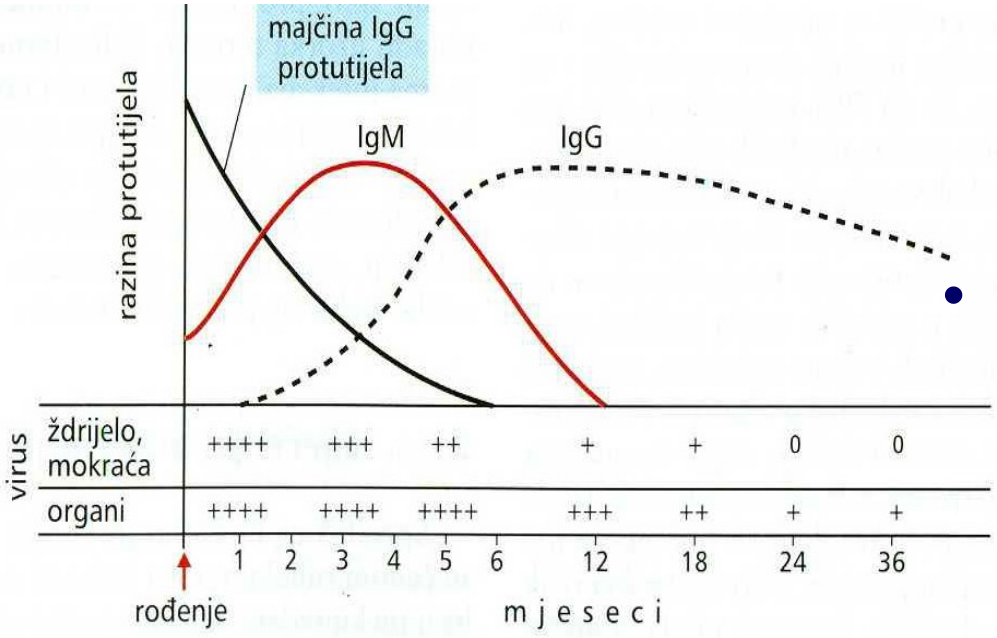
- The timing of the fetal infection determines the extent of teratogenic effect. In general, the earlier in pregnancy infection occurs, the greater the damage to the fetus.
- Infection during the first trimester of pregnancy results in abnormalities in the infant in about 85% of cases, but detectable defects are found in about 16% of infants who acquired infection during the second trimester.
- Birth defects are uncommon if maternal infection occurs after the 20th week of gestation.

Pathogenesis and Pathology

- *Inapparent maternal infections can produce these anomalies as well. Rubella infection can also result in fetal death and spontaneous abortion.*

- *At birth, virus is easily detectable in pharyngeal secretions, multiple organs, cerebrospinal fluid, urine, and rectal swabs.*

Congenital Rubella Syndrome

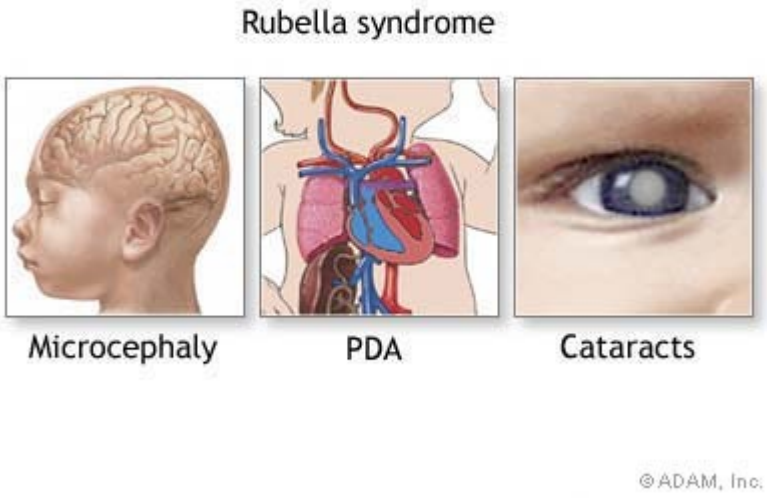


- *Intrauterine infection with rubella is associated with chronic persistence of the virus in the newborn.*
- *Viral excretion may last for 12–18 months after birth, but the level of shedding gradually decreases with age.*

Clinical Findings

- *Clinical features of congenital rubella syndrome may be grouped into three broad categories:*
- *(1) transient effects in infants,*
- *(2) permanent manifestations that may be apparent at birth or become recognized during the first year, and*
- *(3) developmental abnormalities that appear and progress during childhood and adolescence.*

Congenital Rubella Syndrome



- *The classic triad of congenital rubella consists of cataracts, cardiac abnormalities, and deafness.*
- *Infants may also display transient symptoms of growth retardation, rash, hepatosplenomegaly, jaundice, and meningoencephalitis.*

Congenital Rubella Syndrome

- *The most common developmental manifestation of congenital rubella is moderate to profound mental retardation.*
- *Problems with balance and motor skills develop in preschool children.*
- *Severely affected infants may require institutionalization.*

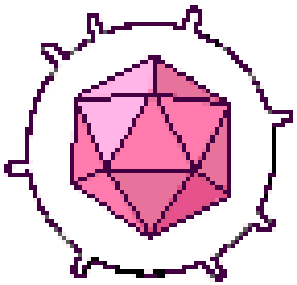
Immunity

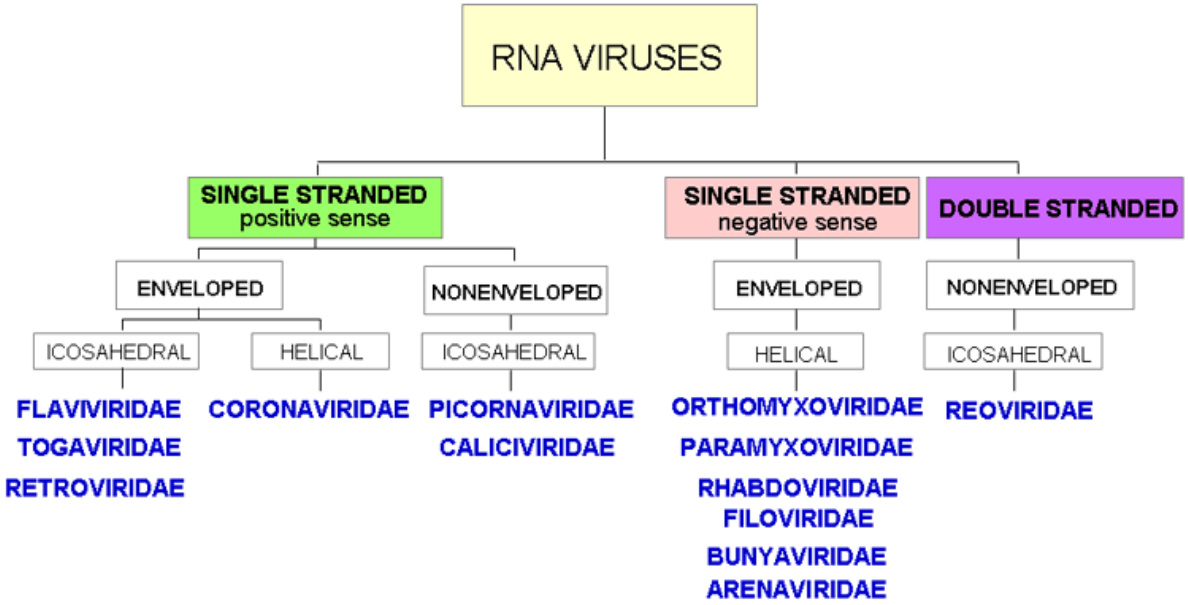
- *Normally, maternal rubella antibody in the form of IgG is transferred to infants and is gradually lost over a period of 6 months.*
- *Demonstration of rubella antibodies of the IgM class in infants is diagnostic of congenital rubella.*
- *Because IgM antibodies do not cross the placenta, their presence indicates that they must have been synthesized by the infant in utero. Children with congenital rubella exhibit impaired cell-mediated immunity specific for rubella virus.*

Treatment, Prevention, and Control

- *There is no specific treatment for congenital rubella.*
- *It can be prevented by childhood immunization with rubella vaccine to ensure that women of childbearing age are immune.*

Flaviviridae

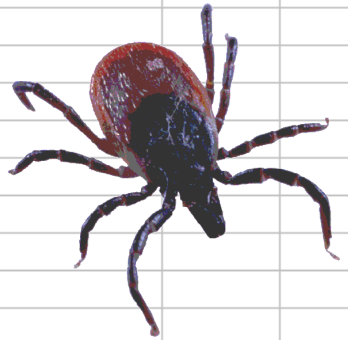


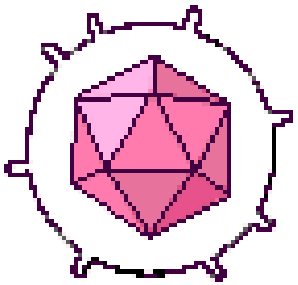


Modified from Volk et al., Essentials of Medical Microbiology, 4th Ed. 1991

Arboviruses

Togaviridae	ss (+) RNA nonsegmented							
	Alphavirus					***Rubivirus***		
	Encephalitis		Fever and Arthritis			Rubellavirus		
	Eastern Equine		Chikungunya					
	Western Equine		O'nyong-nyong					
	Venezuelan Equine		Maryaro					
			Ross River					
			Sindbis					
Flaviviridae	ss (+) RNA nonsegemented							
	Hepacivirus							
	Pestivirus							
	Flavivirus							
	Mosquito-Borne		Tick-Borne					
	Yellow fever		TBE	CEEV	RSSEV			
	Dengue		Louping ill					
	West Nile		Powassan					
			Kyasanur forest disease					
			Omsk hemorrhagic fever					
Bunyaviridae	ss (-) RNA segmented (3 segments)							
	Bunyavirus		***Phlebovirus***		***Nairovirus***		***Hantavirus***	
	Bunyamwera Group		SFNV		Crimean-Congo hemorrhagic fever		Hantaan	
	Čalovo		SFSV		(C-CHFV)		Dobrava	
	California Group		TOSV		(Tick-Borne)		Seoul	
	La Crosse		(Phleobotmus papatasi)				Pumala	
	Tahyna		Rift Valley (RVFV)				Sin Nombre	
	(Mosquito-Borne)		(Mosquito-Borne)				(Rodent-Borne)	
			Uukuniemi virus group					
			(Ticks)					





Flaviviridae

Genera

Flavivirus

62 viruses
YFV,DENV, JEV
TBE, WNV …

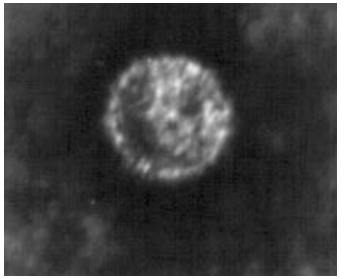
(arboviruses)

Hepacivirus

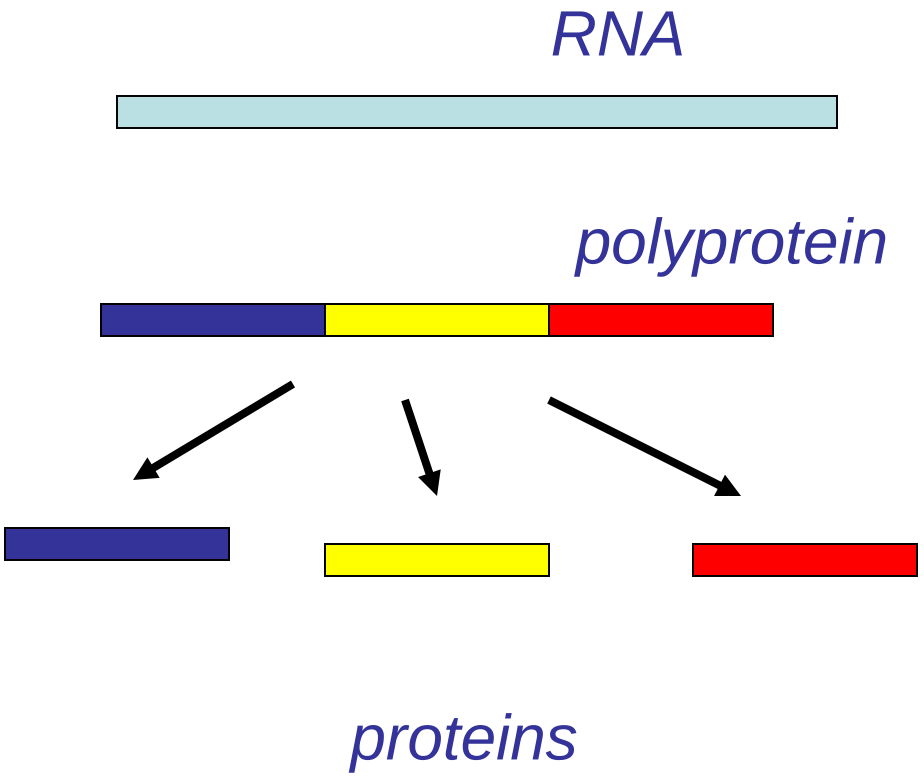
Hepatitis C virus
(Hepatitis G virus)

Pestivirus

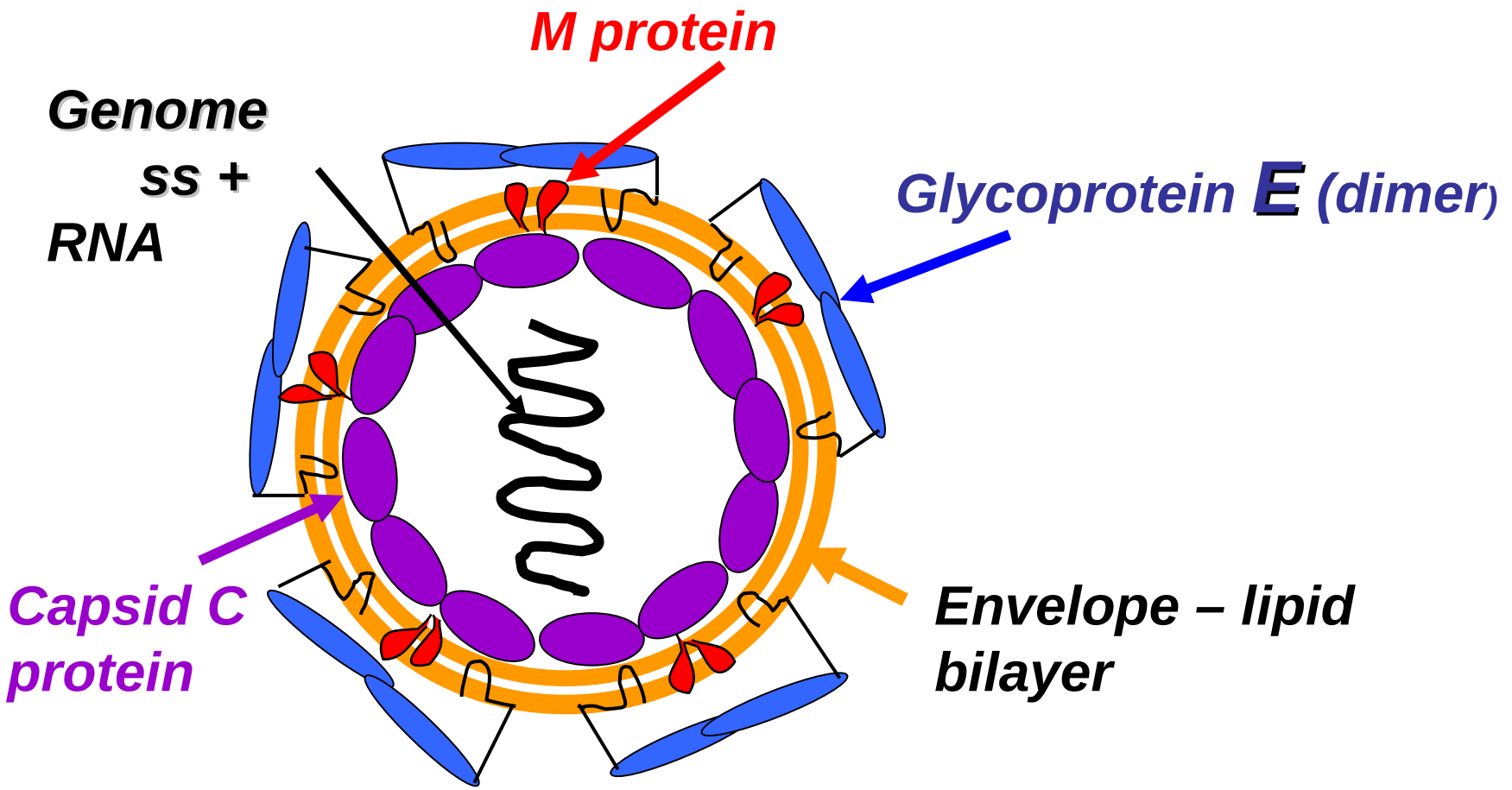
Flaviviridae



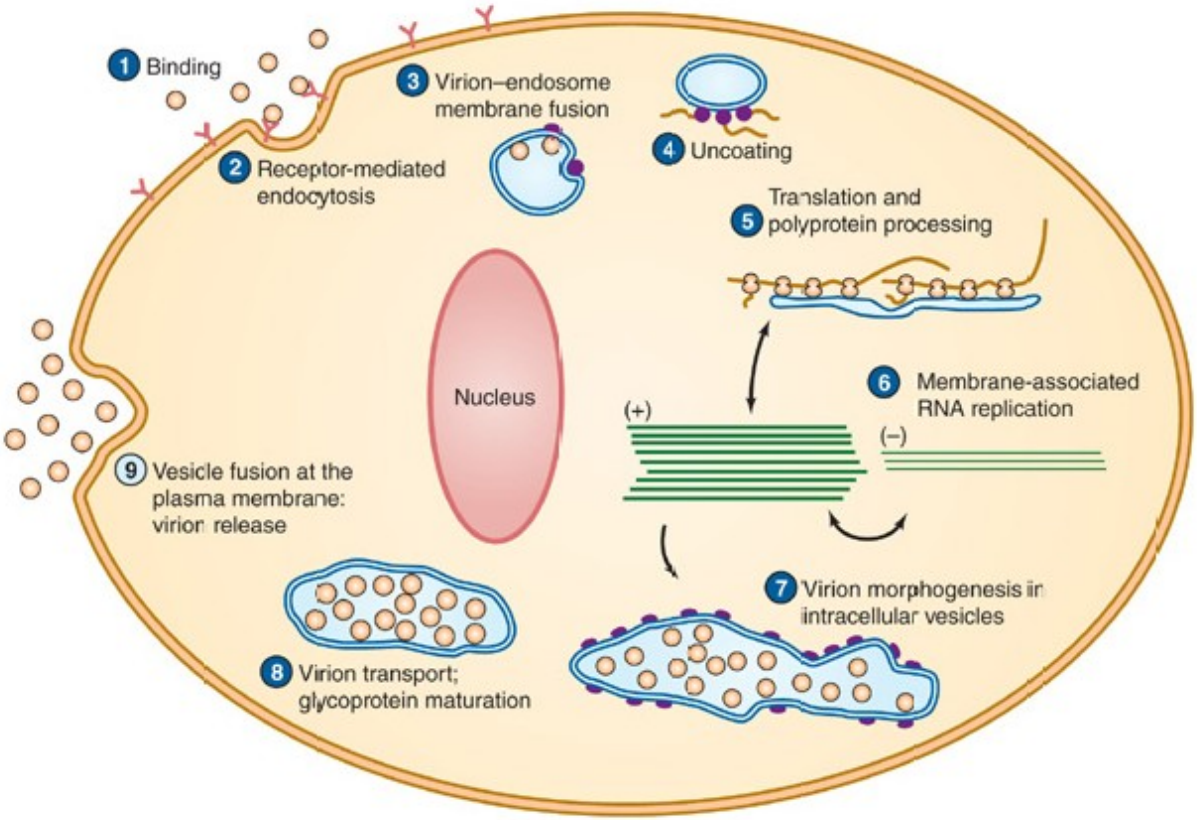
- *Enveloped viruses (40-50 nm)*
- *Genome: ss (**+) RNA***
- *polyprotein →*
  - *3 structural proteins*
    - ***capsid (C),***
    - ***membrane (M),***
    - ***envelope (E)***
  - *7 nonstructural proteins*



Flaviviridae - Structure



Flaviviridae Life Cycle



Flavivirus E glycoprotein = VIP antigen

- *Binding to cellular receptors*
- *Responsible for **membrane fusion***
- *Tissue tropism*
- *Induction of protective immunity*
- *Contains **3** structural and functional domaines with specific epitopes for strain, species and gfenus of viruses*

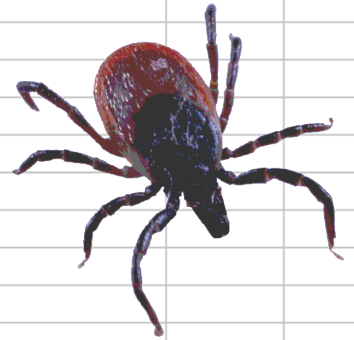
Flaviviridae - Transmission

Arthropod vectors

- *Mosquitoes - 27 viruses*
- *Ticks - 12 viruses*

Arboviruses

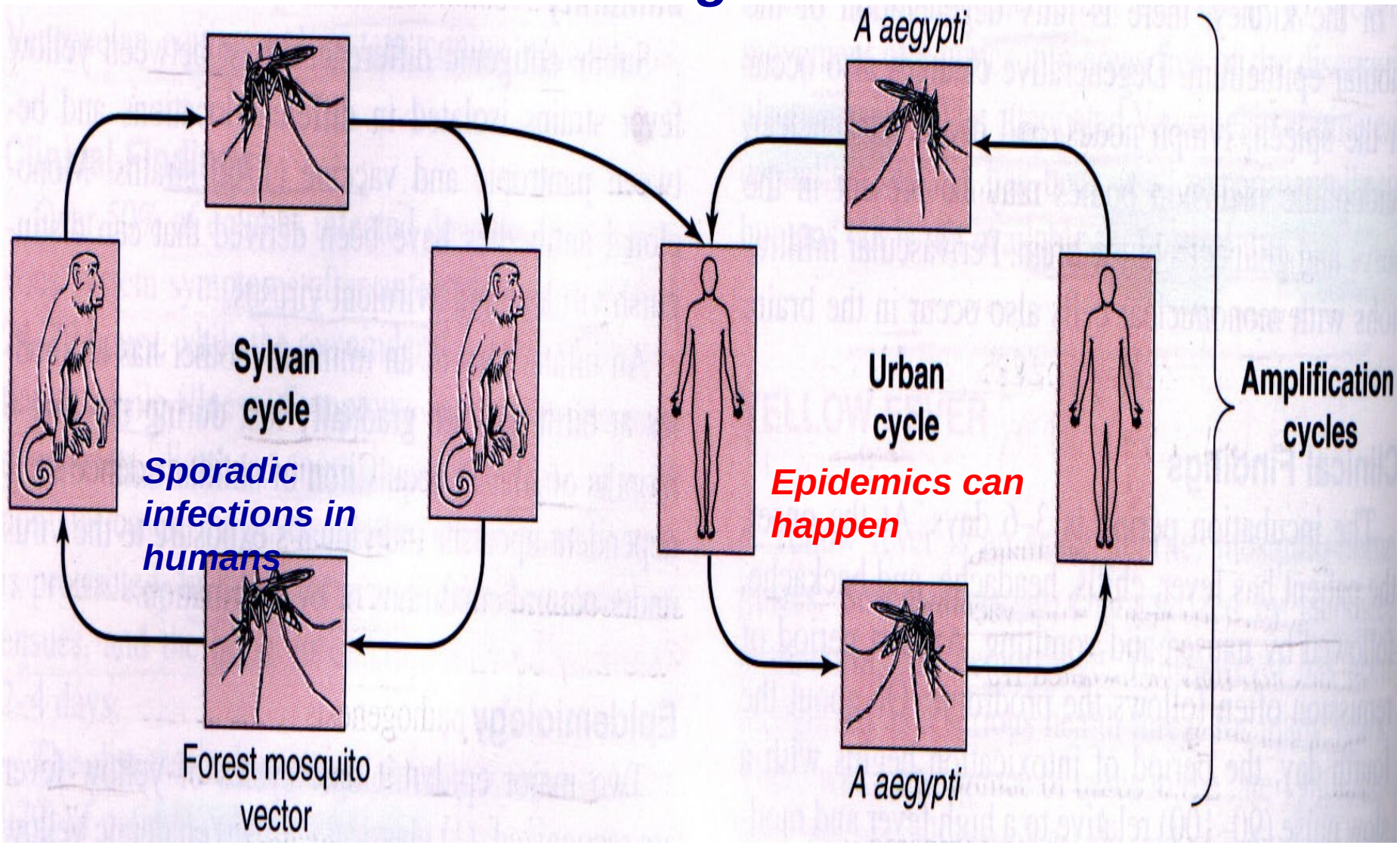
Togaviridae	ss (+) RNA nonsegmented							
	Alphavirus					***Rubivirus***		
	Encephalitis		Fever and Arthritis			Rubellavirus		
	Eastern Equine		Chikungunya					
	Western Equine		O'nyong-nyong					
	Venezuelan Equine		Maryaro					
			Ross River					
			Sindbis					
Flaviviridae	ss (+) RNA nonsegemented							
	Hepacivirus							
	Pestivirus							
	Flavivirus							
	Mosquito-Borne		Tick-Borne					
	Yellow fever		TBE	CEEV	RSSEV			
	Dengue		Louping ill					
	West Nile		Powassan					
			Kyasanur forest disease					
			Omsk hemorrhagic fever					
Bunyaviridae	ss (-) RNA segmented (3 segments)							
	Bunyavirus		***Phlebovirus***		***Nairovirus***		***Hantavirus***	
	Bunyamwera Group		SFNV		Crimean-Congo hemorrhagic fever		Hantaan	
	Čalovo		SFSV		(C-CHFV)		Dobrava	
	California Group		TOSV		(Tick-Borne)		Seoul	
	La Crosse		(Phleobotmus papatasi)				Pumala	
	Tahyna		Rift Valley (RVFV)				Sin Nombre	
	(Mosquito-Borne)		(Mosquito-Borne)				(Rodent-Borne)	
			Uukuniemi virus group					
			(Ticks)					



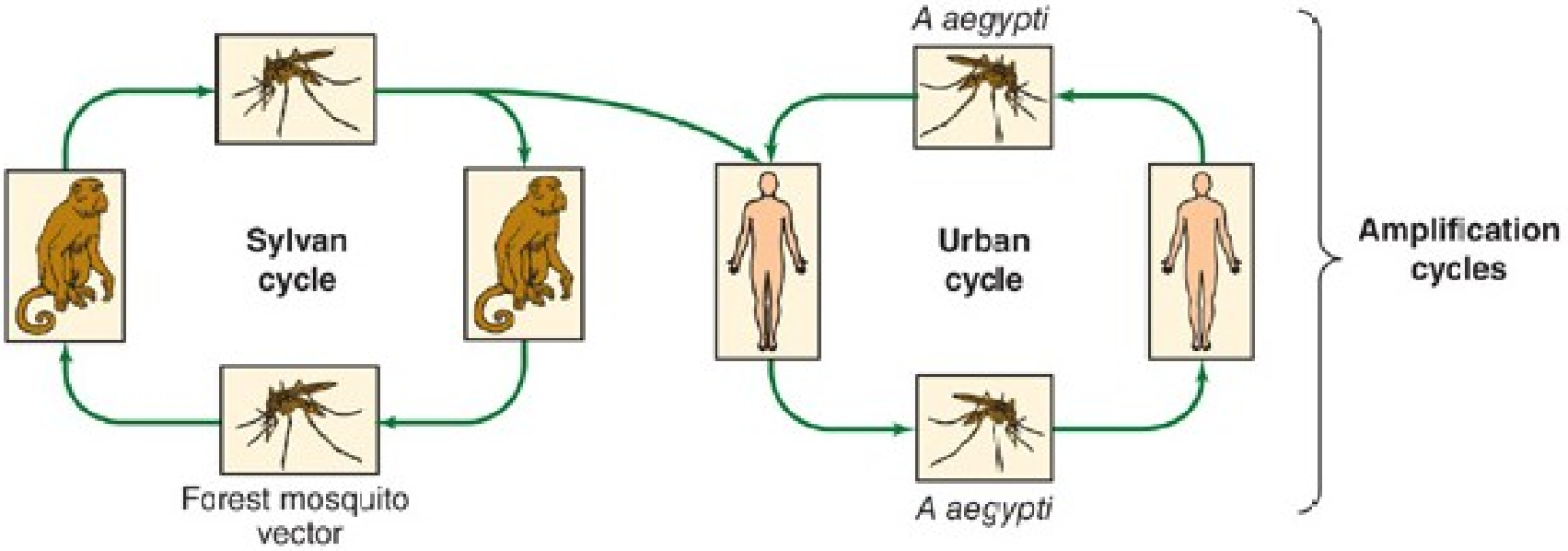
Flaviridae - Hemorrhagic fevers (HF)

Virus	*Disease*	*Distribution*	*Vector*	*Incubation (days)*
Yellow Fever	*Yellow fever*	*Tropical Africa, South America*	*Mosquito*	*3-6*
Dengue	*Dengue fever, Dengue HF, Dengue shock syndrome*	*Asia, America, Africa*	*Mosquito*	*3-5*
Kyasanur forest fever	*Kyasanur Forest disease*	*India*	*Tick*	*3-8*
Omska HG	*Omska HG*	*Russia*	*Tick*	*3-8*

Generalized transmission cycle of Yellow fever and Dengue



Generalized transmission cycle of Yellow fever and Dengue

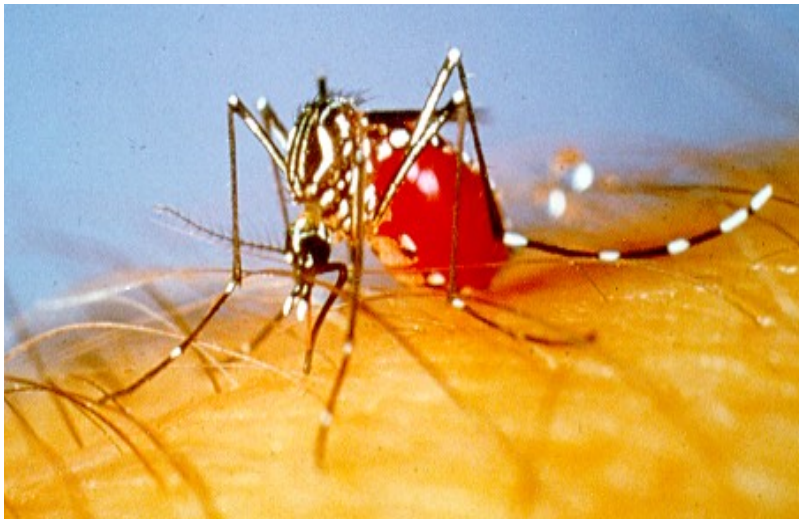


Sporadic infections in humans

Epidemics can happen

Aedes aegypti *- anthropophilic mosquitoes*

- ***Dengue and Yellow fever transmitted by female mosquitoes***



Yellow fever

- *Lever is target organ*
- *Replication in Kupffer cells*
- *Massive hepatocyte necrosis*
- *Liver and kidney degeneration*
- *Massive GI bleedings (vomito negro)*
- *Hypotension, dehidration*
- *Mortality from 20 – 50 %*

Yellow fever endemic areas

Yellow fever – Prevention and Control

- ***Aedes aegypti control***
- ***Vaccine*** ***YF-17D*** *very efficient, live, attenuated*
- *Immunity lifelong (HI and Nt antibodies detected 40 years after vaccination)*

Dengue

Major vectors ***Aedes aegypti***
and ***A.albopictus***

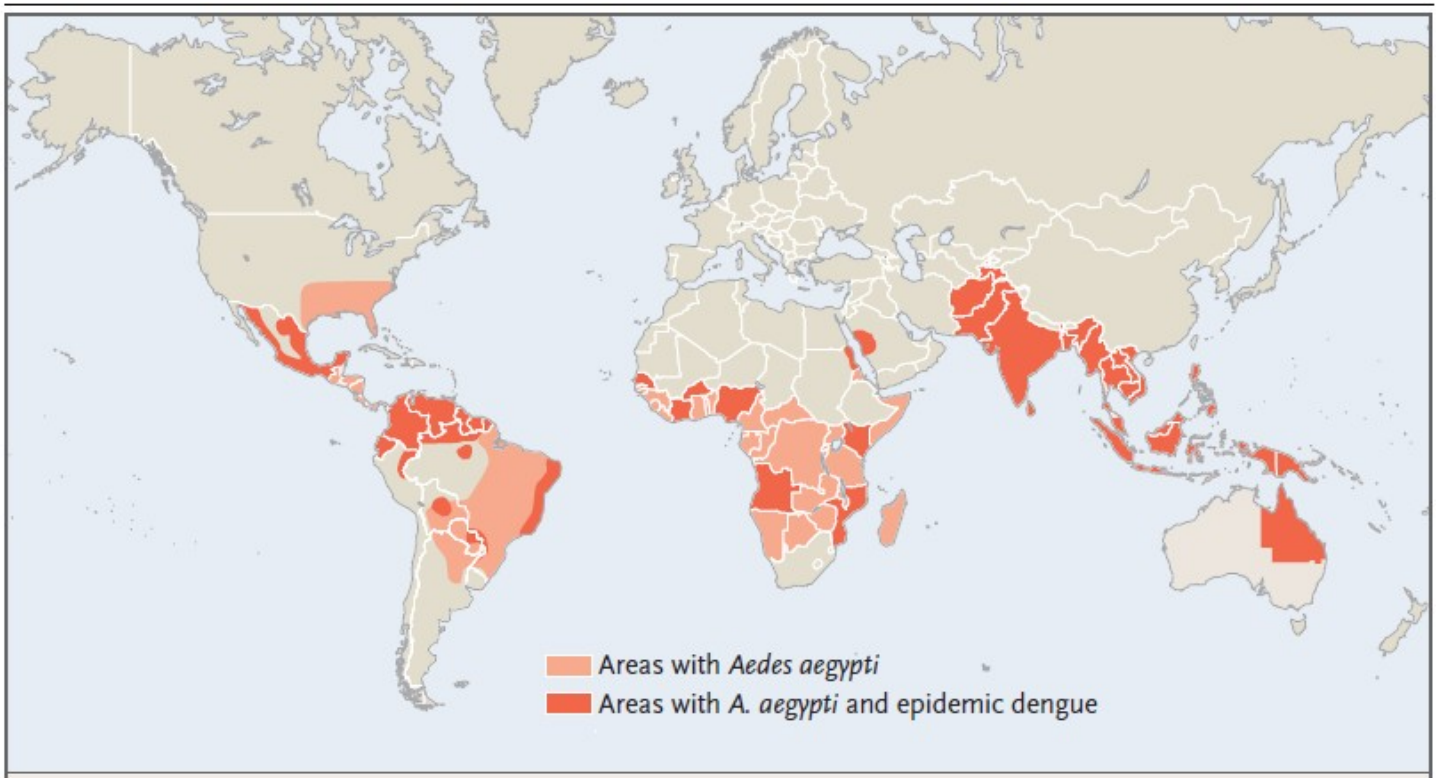
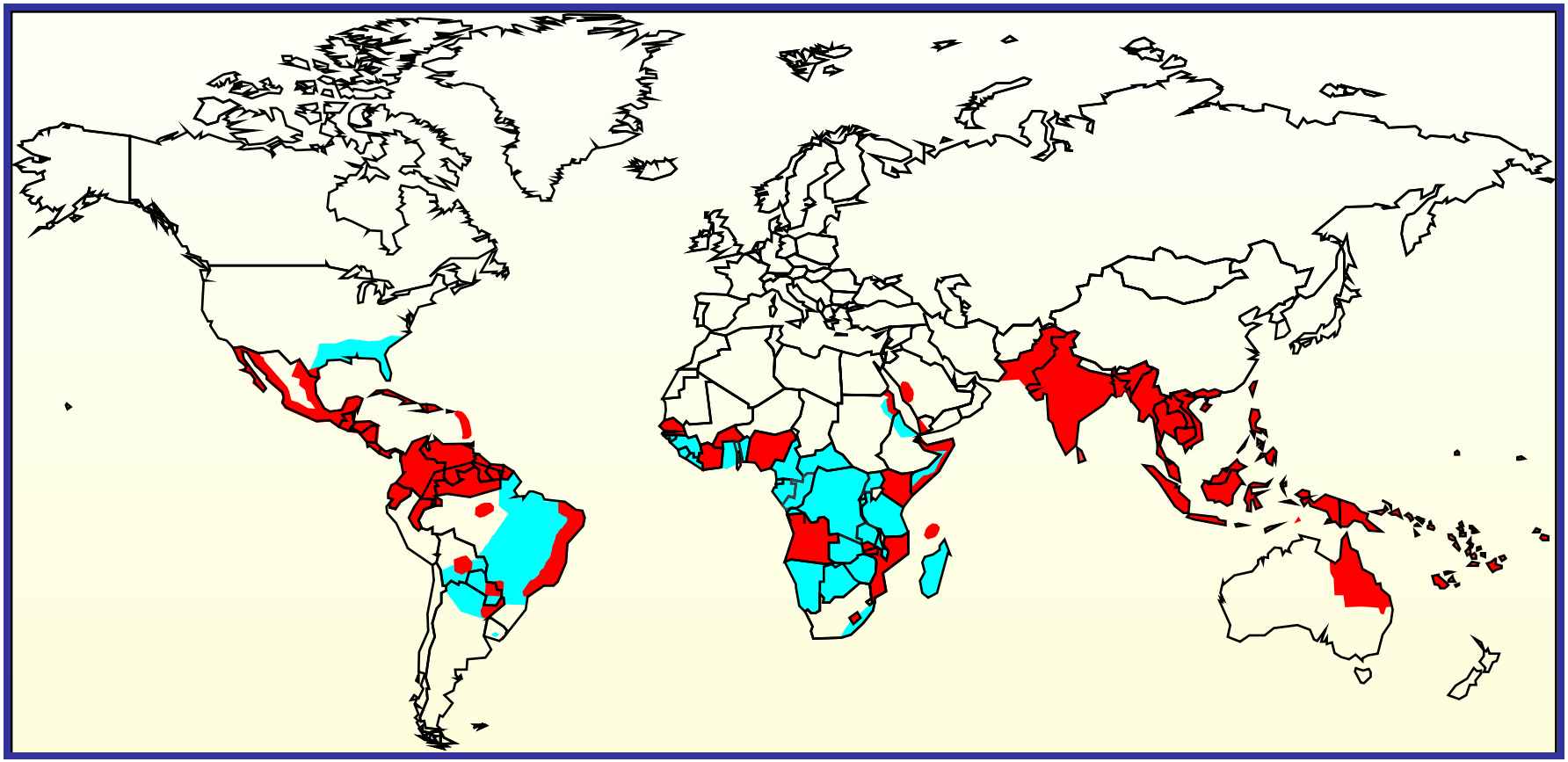


Figure 1. World Distribution of Dengue, 2002.
Adapted from the Centers for Disease Control and Prevention.[8]

- Dengue virus is now the most common cause of arboviral disease in the world, with an estimated annual occurrence of 100 million cases of dengue fever and
- 250,000 cases of dengue hemorrhagic fever and
- a mortality rate of 25,000 per year.
- Dengue virus infection has been reported in more than 100 countries, with 2.5 billion people living in areas where dengue is endemic

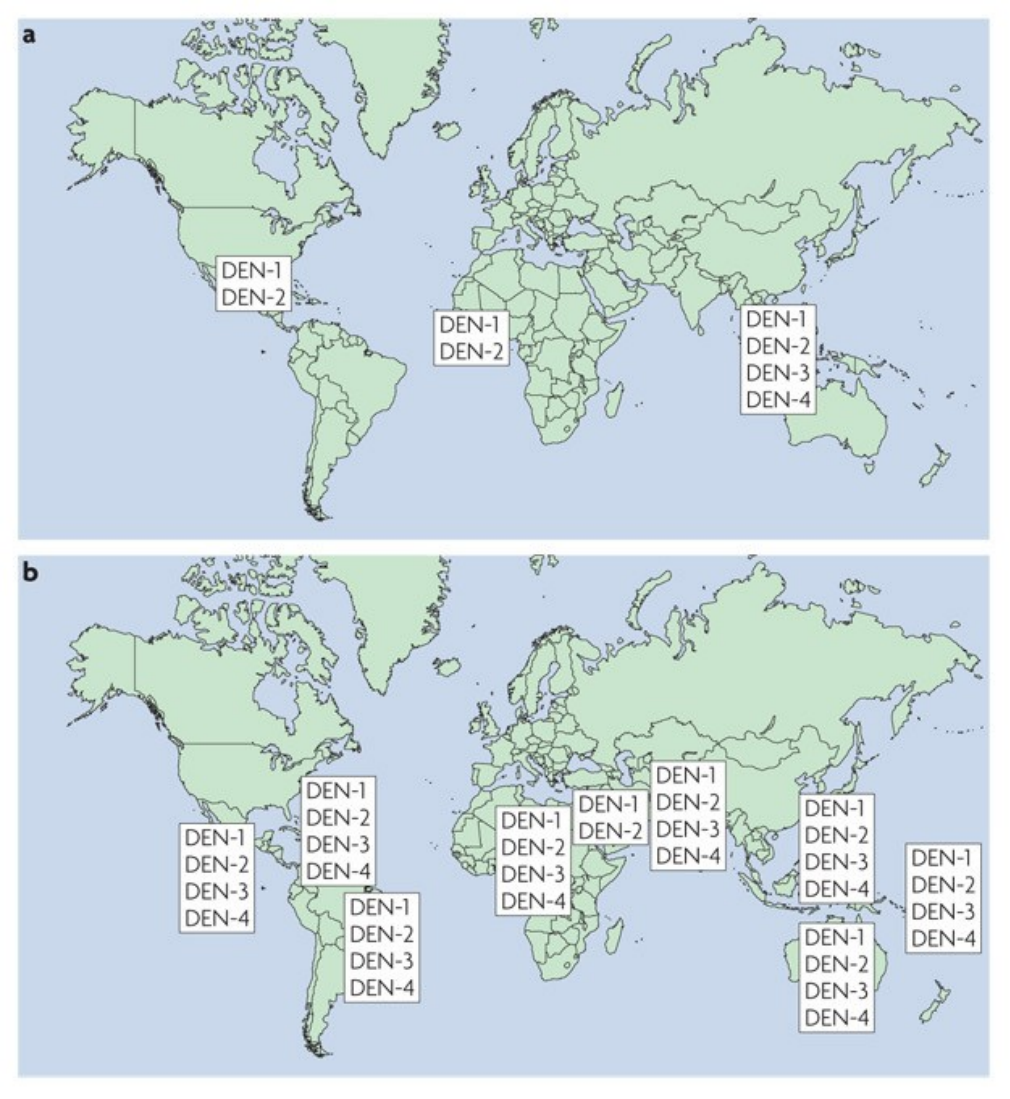
Distributionija Dengue u svijetu 2000.



Područja infestirana s Aedes aegypti

Područja s Aedes aegypti i nedavnim epidemijama dengue

The change in distribution of dengue serotypes



- The distribution of dengue serotypes in 1970 (a) and 2004 (b).

Dengue viruses

4 serotypes *(DEN-1, 2, 3, 4)*

- ***Infection with any one serotype confers lifelong immunity to that serotype but only two to three-months' immunity to other serotypes.***
- ***All serotypes can cause severe and lethal disease***

Dengue clinical syndromes

- *Undifferentiated Fever*
- *Classic Dengue fever*
- *Dengue hemorrhagic fever (DHF)*
- *Dengue shock syndrome (DSS)*

Dengue hemorrhagic fever (DHF), Dengue shock syndrome (DSS)

- *bleeding*
- *hemoconcentration*
- *hypotension*
- *circulatory collapse*
- *shock*

Caption: A large subcutaneous haemorrhage on the upper arm of a patient with dengue haemorrhagic fever. (Image courtesy of the Wellcome Trust)

Dengue hemorrhagic fever (DHF)

- *Immunopathologic reaction*
- *4 serotypes*
- *Antibodies from previous infection*
- *Illness in children more severe*

Laboratory Diagnosis

- ***Virus isolation from patients blood within first 2 to 4 days***
- ***Molecular methods***
- ***Serology***
  - *IgM capture ELISA,*
  - *IHA,*
  - *PRNT*

Aedes albopictus in Europe

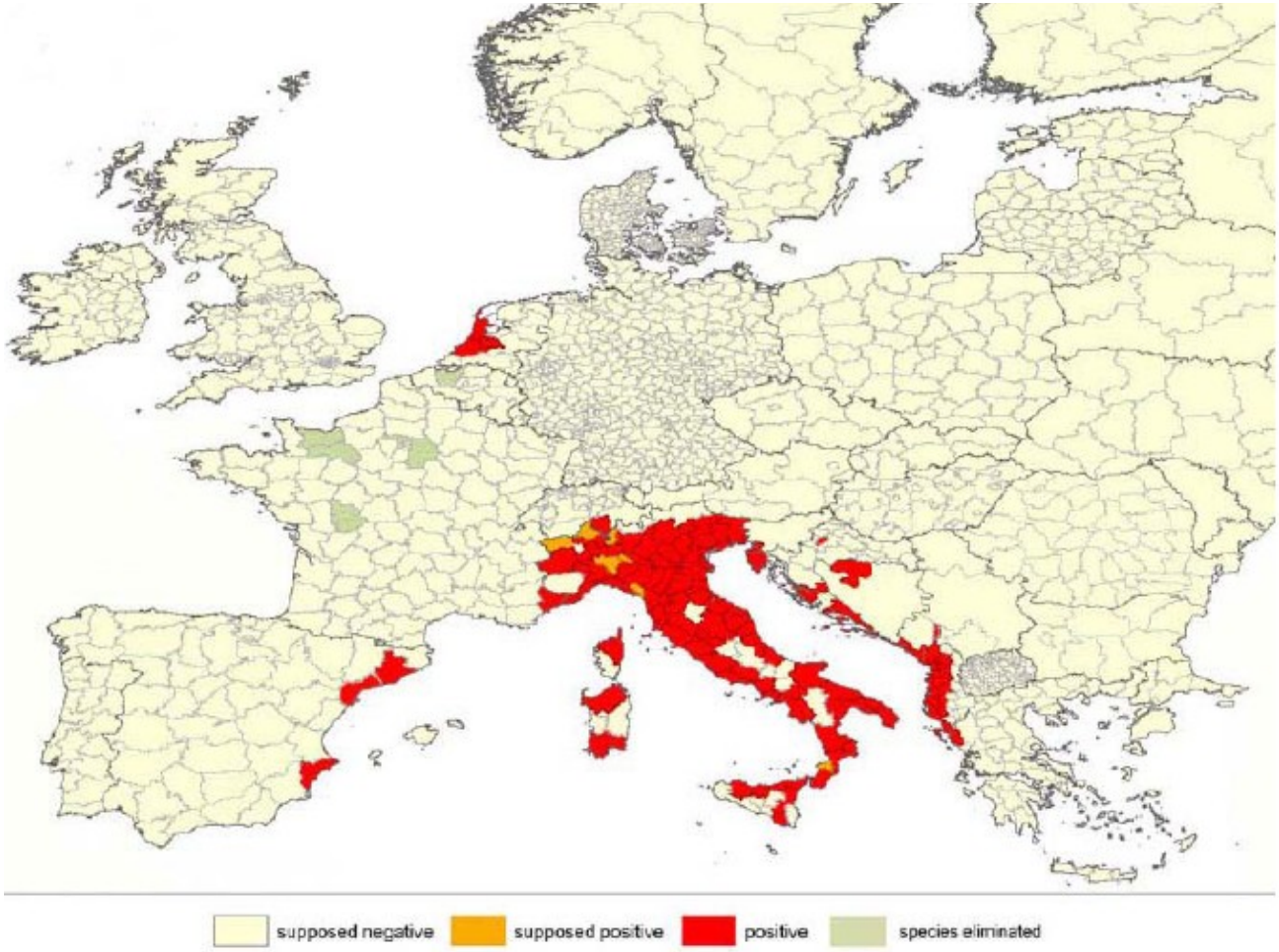


Figure 3: Presence of *Aedes albopictus* in Europe, per province, as of January 2007.[2]

Schmidt-Chanasit J, et al. Dengue virus infection in a traveller returning from Croatia to Germany. Euro Surveill 2010; 15 (40): pii=19677

Pelješac- Kolovoz 2010.-prvi autohtoni bolesnici s denga groznicom

Flaviviridae - Encephalitis

Virus	Distribution	Vector
St Louis encefalitis	North America	mosquito
Japanese B encephalitis	SE Asia	mosquito
West Nile	Africa, SE Europe, USA, Canada	mosquito
Murray Valley enceph.	Australia	mosquito
Tich borne encephalitis	Europe, Russia	tick
Powasan	North America, Russia	tick

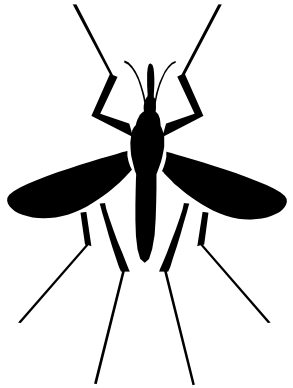
West Nile Virus

- ***First isolated in 1937 in Uganda***
- ***Widespread***
- ***Africa, Western Asia, Europe and Middle East***

West Nile virusa in Europi

WNV Reservoire

- *Migratory birds*
- *Usually without signs if disease*
- *Vectors: over 40 Mosquito-species (**Culex** spp.)*

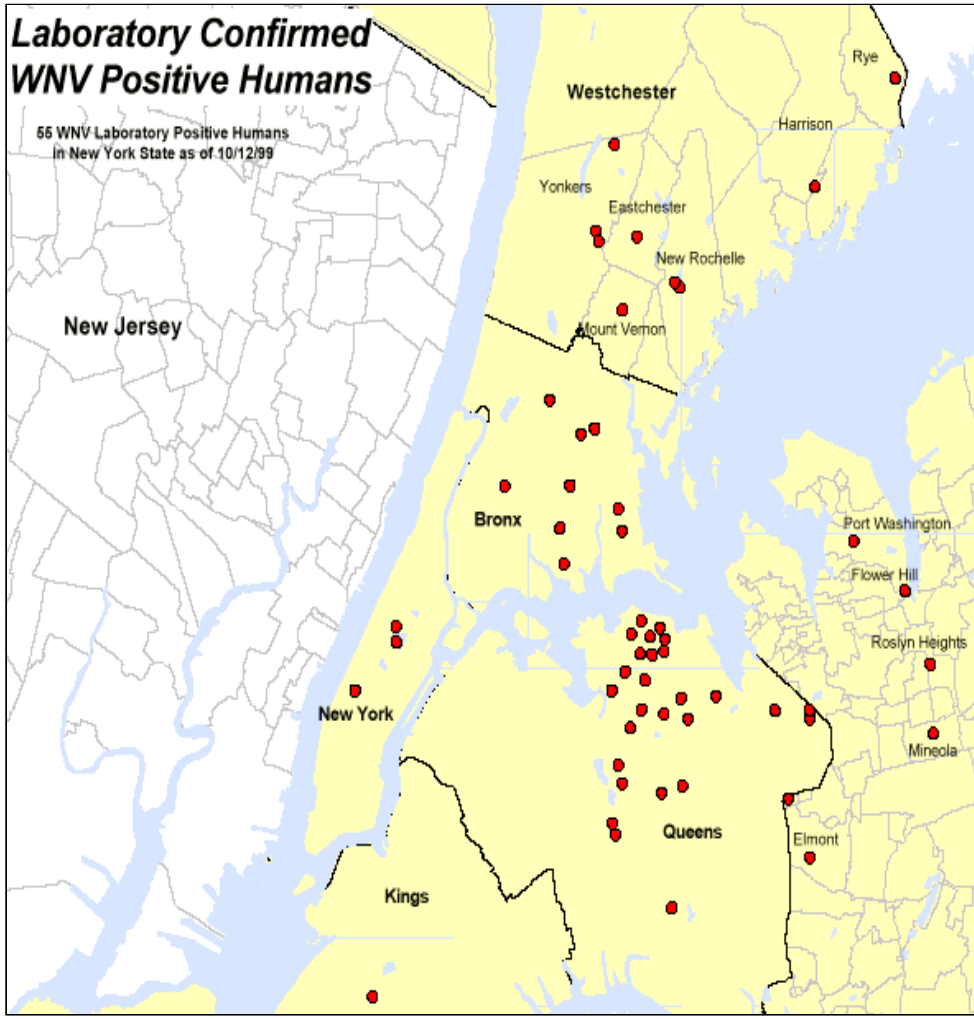


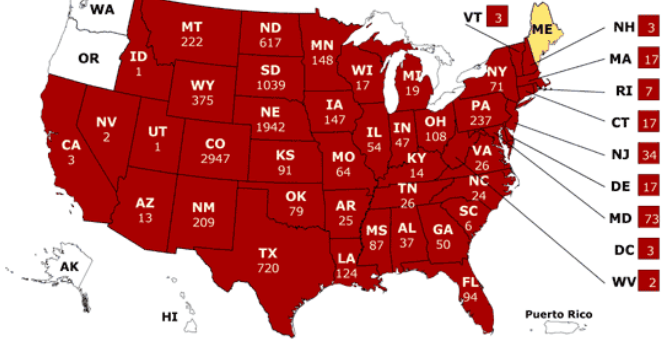
WNV → Human

- *Febrile "influenza-like" illness with sudden onset*
- *Moderate to high fever*
- *Headache, myalgia, arthralgia, malaise*
- *Rash, lymphadenopathy*
- *Acute aspetic meningitis or encephalitis in elderly people*

WEST NILE VIRUS in the USA

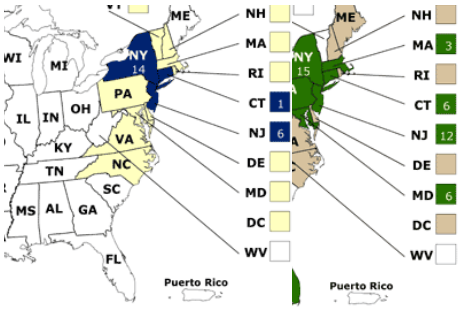
- *Firts illness in 1999.*
- *Meningoencephalitis*
- *Mortality ~10%*



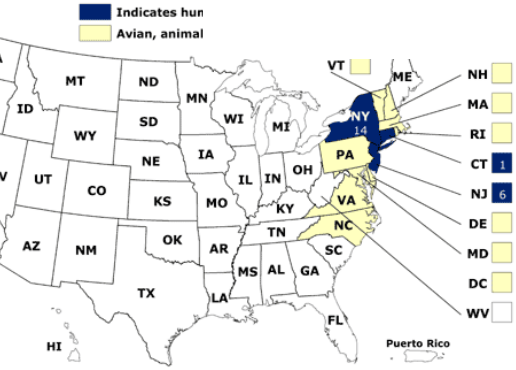


2003

52

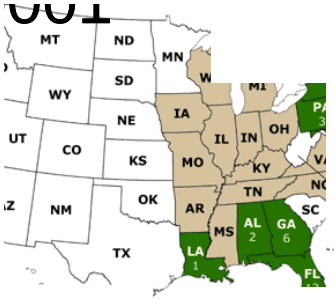


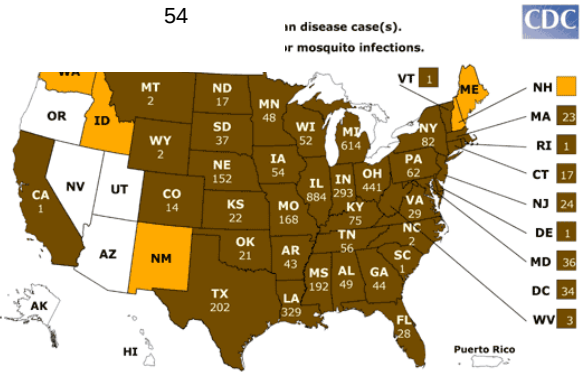
20



2000

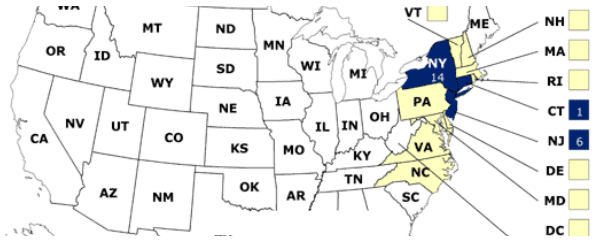
54





2002

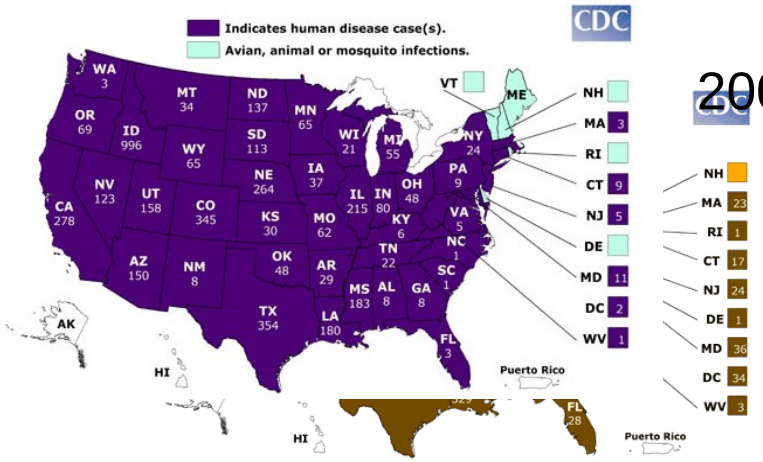
52



51

2003

2000

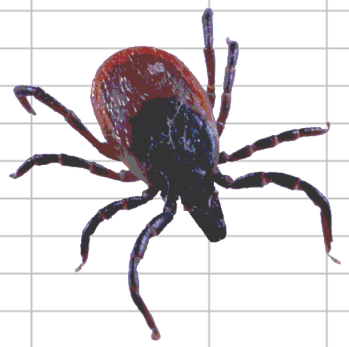


2008

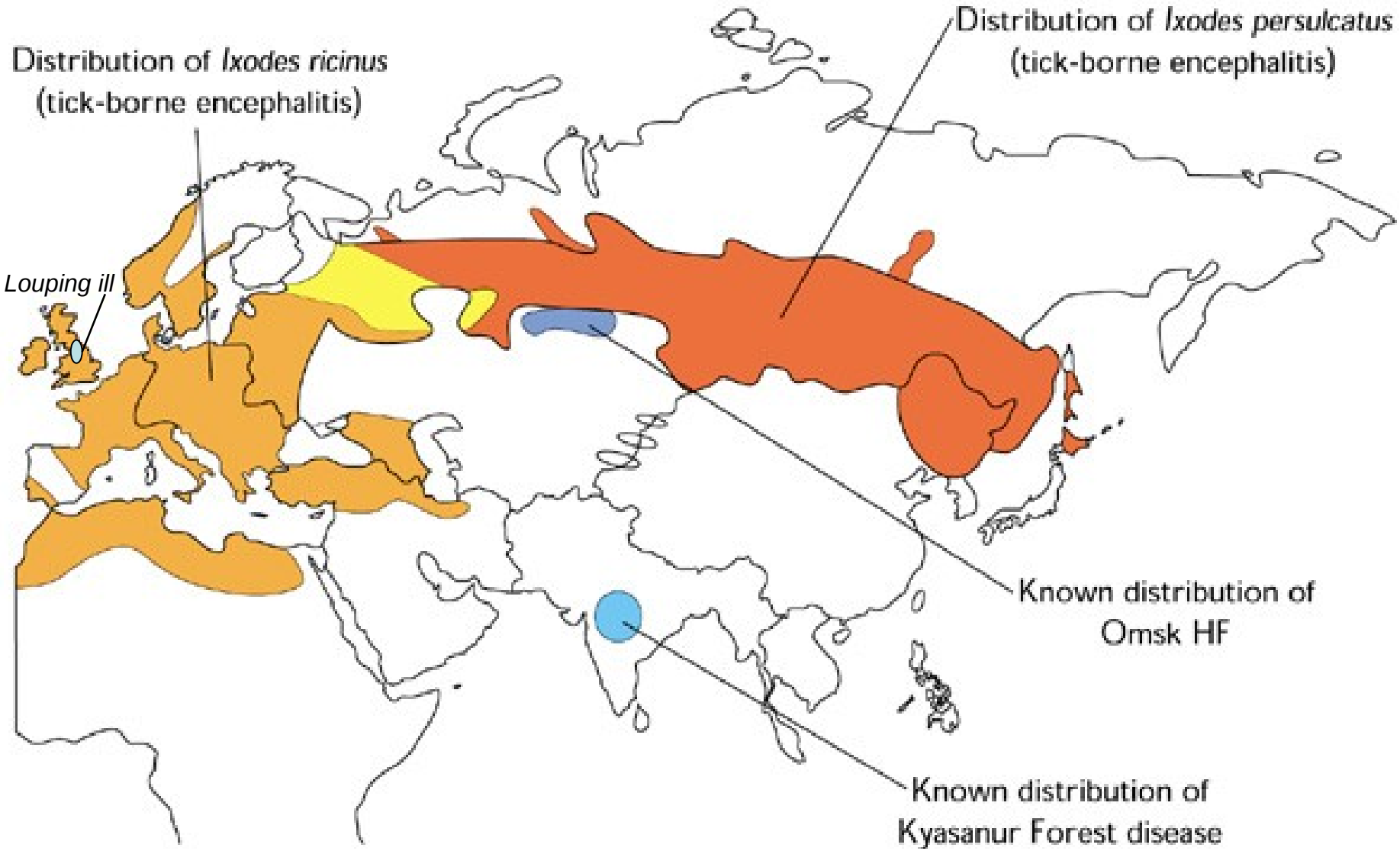
2002

Tick-borne Flaviviruses

Togaviridae	ss (+) RNA nonsegmented							
	Alphavirus					***Rubivirus***		
	Encephalitis		Fever and Arthritis			Rubellavirus		
	Eastern Equine		Chikungunya					
	Western Equine		O'nyong-nyong					
	Venezuelan Equine		Maryaro					
			Ross River					
			Sindbis					
Flaviviridae	ss (+) RNA nonsegemented							
	Hepacivirus							
	Pestivirus							
	Flavivirus							
	Mosquito-Borne		Tick-Borne					
	Yellow fever		TBE	CEEV	RSSEV			
	Dengue		Louping ill					
	West Nile		Powassan					
			Kyasanur forest disease					
			Omsk hemorrhagic fever					
Bunyaviridae	ss (-) RNA segmented (3 segments)							
	Bunyavirus		***Phlebovirus***		***Nairovirus***		***Hantavirus***	
	Bunyamwera Group		SFNV		Crimean-Congo hemorrhagic fever		Hantaan	
	Čalovo		SFSV		(C-CHFV)		Dobrava	
	California Group		TOSV		(Tick-Borne)		Seoul	
	La Crosse		(Phleobotmus papatasi)				Pumala	
	Tahyna		Rift Valley (RVFV)				Sin Nombre	
	(Mosquito-Borne)		(Mosquito-Borne)				(Rodent-Borne)	
			Uukuniemi virus group					
			(Ticks)					



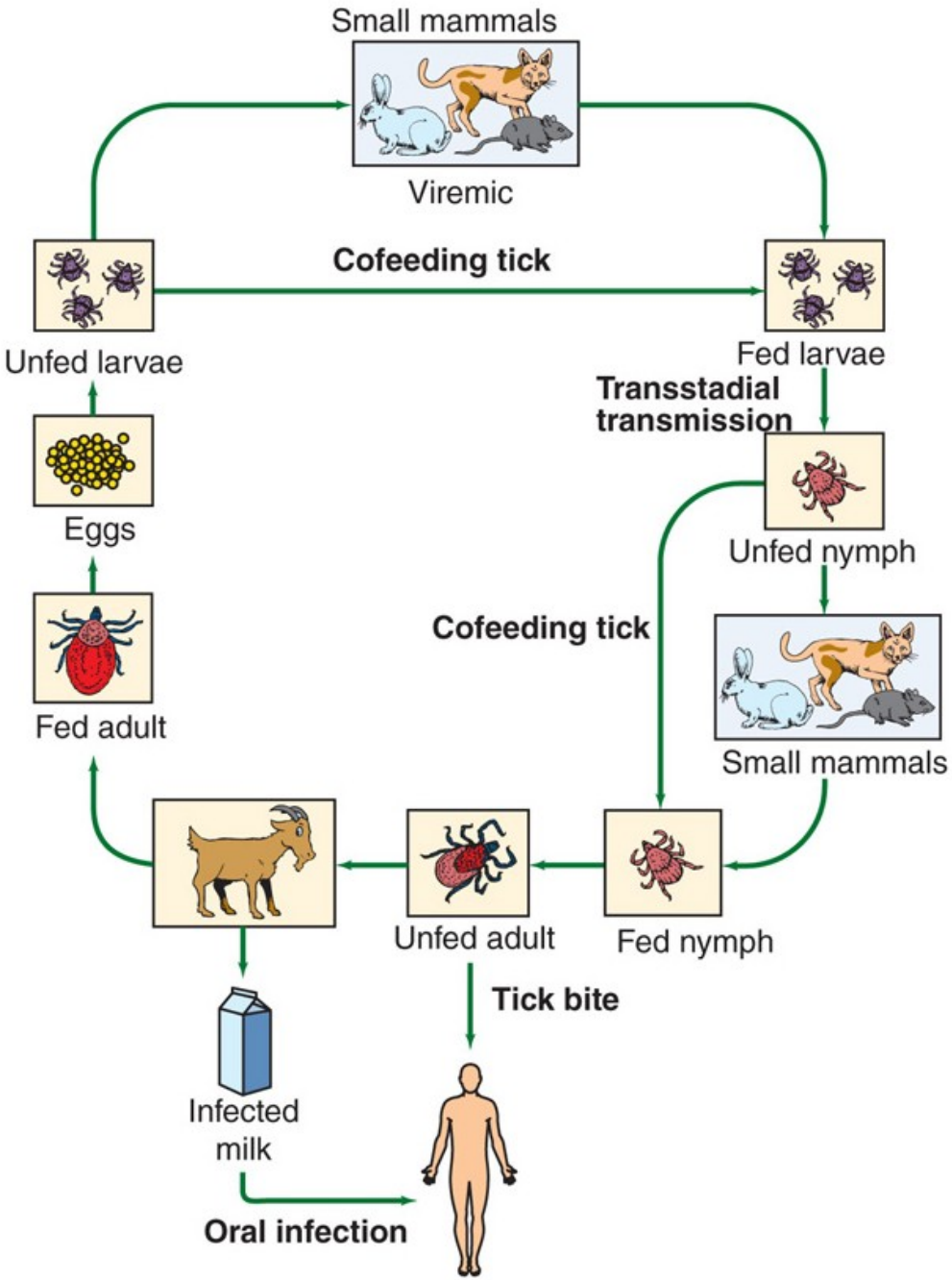
Distribution of Tick-borne Flaviviruses



TBE Virus
3 subtypes

- *Central European Encephalitis (CEEV) – vector* ***Ixodes ricinus***
  - ***European subtype***

- *Russian Spring Summer Encephalitis (RSSEV)- vector* ***Ixodes persulcatus***
  - ***Siberian subtype***
  - ***Far-East subtype***



- *Generalized transmission cycle of tick-borne flaviviruses, showing hosts of larval, nymphal, and adult ticks.*

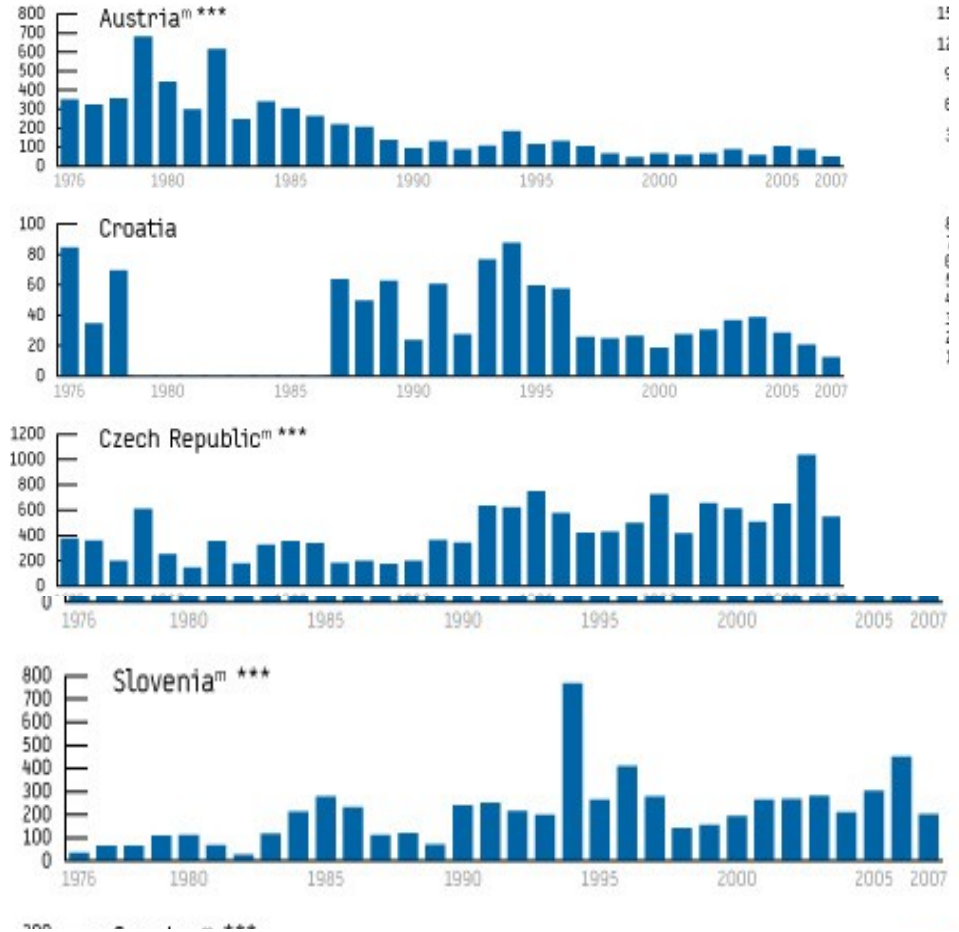
TBE Laboratory Diagnosis

- Virus detetction or Isolation
- Serology

Vaccination

FIGURE 1

Tick-borne Encephalitis (TBE) cases in Europe 1976 – 2007, 19 TBE endemic



* Austria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Norway, Poland, Russia, Slovakia, Slovenia, Sweden, Switzerland

** The numbers represent reported individual cases of TBE and not incidence, as in most countries the risk for TBE is restricted to some areas or regions and therefore a calculation of the incidence for the entire country might lead to false interpretations.

*** European Union Member State

m= mandatory notification