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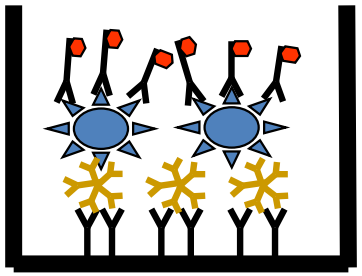
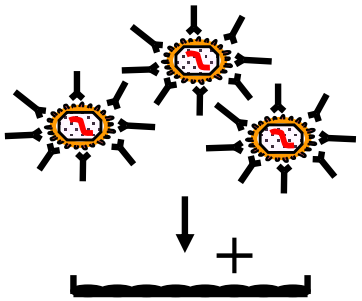
Canada

The Emergence of Zika Virus and Other Arboviruses: Public Health Impacts At Home and Abroad





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May 4, 2017

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Presentation Summary:

1. An Introduction to Zika Virus and other Emerging Mosquito-Borne Arboviruses: Ecology , Epidemiology, and Clinical Aspects

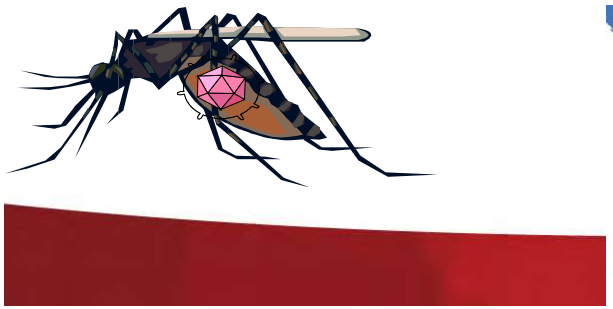
2. Zika Virus Global Expansion and Outbreak Response

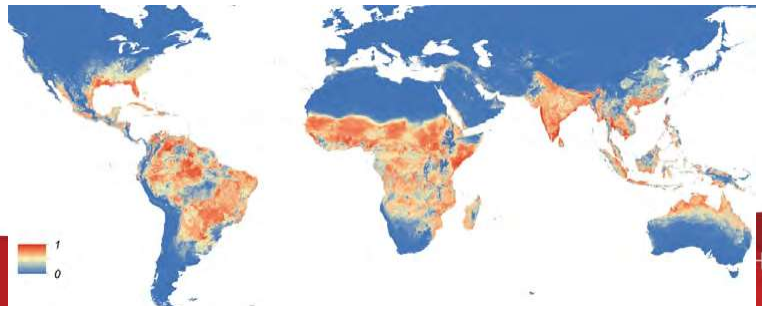
3. Zika / Arbovirus Diagnostic Test Complexities and Caveats

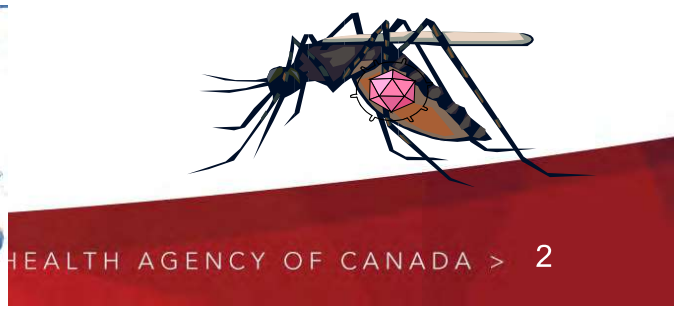
4. Zika Research: New Diagnostic Platforms, Vector Competence, Surveillance, Models of Pathogenesis, Therapeutics and Vaccines

5. Other Arboviruses to Consider During the Canadian Mosquito Season

* I have No Conflict of Interests to Disclose

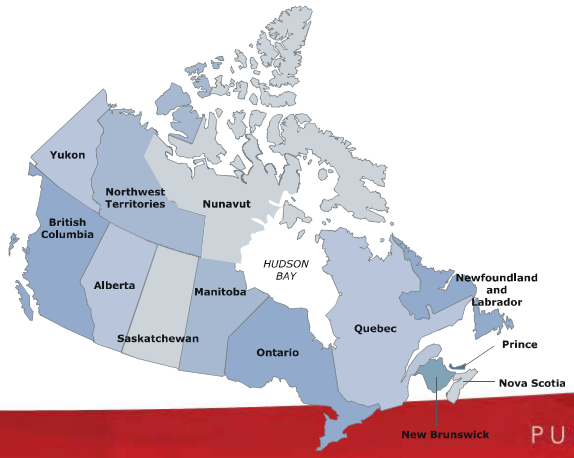






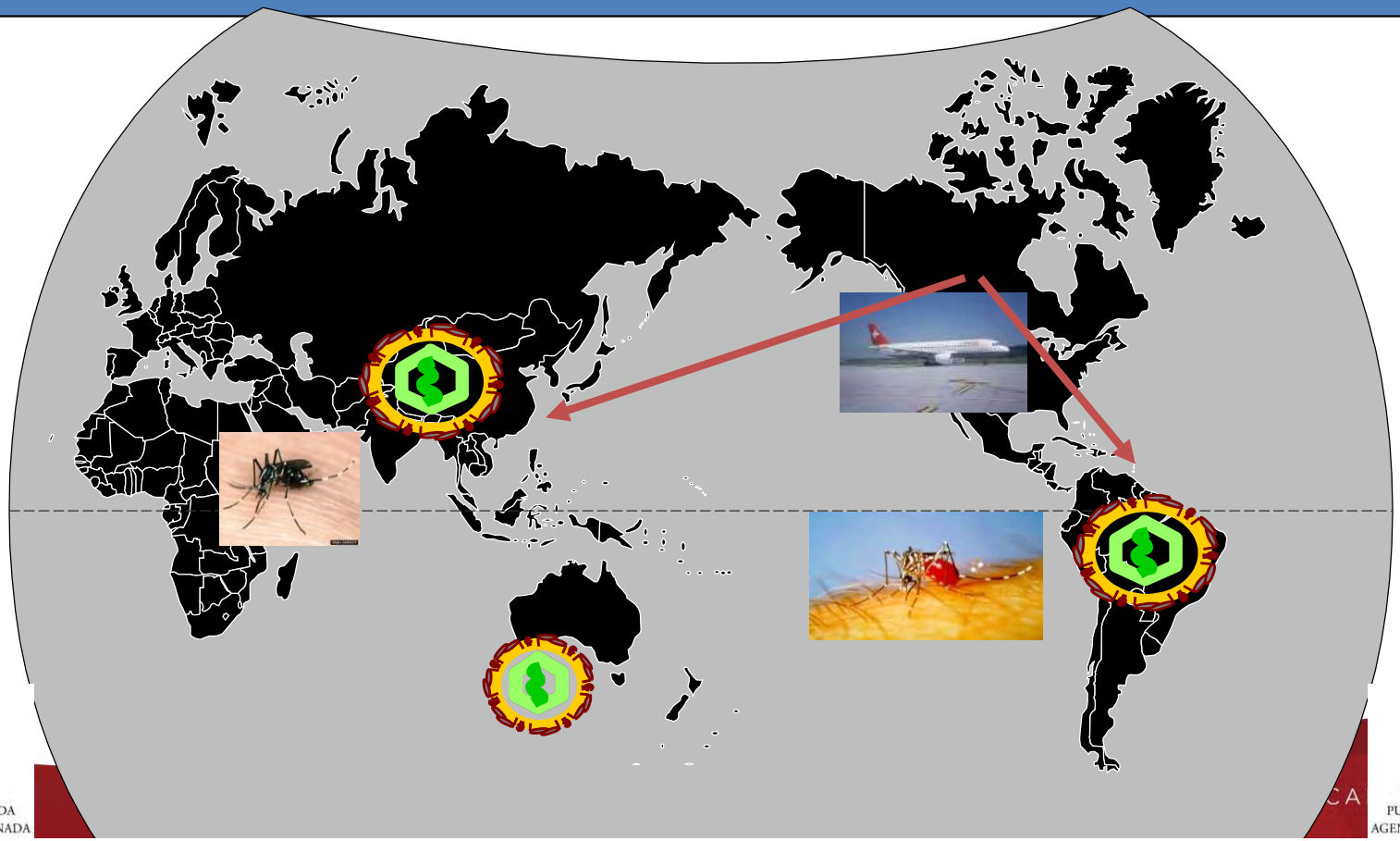
Mosquito-Borne Pathogens (MBP) Are Significant Contributors to Emerging Infectious Disease – ie. Arboviruses

MBP / Arbovirus associated disease is a concern both for travellers and "stay at home" Canadians



"Emerging" and Re- EmergingArboviruses of Concern to Travelling Canadians:

Zika, Chikungunya, Dengue, Yellow Fever, Murray Valley, Japanese Encephalitis, etc



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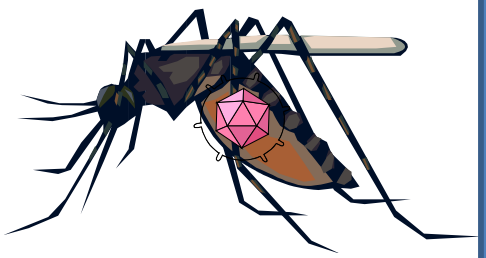
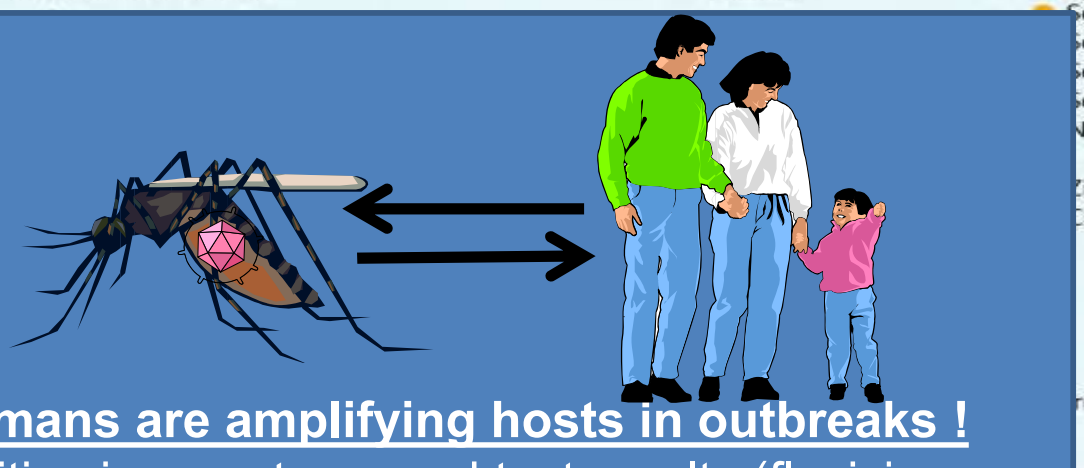
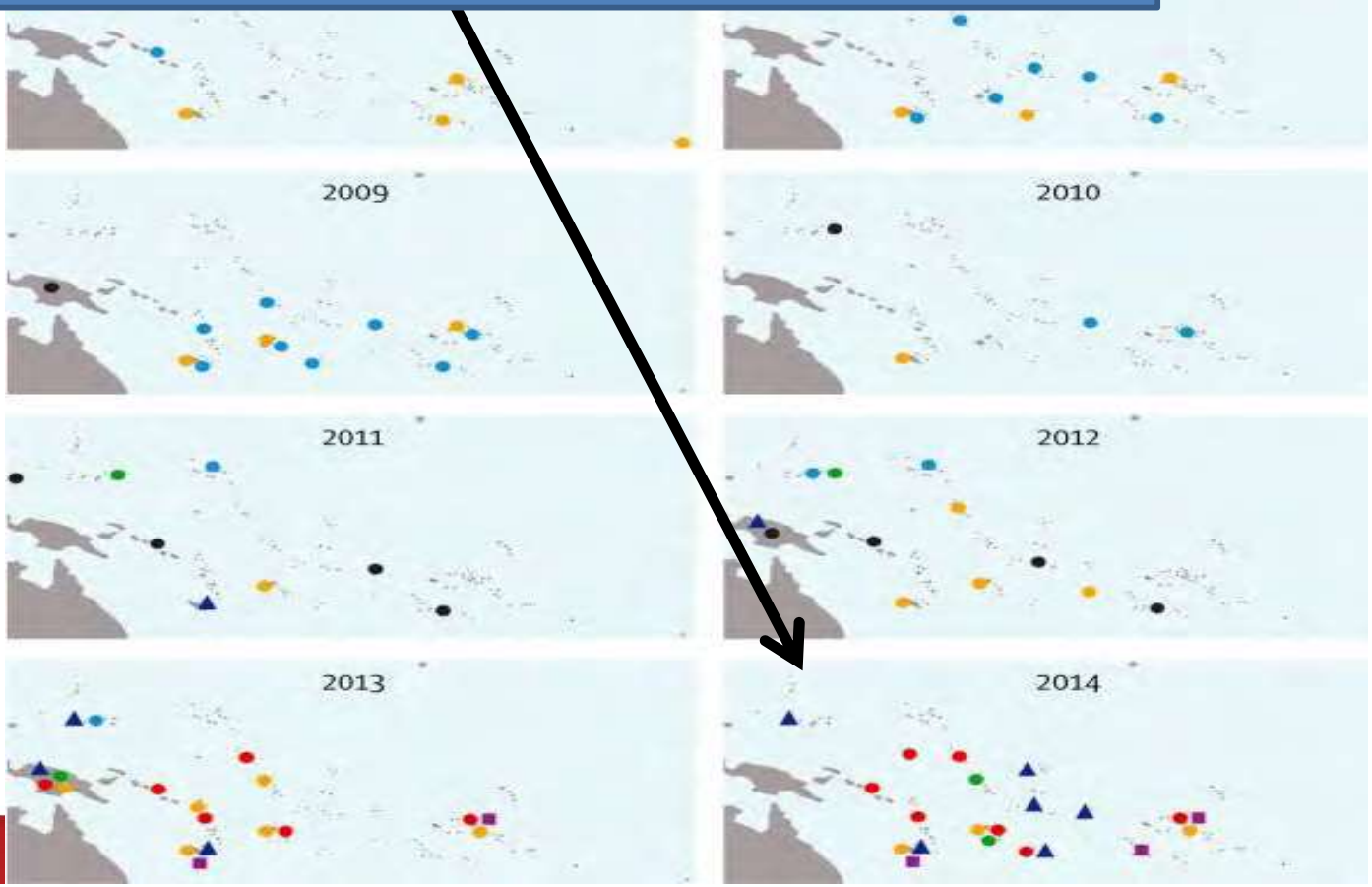




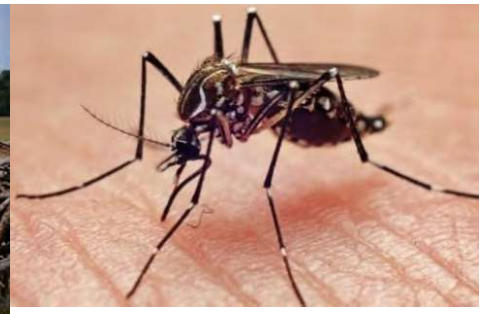
Humans are amplifying hosts in outbreaks !

Similarities in symptoms and test results (flaviviruses - Zika Den etc.) may confound initial diagnosis

Vector Borne Disease Expansion : Emerging Arboviruses in the Pacific – Dengue, Chikungunya, and Zika in 2014

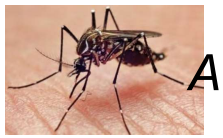


ZIKA Virus Introduction & History



Zika virus (ZIKV):

- Family *Flaviviridae,* genus *Flavivirus*
  - Related to Dengue, West Nile, Yellow fever, Japanese encephalitis viruses
- Enveloped virus with +ssRNA genome
- Originally isolated in Uganda from sentinel monkeys in Zika forest in 1947 & from *Aedes africanus* mosquitoes in 1948
- First human cases in early 50's, only sporadic small outbreaks of mild disease
- Primates including humans likely reservoir



A aegypti – "ideal vector"

- ZIKV from sylvatic to urban settings in Africa and Asia – *Aedes aegypti* strongly suspected as key vector
- Previously assumed that clinical cases -- mild disease, 80% asymptomatic
- Sexual transmission (cases in 2008 US resident, 2013, French Polynesia patient)

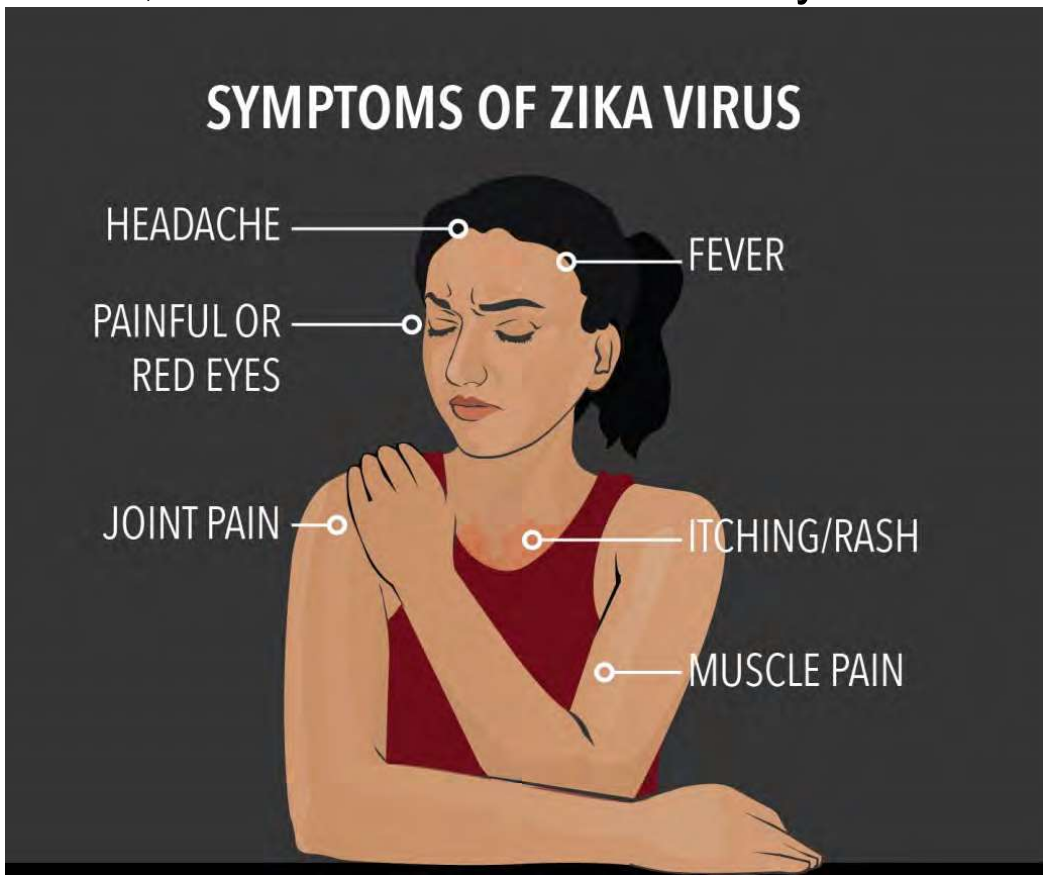
- First report of ZIKV outside of Asia/Africa
- Attack rates: 3.6 – 21.5 / 1.000
- ~ 73% of population developed antibodies
- Only 18% reported symptoms
- Clinical features were mild and no hospital admissions or other complications reported

Clinical Features

- Incubation period is 3-12 days
- Approximately 80% of infections are asymptomatic
- Among those that are symptomatic, symptoms are mild, self limited and last 2 – 7 days

Clinical illness is usually mild with acute onset. Symptoms include:

- ✓ Fever
- ✓ Conjunctivitis (no purulent)
- ✓ Arthralgia
- ✓ Myalgia
- ✓ Headache
- ✓ Asthenia
- ✓ Maculopapular rash
- ✓ Swelling in lower limbs
- ✓ Pruritus (ithc)



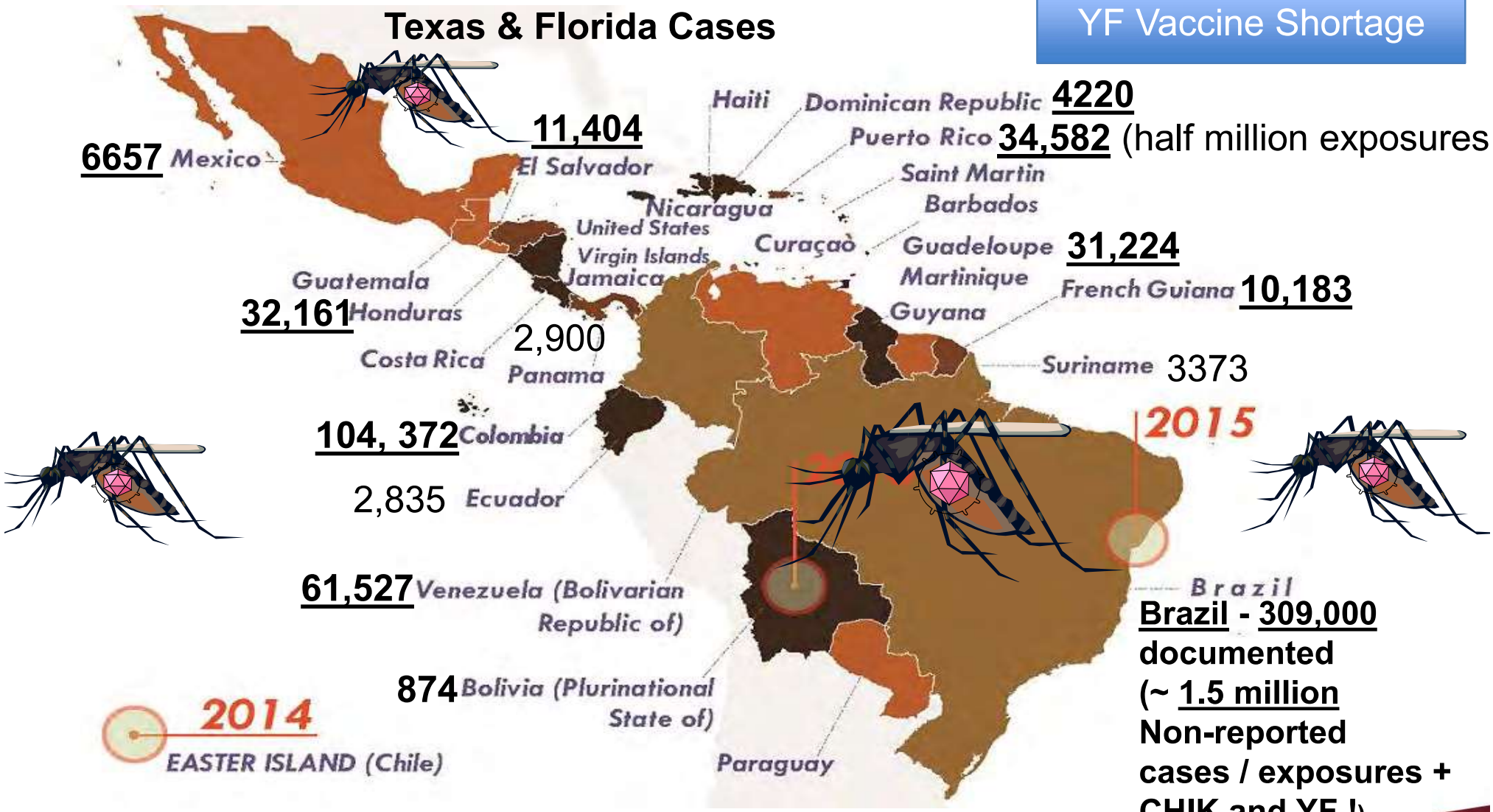
http://www.cdc.gov/zika/hc-providers/clinicalevaluation.html
PROTOCOLO DE VIGILANCIA EN SALUD PUBLICA ENFERMEDAD POR VIRUS ZIKA. INS Colombia. Versión 01 2016-01-21

Pacific Islands Outbreaks: 2013-2015

- Islands of French Polynesia
- 383 confirmed cases of ZIKV
- 32,000 estimated cases (~12%)
- **First reports of Guillain-Barré syndrome** in ZIKV patients
- One case of perinatal transmission
- 2014 Cook Islands, Pascua, New Caledonia
- 2015 New Caledonia, Solomon Islands, Fiji, Samoa, Vanuatu
- January 2014 – First report of ZIKV in Americas when reported on Easter Island (Chile)

Significant Burden of ZIKA Disease: 2015- 2016-

- But additional outbreaks of **Dengue, Chikungunya, and recently Yellow Fever !!**



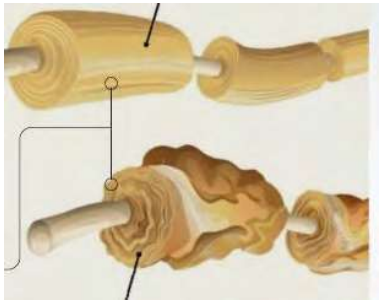
NML - End of 2016: **21,038 Zika tests** performed on **13,966 samples** from **12551 patients from Canada !**

Febrile, Microcephaly, GBS

Other Modes of Transmission Confirmed or Suspected

- Sexual transmission (all possible combinations; persistence in sperm)
- Blood products/transfusion
- Virus/RNA detected in urine, saliva & breast milk
- Intrauterine and perinatal infections

Spectrum of ZIKV Disease Appears to Change in Brazil



- Neurological complications including: Guillain-Barré Syndrome in adults and microcephaly in newborns reported at heightened frequency
- Association with microcephaly prompts WHO to declare ZIKV “Public Health Emergency of International Concern” (February 1 2016)

Microcephaly now observed in other countries, other developmental effects, New Study: infected babies with no apparent microcephaly at birth, head growth deceleration after birth observed, other neuro issues (MMWR,CDC)

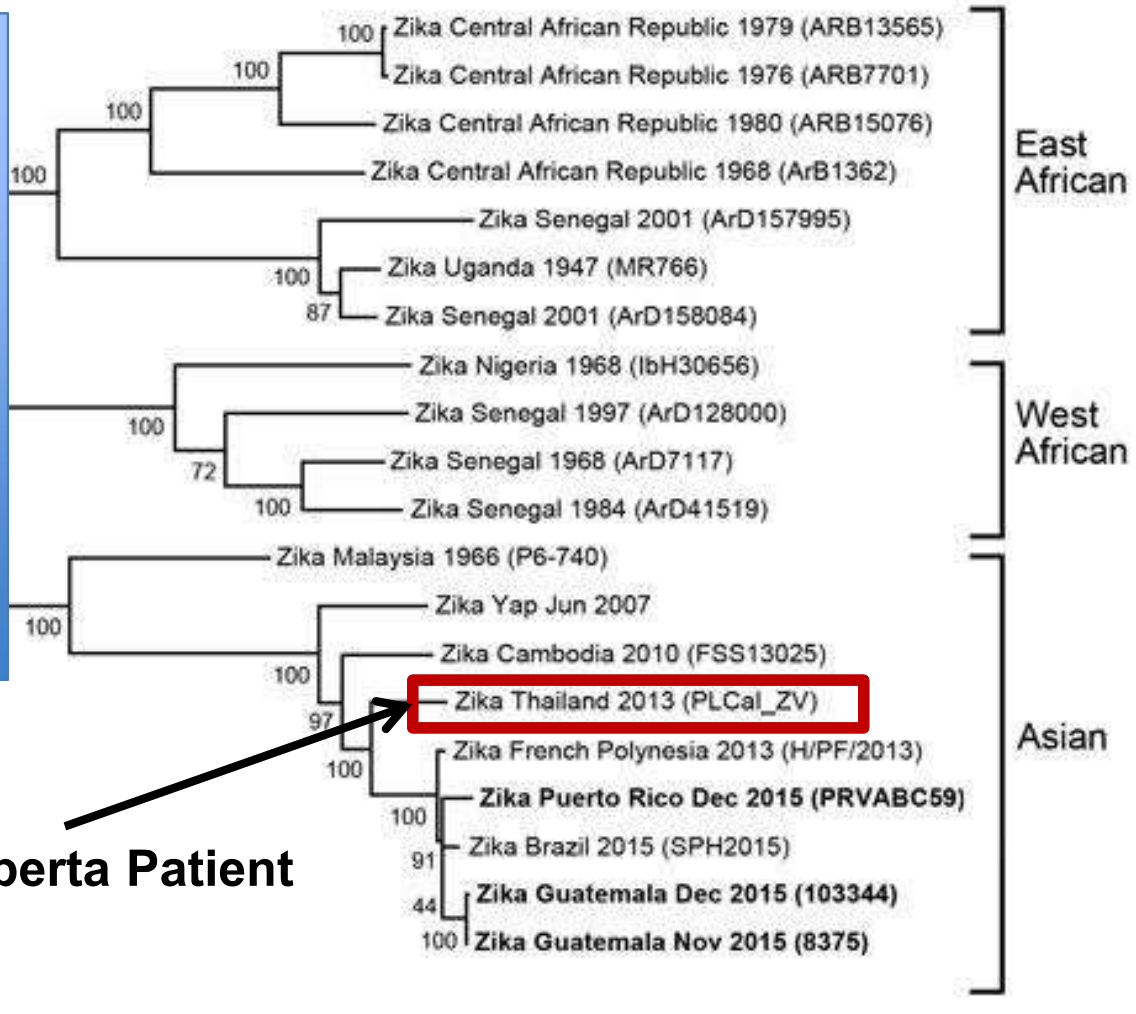
Did virus mutate or were “novel” clinical aspects of ZIKV previously not detected ? Perhaps **Both** are Factors ?

ZIKV Phylogenetics

American strains constitute a "Western Hemisphere Group"

Epidemic strain emerged via genetic changes in Asian lineage virus in Yap State and French Polynesia (increased virulence ?)

Genetic recomb & amino acid changes identified, significance ?



Canadian Imported Case, Alberta Patient

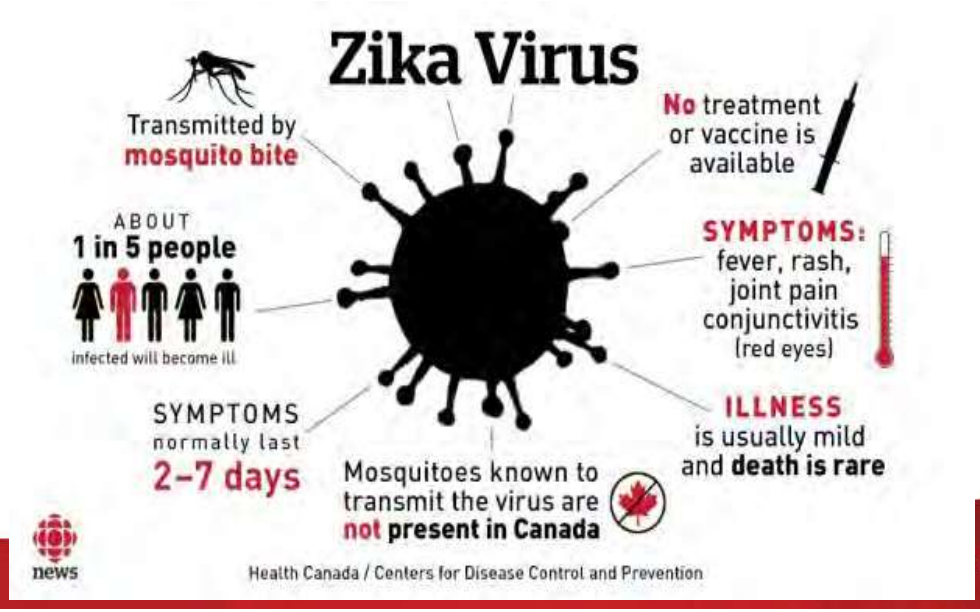
Lanciotti et al., EID 2016:
http://wwwnc.cdc.gov/eid/article/22/5/160065_article

Initial & Ongoing Canadian Public Health Responses

1. Rapid risk assessment for Canadian travelers (sexual partners) including travel advice

2. Development of case definitions and guidelines for diagnostic testing (Canadian Public Health Laboratory Network – CPHLN, CATMAT, PHAC)

3. Diagnostic testing for ZIKV infection and evaluation of new assays (with provincial labs) and ZIKV research



Ongoing Impact of a Non-Endemic Virus With Severe Clinical Implications (ZIKV) on Canada:

- Travel related infections
- Estimated the 4+ million Canadians travel annually to affected regions
- Additional travel to Florida (ZIKV endemic?) significantly increases the population of travelling Canadians
- 1% of those pregnant or conceived?
- Possibility of sexual transmission upon return home
- Vector-borne transmission in Canada (endemic, establishment) ?

Who should get tested:

Recommended:

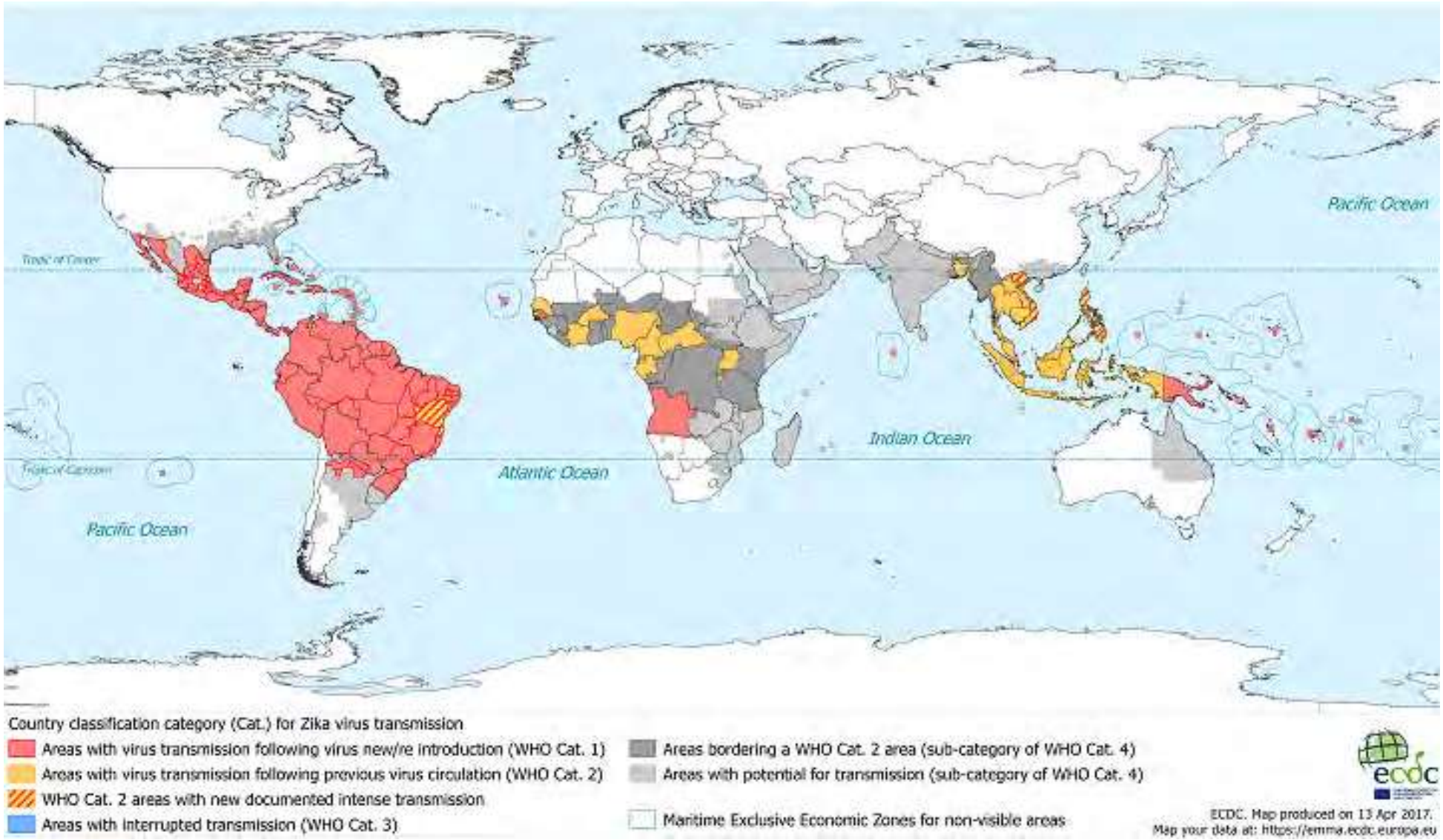
- Any symptomatic traveller returning from an affected region
- Asymptomatic pregnant women with travel history
- Sexual contacts of a confirmed Zika case
- Asymp. men or women with travel history who cannot delay pregnancy for medical reasons (IVF)

Not currently recommended:

- Asymptomatic men with travel history to an affected region

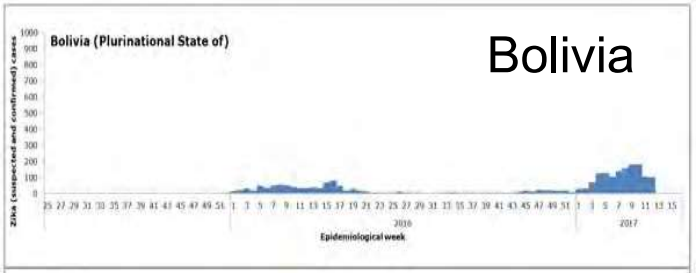
There are some caveats !

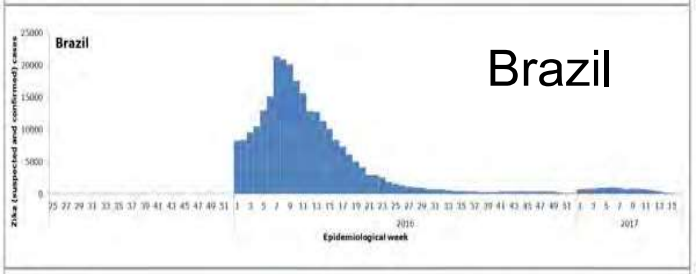
Current Zika Transmission

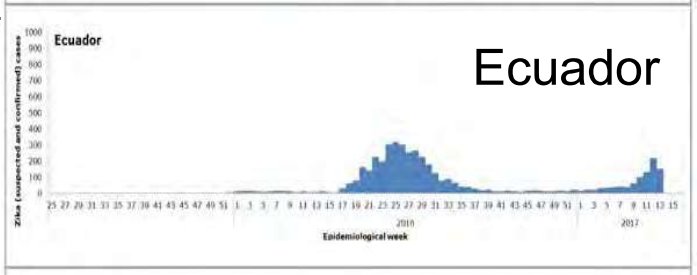


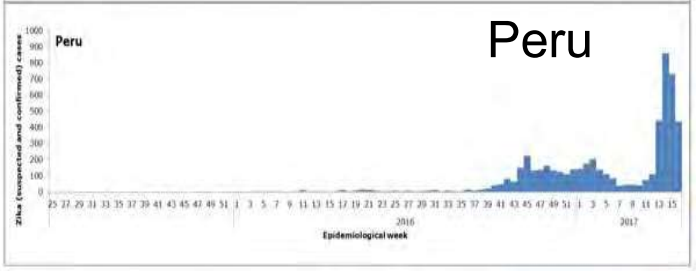
Situation Summary in the Americas, April 27, 2017

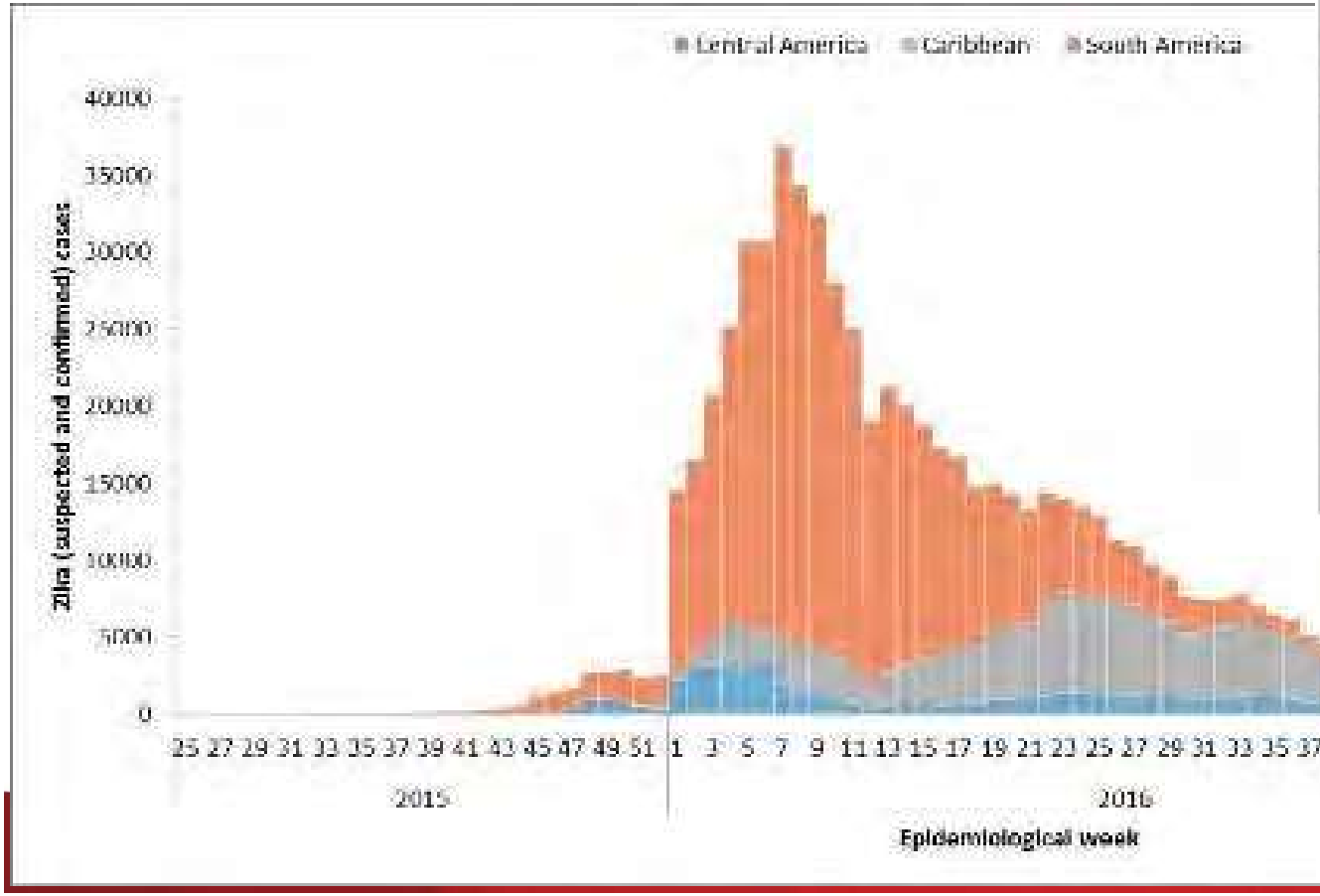
Declining activity, but not in all areas and resurgence possible







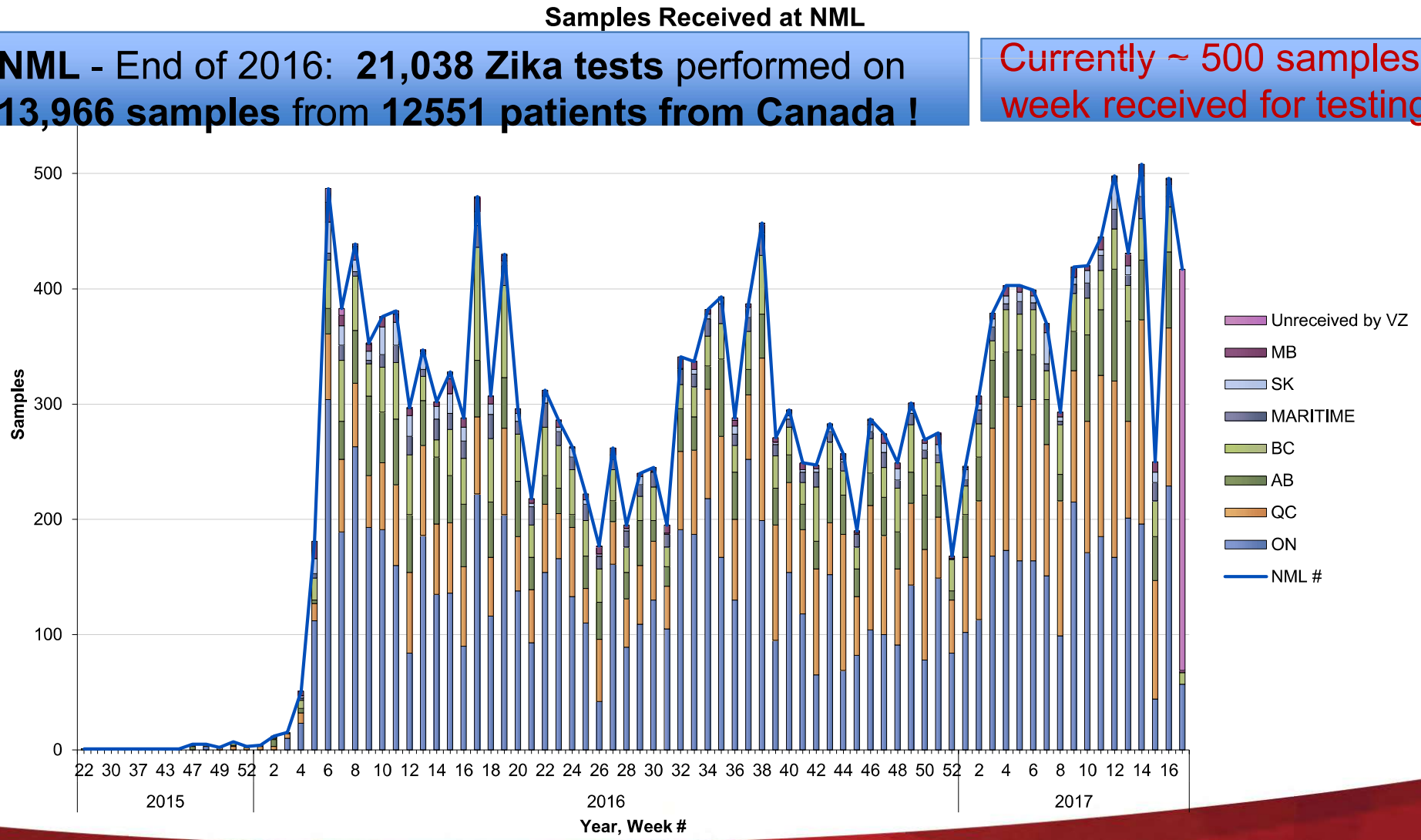




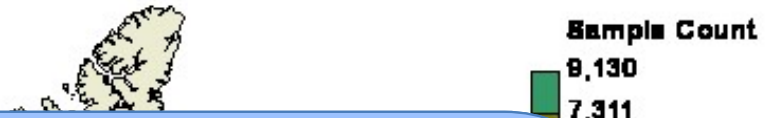
However, the NML continues to receive large numbers of samples for testing !

NML - End of 2016: **21,038 Zika tests** performed on **13,966 samples** from **12551 patients from Canada !**

Currently ~ 500 samples a week received for testing !



Sample Submissions By Province and Demographics

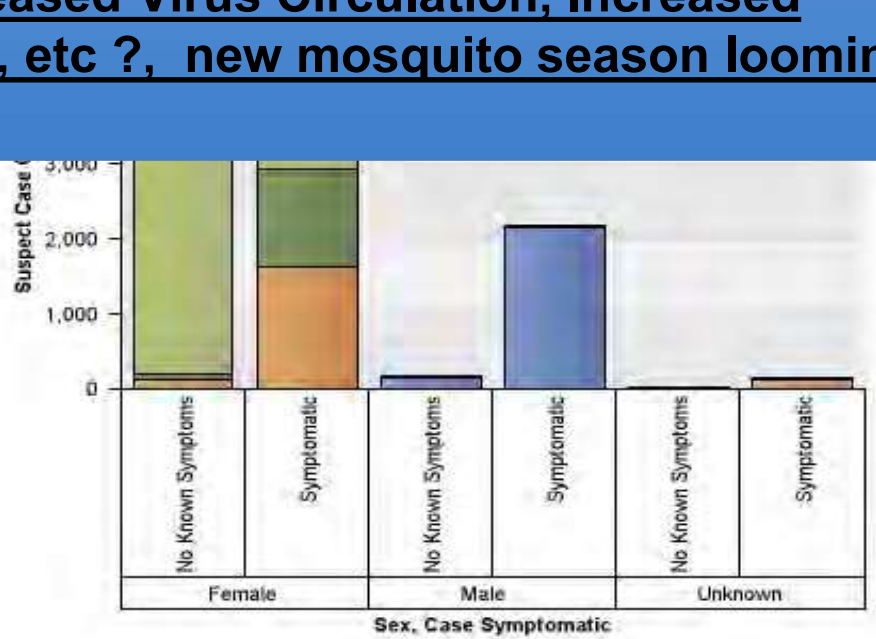


Summary:

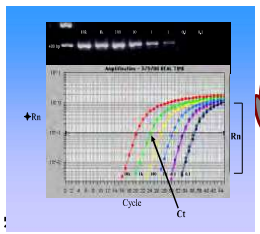
2016: **21,038 Zika tests** performed on **13,966 samples** from **12551 patients**

Cases to date 2015-2017:

- 486 travel related cases
- 3 cases associated with sexual transmission
- 28 pregnant women tested positive
- 2 newborns with anomalies, 2 without
- **Positivity Rates Have Decreased (Seasonal Factors - Mosquito Abundance, Viral Ecology - Decreased Virus Circulation, Increased Immunity, Preventative Measures, etc ?, new mosquito season looming !)**



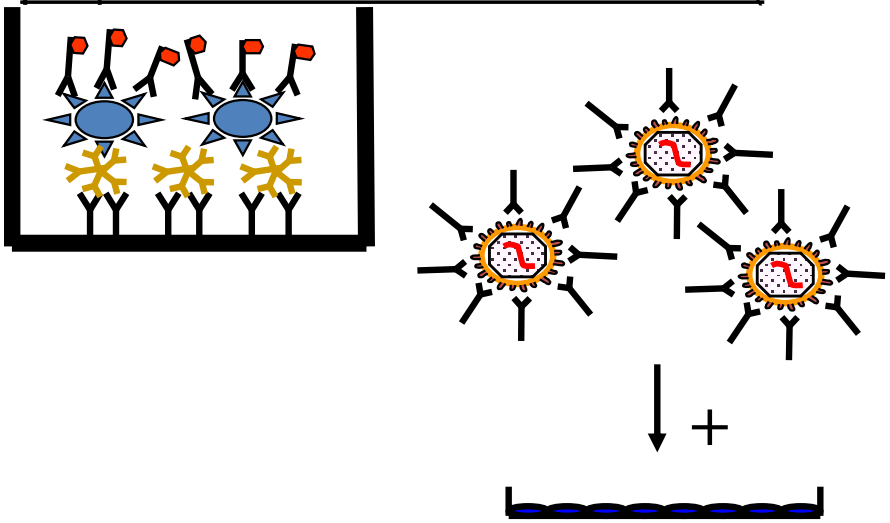
Laboratory Case Definitions for Confirmation of ZIKV Infections



1. **Detection of ZIKV** by **PCR**, antigen presence (IHC), or viral isolation,
   Specimens for PCR & Isolation include: serum, urine, CSF, semen, etc.

OR

2. **Detection of ZIKV-specific Antibodies**
   IgM positive (*e.g.*, **ELISA**) and presence of **ZIKV-specific neutralizing antibody** using plaque reduction neutralization tests (**PRNTs**)



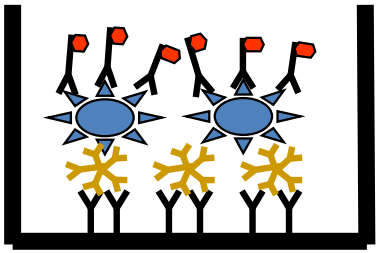
In a PRNT assay Zika virus is mixed with a patient's serum sample and added to a cell culture monolayer to see if the patient has antibodies that will neutralize the ability of the virus to infect and kill the cells.
Patient's sera is also mixed with dengue virus to compare neutralization titres (dilution of sera)

(**PRNT** assays, **ZIKV vs Dengue titres**, see below) in acute and/or convalescent samples

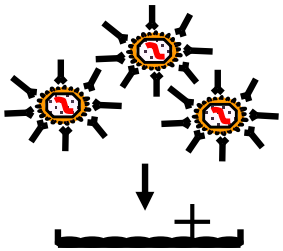
Eg. PRNTs -- Zika 640 Dengue 20/40 (observed in PCR positive patients)

Diagnostic Testing

IgM ELISA

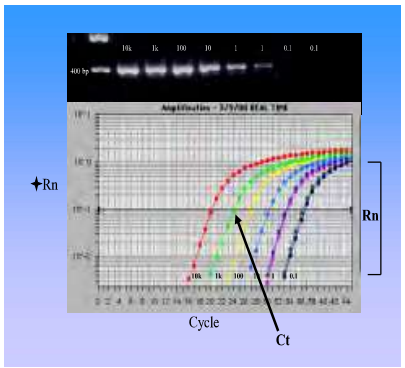


Neutralization Assay (PRNT)



Molecular

- Two target **real-time RT-PCR** specific for ZIKV
- Works best on **acute specimens**
  - **Serum:** 10-14 days onset (peak 3-5 days post-onset)
  - **Urine**: 14 days onset
- **Viral Isolation is difficult**

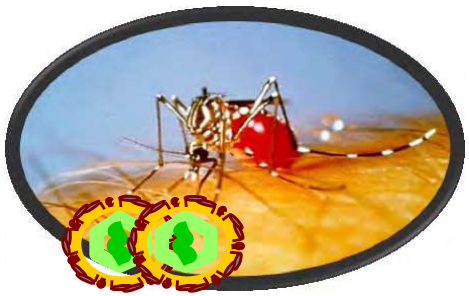


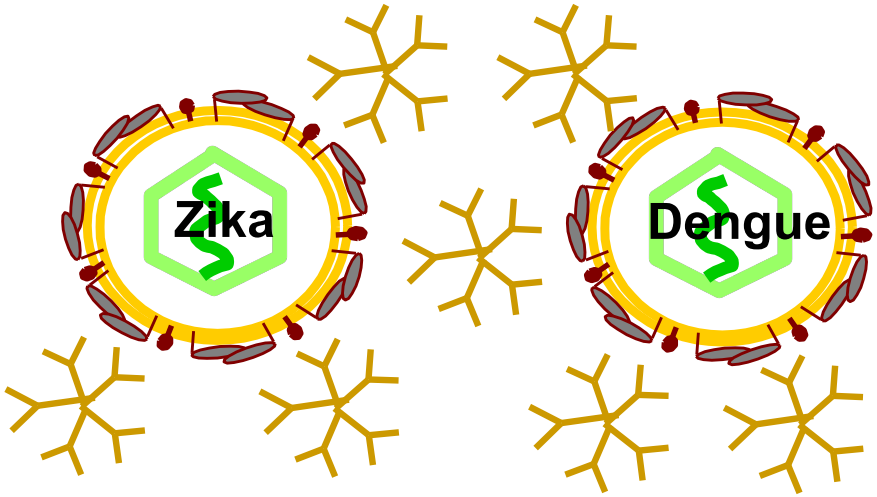
Serological

- **IgM capture ELISA**
  - Screening assay
  - Sensitive, not specific
  - Fast, 2 days
- **ZIKV PRNT**
  - Confirmatory assay to detect and titer virus-specific antibodies
  - Cross PRNTs performed (ZIKV and DENV)
  - Laborious & time consuming (7days)
- **Significant serological cross-reactivity amongst flavi's can make interpretations difficult even when PRNTs are used !**

Different Cell Lines need to evaluated for test refinements

Zika virus is a "flavivirus" closely related to West Nile, Dengue, Yellow Fever and other members of this virus genus

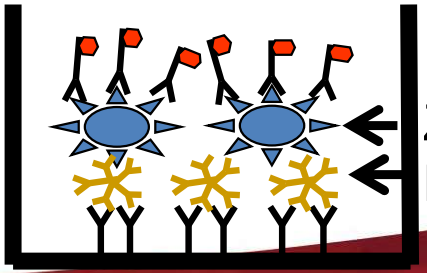




In exposed individuals both can induce a set of antibodies that can bind both viruses

Both are transmitted by the same mosquito:
Aedes aegypti – the "yellow fever mosquito"

Because of this ab cross reactivity a patient's serum from a dengue infection can give a positive result in a standard Zika ELISA test



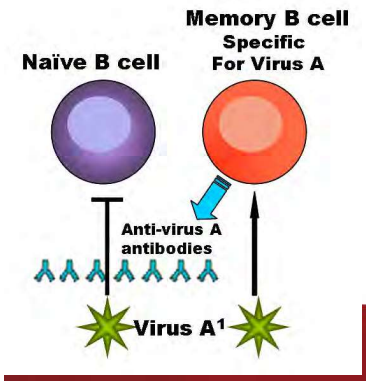
ORIGINAL ANTIGENIC SIN & DECREASED IgM INDUCTION

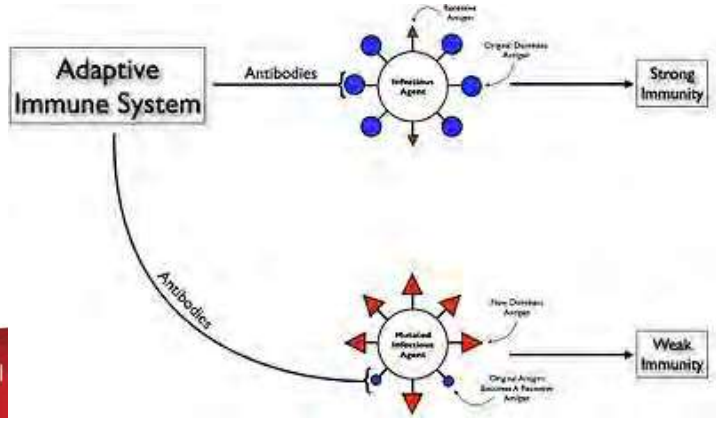
Original Antigenic Sin, immune system preferentially utilizes immunological memory based on a previous infection when a second slightly different version of that foreign entity (*e.g.* a virus or bacterium) is encountered.

Ie. **Acute exposure to a pathogen** initially generates specific Abs / **"immune boost" to a distinct but related pathogen (antigen)** that the individual was **previously exposed to in the past**, the **immune response to the current infection may be significantly decreased / sub optimal (until later in infection)**

--- First described in 1960 - Thomas Francis "On the Doctrine of Original Antigenic Sin"
Associated with Influenza, HIV, dengue infections, etc. **Den1→ Den2, ↑ abs to Den1**

--- **suboptimal immune response** during secondary infection, **decreased IgM**
(implications for vaccination, immunopathology, & diagnostics)



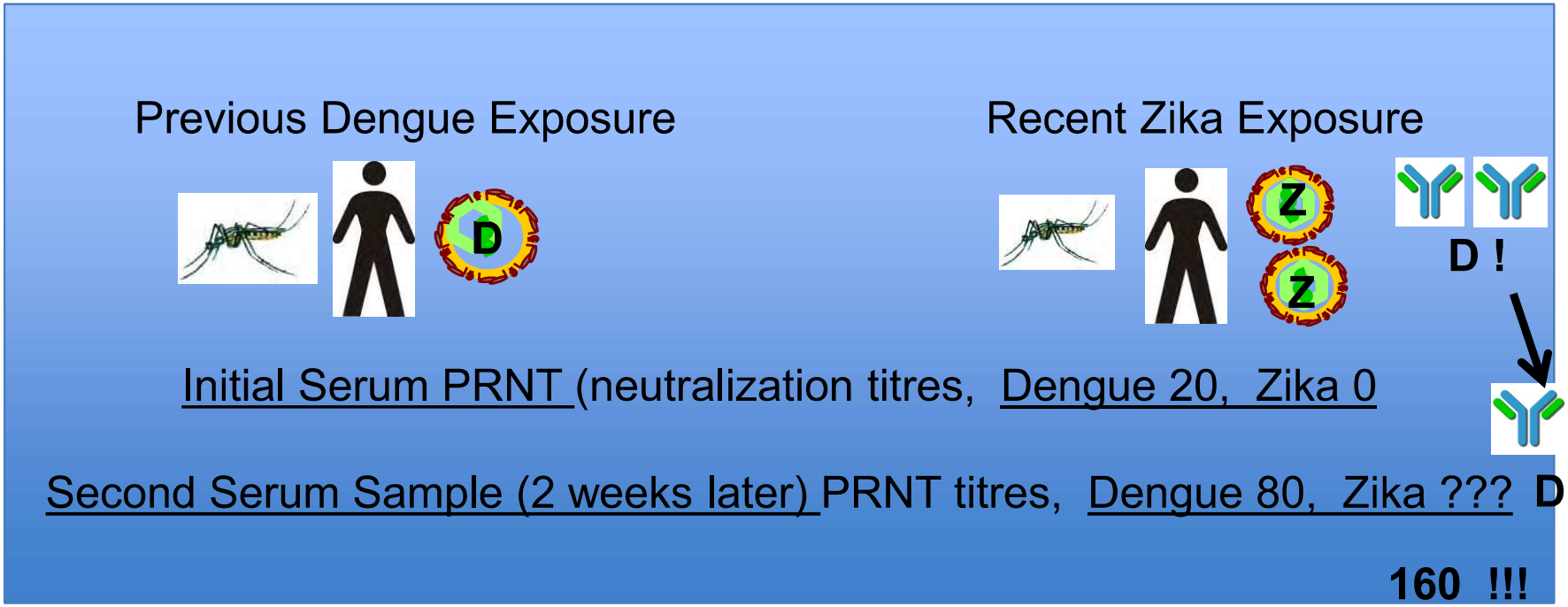


Antibody Testing Caveats: Significant cross-reaction problems especially for IgM ELISA tests but can also confound interpretation **of PRNTs** when **Secondary Exposures** occur

e.g., Classic "original antigenic sin" issues caused by other flavivirus infections (travellers) followed by ZIKV exposure, or previous flavivirus vaccinations (YFV, JEV). Paired samples may help resolve the identity of infecting virus on a neutralization assay (PRNT)

But Not Always !!!! As well flavivirus secondary infections may lead to **"Impaired IgM Responses"** so **screening IgM ELISAs need to be sensitive !** Commercial assays so far lack appropriate sensitivity !

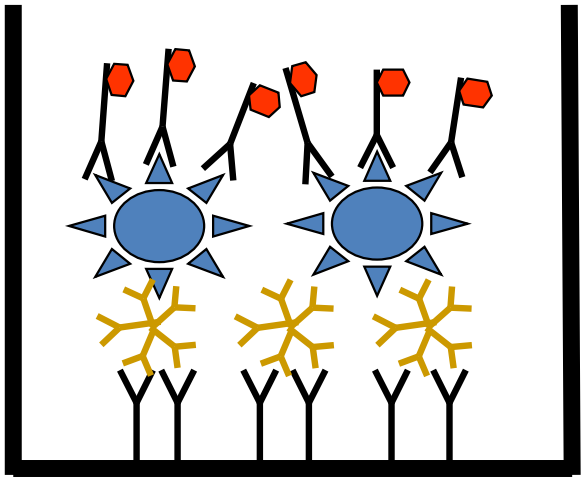
Secondary Flavivirus Exposure Case Example:



Continuing Co-circulation of Dengue, Zika, Yellow Fever, - Diagnostic Challenges !

ZIKA Virus IgM ELISA Kit Formats and Evaluations:

Eg. Euroimmun (NS1), NovaTec (NS1), Diasorin (NS1), In Bios (Env)



Initial assessment of **NS1** based assays indicate increased **specificity** for distinguishing between antibodies to related flaviviruses such as ZIKV and DENV.

However**, the sensitivity** for detecting the presence of IgM in acute samples is decreased as compared to the CDC – NML "in house" IgM ELISAs

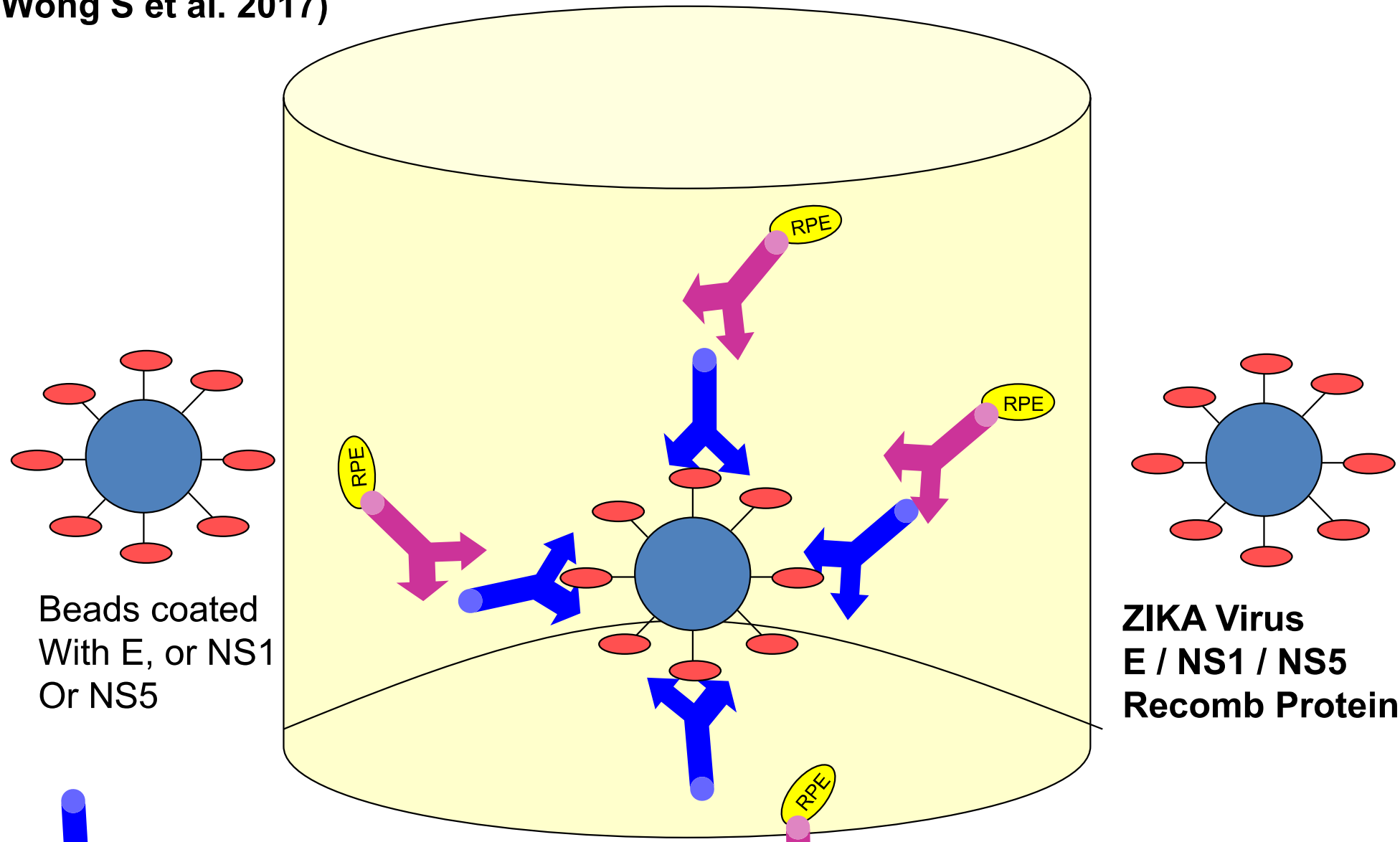
"Whole virus" / E based antigens in ELISAs appear to provide required sensitivity but may have decreased specificity characteristics

Combining NS1 IgM & IgG ELISAs increase overall sens, however, some issues with distinguishing current from past infections, cost

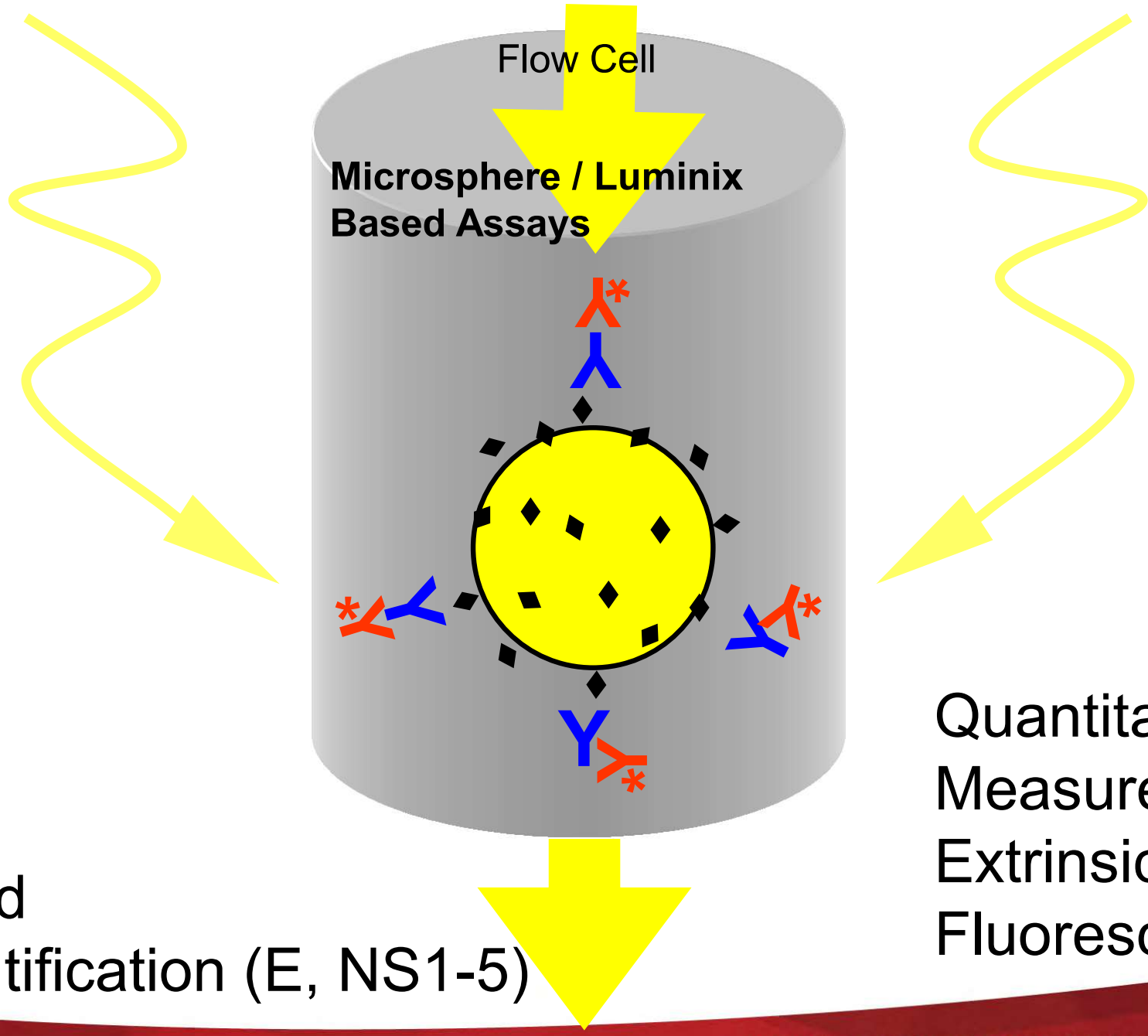
Multiplex E, NS 1, 5 platforms (MIAs) & avidity measurement "promising" (See Friday Session D 05)

Combining New Technology with Old ! Utilizing Various DIAGNOSTIC FORMATS

"Multiplex" Microsphere / Luminix Platform - Detection of antibodies to Zika proteins (Wong S et al. 2017)



Laser 1 **Measurement of Antibody / Antigen Binding on Tagged Beads** Laser 2



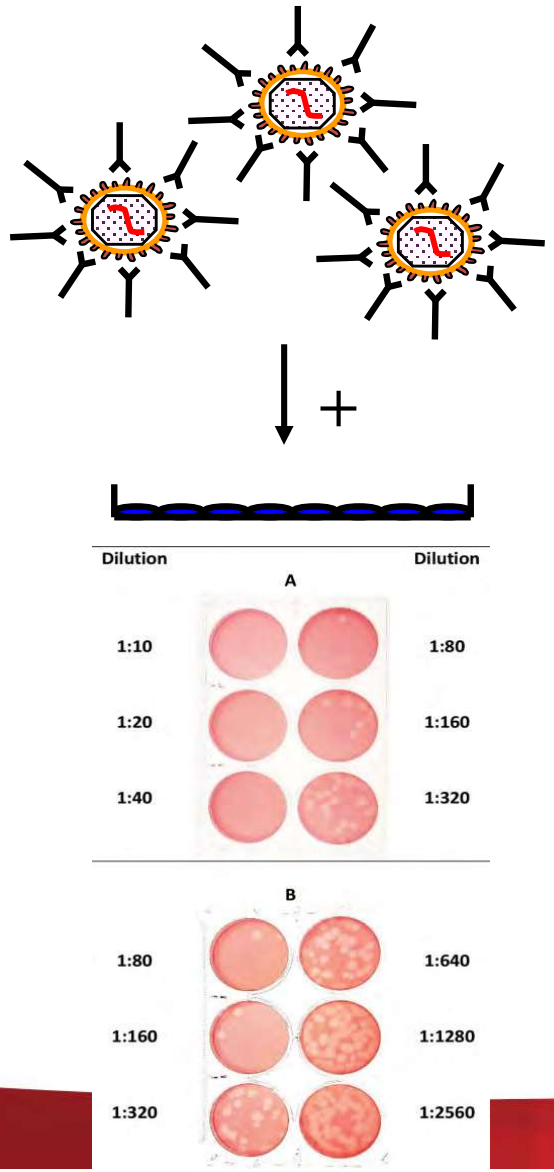
Bead
Identification (E, NS1-5)

Quantitative
Measure of
Extrinsic
Fluorescence

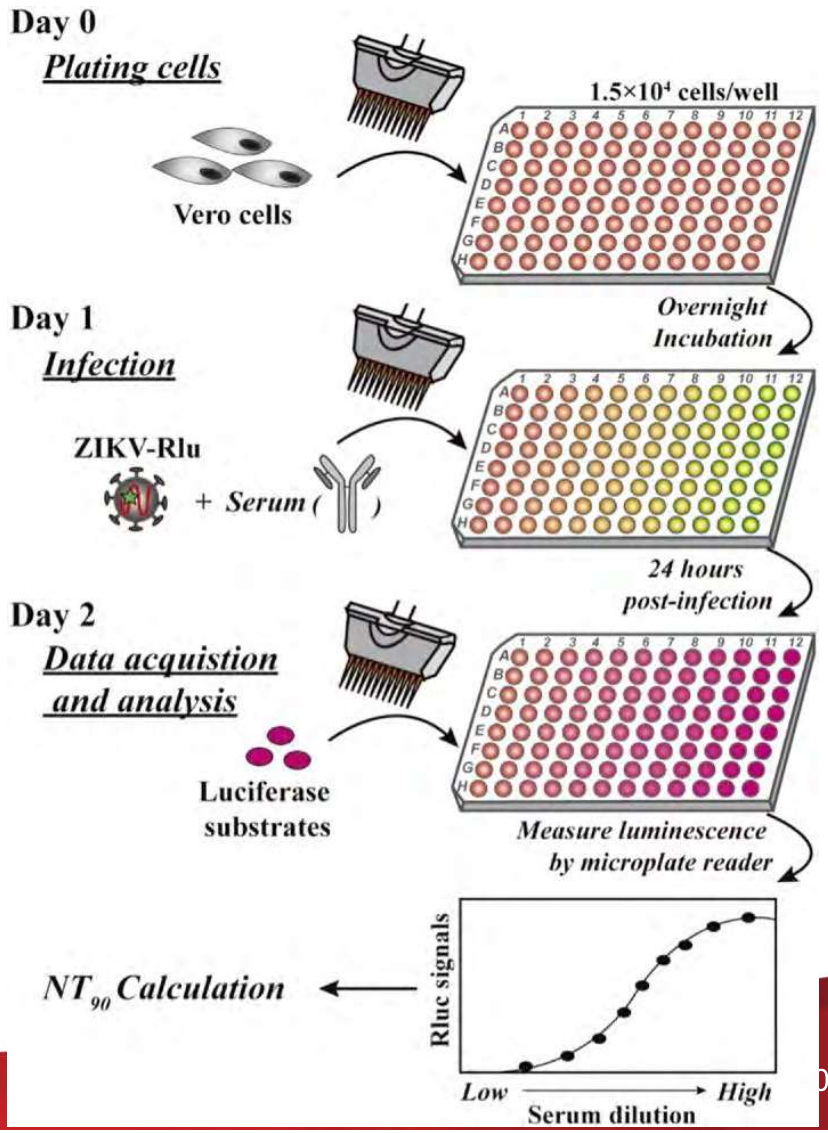
Application of New and Higher Throughput Neutralization Assays for Serological Testing

Conventional PRNTs versus neutralization assays employing ZIKV Luciferase Platform

(Shan et al 2017)



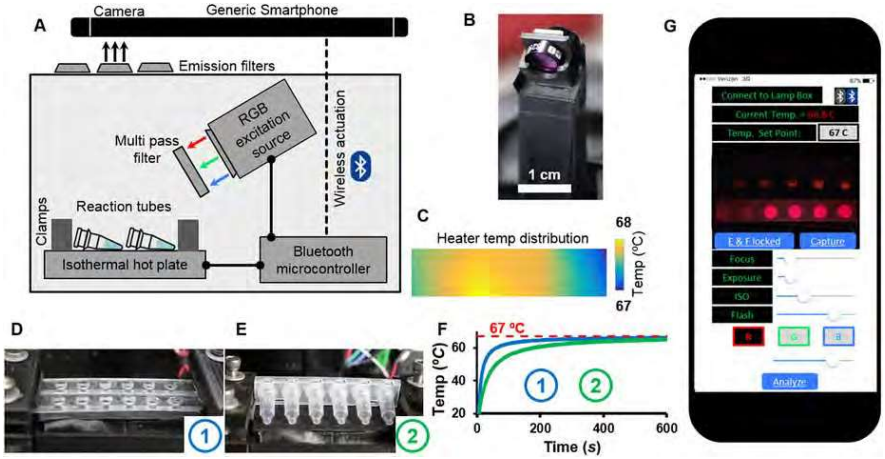
VS



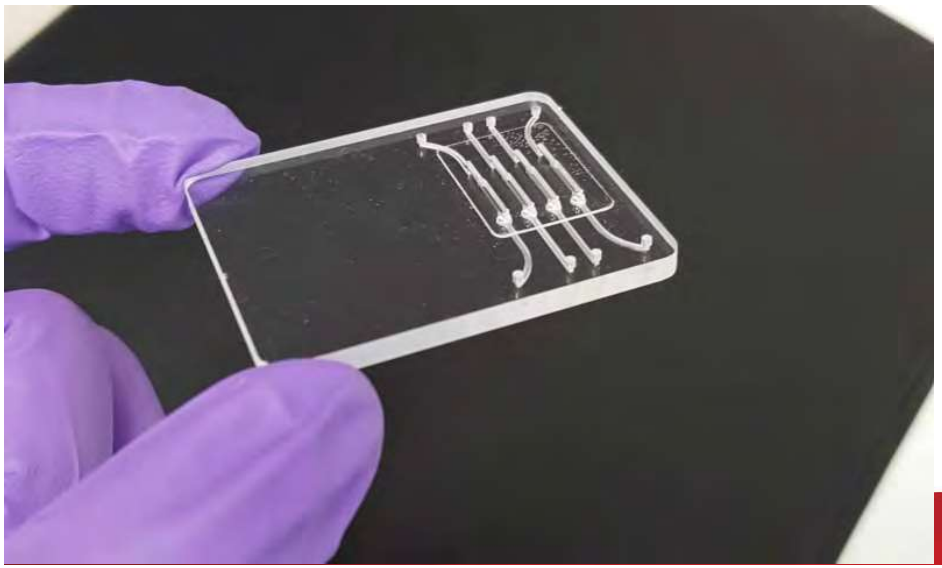
Novel **Point of Care** Molecular Detection Platforms for ZIKA, etc. :

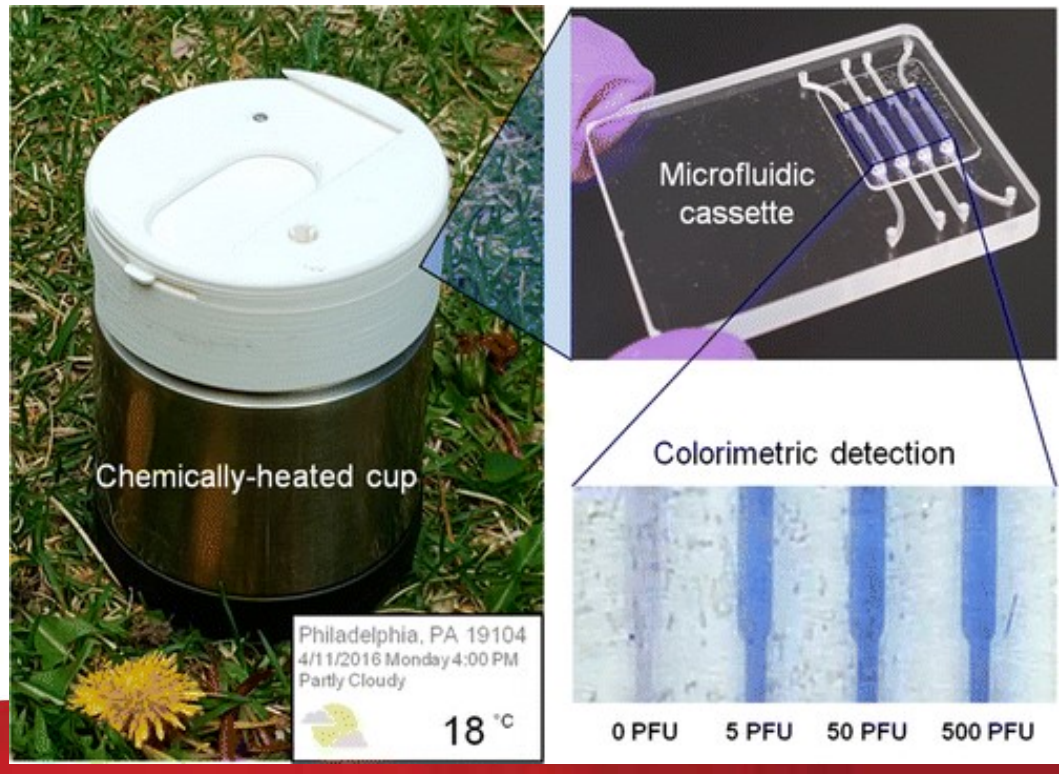
Multi-Plex **RT – LAMP** based procedures being developed with SmartPhone monitoring / recording capabilities

Tubes, Reaction Wells and Microfluidic Cassette Variations (Saliva, Blood and Urine matrices).

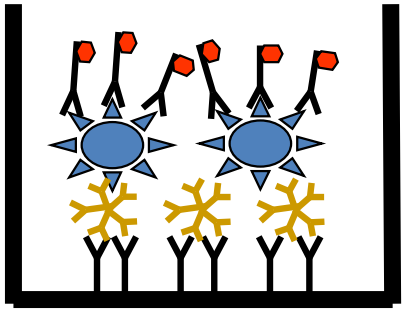


Priye A et al 2017
Song J et al 2016



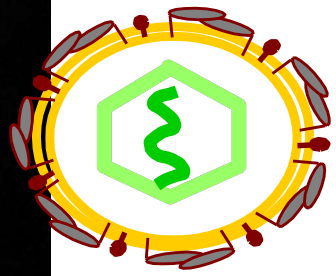


Additional Zika Research

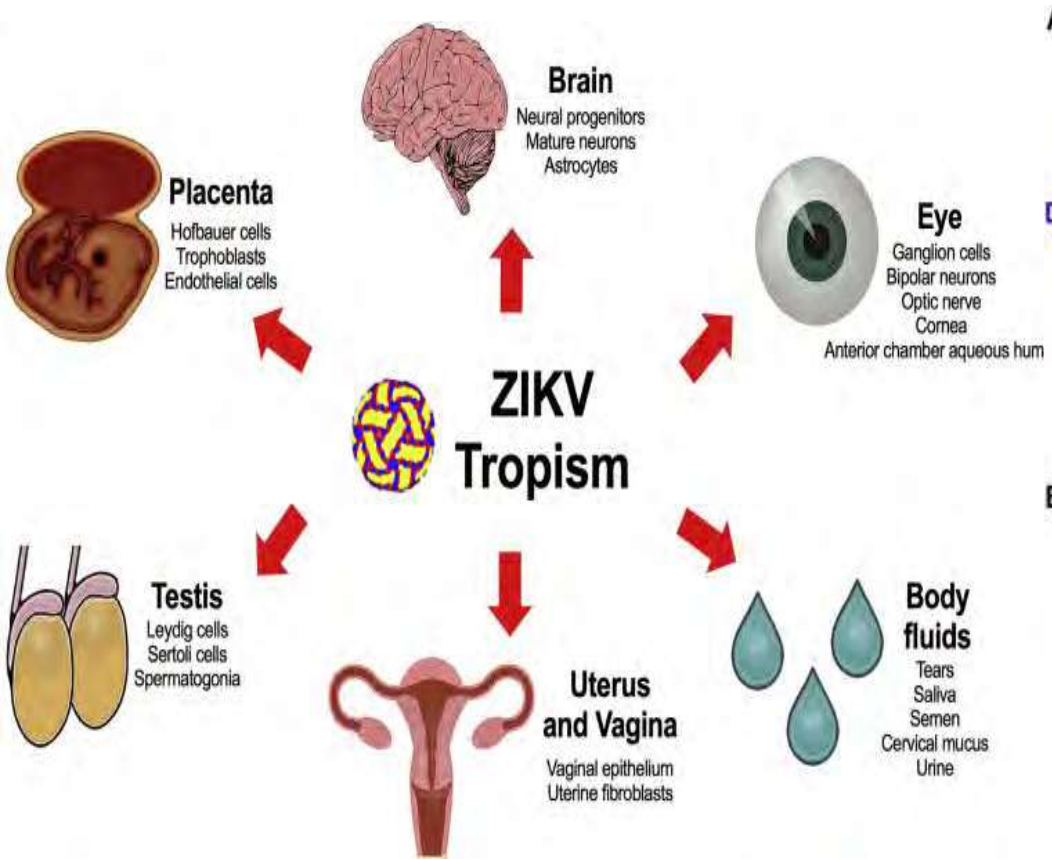


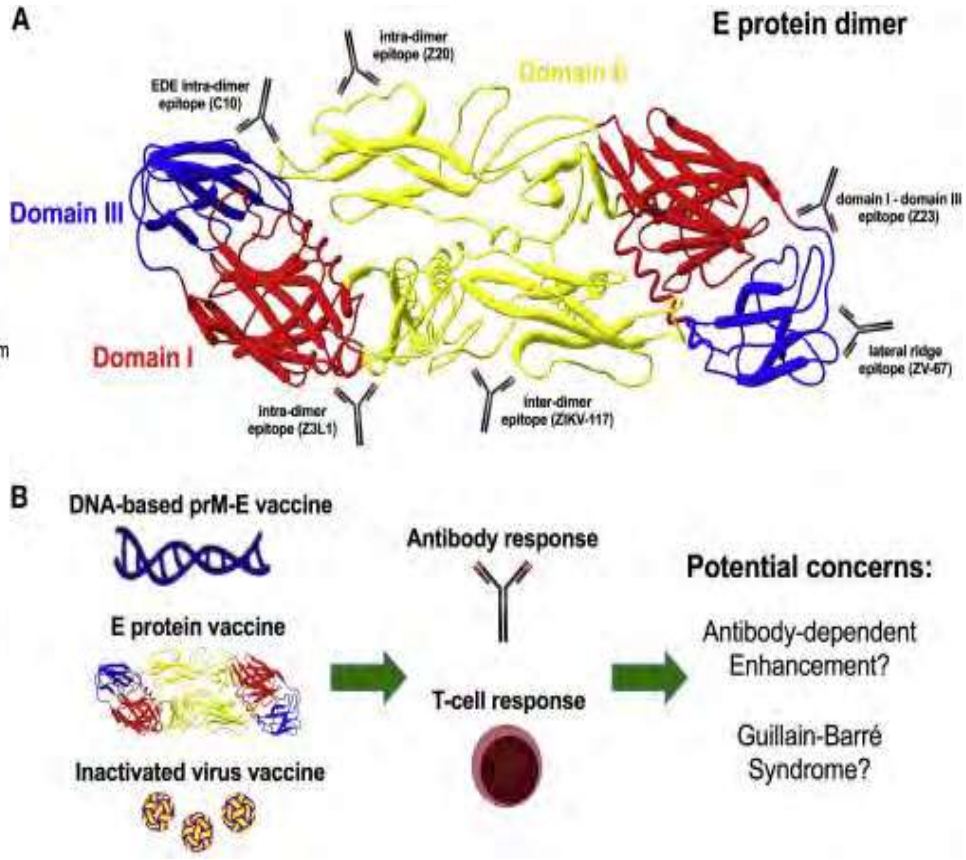
Commercial ELISA, etc. kit evaluations, ---

Models for Pathogenesis, Therapeutics – Vaccines, Studies on Vector Competence, Mosquito Surveillance.



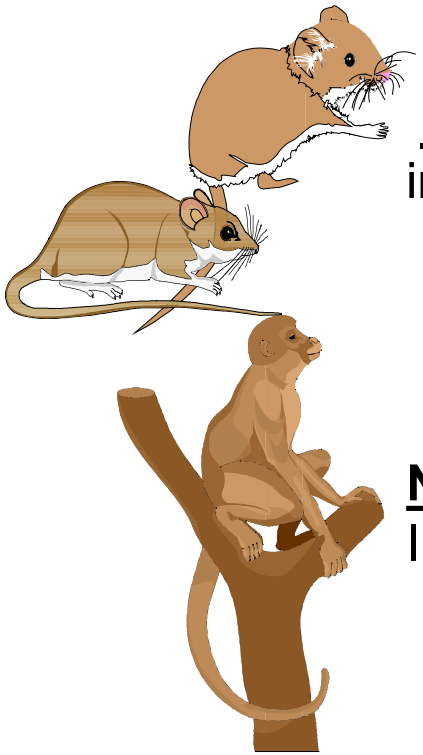
Zika Virus Tissue Tropism and Vaccine Considerations: Research Models and Experimentation





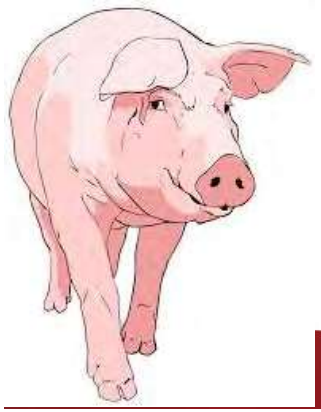
From Diamond, 2017

Animal Models Are Essential For Determining Factors Associated With **ZIKV Virulence (Fetal, GB, etc.)**, Mechanisms of **Virus-Host Interaction**, and Provide Framework For **Design & Efficacy Testing of Therapeutics and Vaccines**



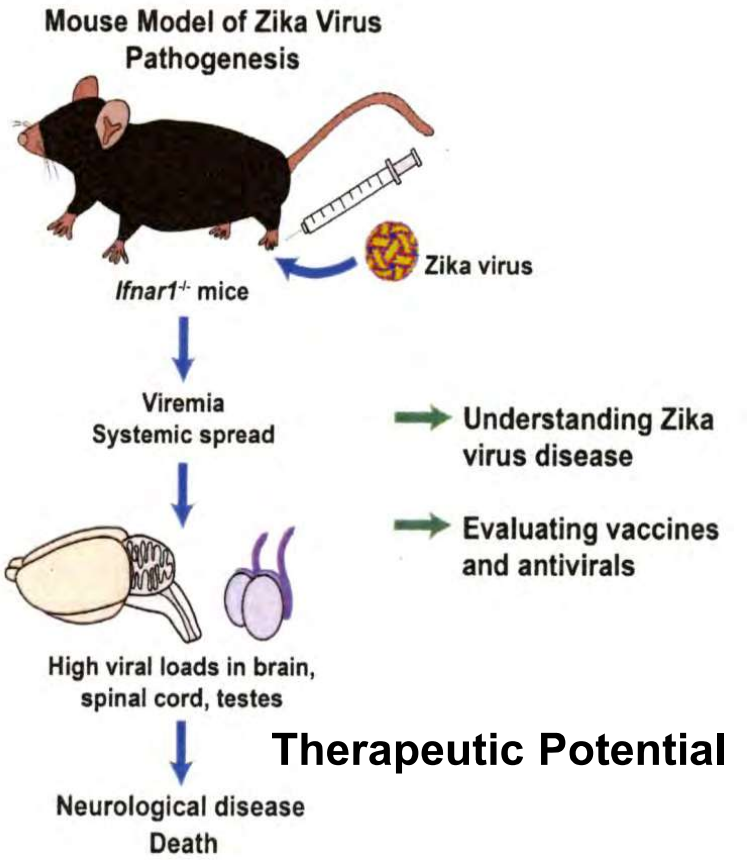
MICE --- Various types of immunocompromised mice available including those lacking interferon genes or receptors -- ZIKV strains

Non-Human Primates --- eg. Rhesus – Cynomolgus Macaques Infected with Asian – lineage / outbreak ZIKV strains



Pig Models --- viremia, organ infection immune responses, placental piglet transmission, potential reservoir ?
Darbellay et al. 2016

Current Mouse Model Research Findings: (NML carrying out similar research, manus in prep)

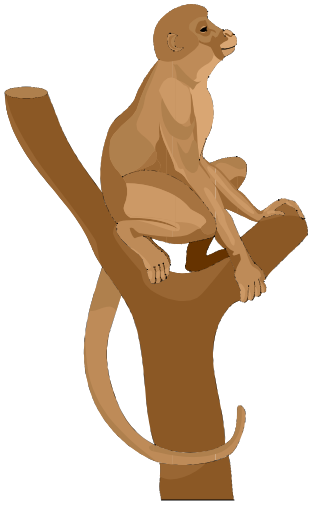


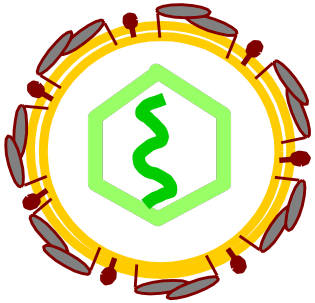
Lazear et al 2016 --- Infected Ifnr1 mice had high viral loads in brain, spinal cord and testes.

Govero et al 2016 --- used mouse adapted ZIKV to compare infection and pathology with Dengue

- Persistence in testes with ZIKV not Dengue
- Diminished testosterone and oligospermia, cell death and destruction of seminiferous tubules

Sapparapu et al 2016 --- mAbs against ZIKV E protein reduced tissue, plaental and fetal infection & mortality





NHP Models

Dudley et al 2016 --- rhesus macaques susceptible to Asian Lineage ZIKV present in saliva, urine, and CSF. Non-pregnant animals remain viremic 21 days, Pregnant 57 days ! Rechallenge – no viral replicatior

(**NML co- authors**) **Osuna et al 2016** --- rhesus and cynomolgus macaques infected with similar results but also detected in brain, semen and vaginal secretions.

Vaccines Being Developed / Initial Phase 1, 2 Trials

1. Two DNA vaccine candidates (Inovio, NIH) - Phase 1 trials, Phase 2 initiated

2. Inactivated virus vaccines (Walter Reed Army Research Institute)

3. Live attenuated vaccine platforms using chimeric flavivirus formats (pre M-E)
-- Combined Dengue and Zika LAV formulations may provide utility
(Laboratory of Infectious Diseases, NIAID)

4. Attenuated weakened live virus (NIH)

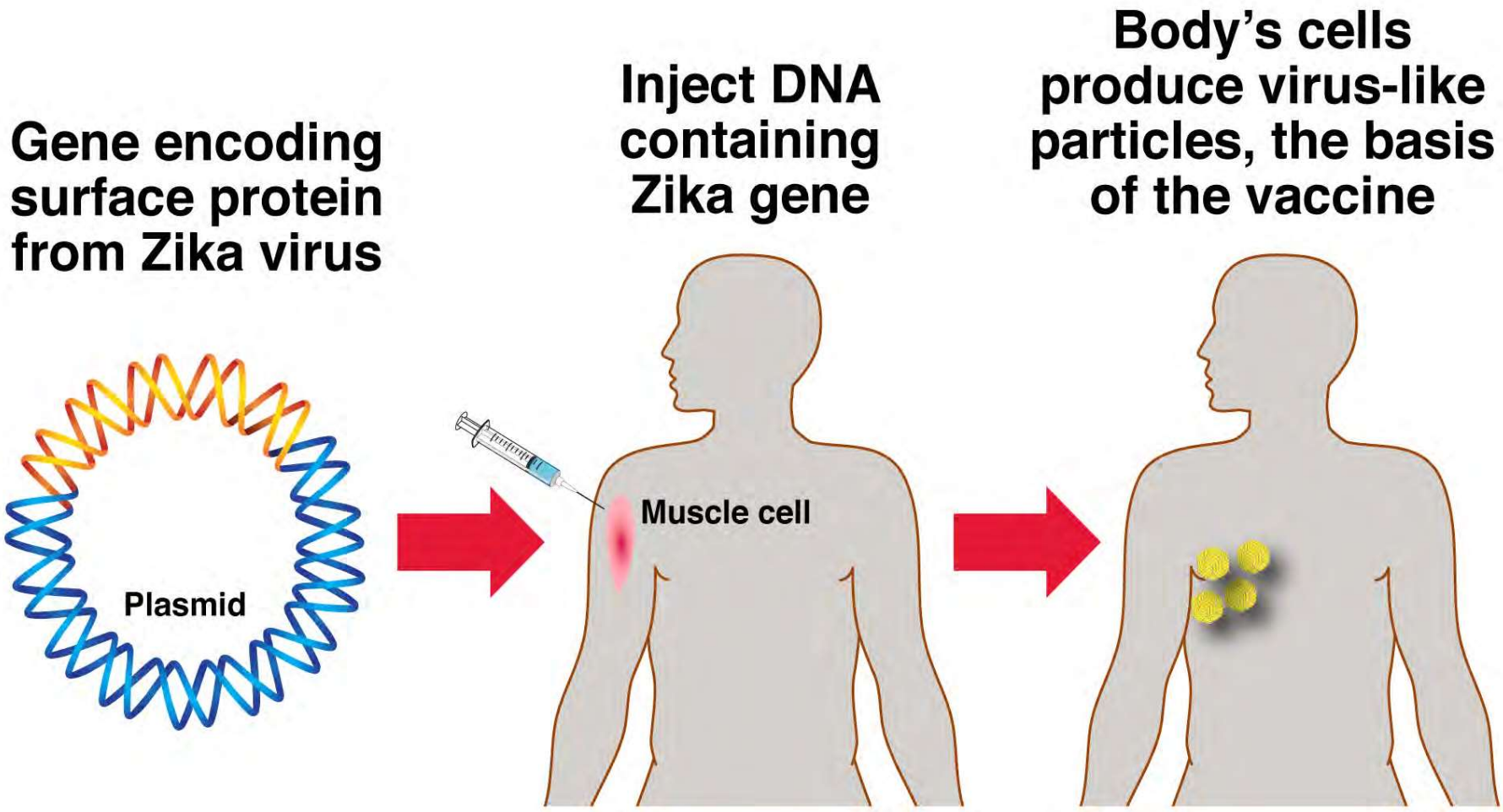
Possible Factors/Concerns Effecting Vaccine Development and Application:

---- "Antigenic Sin"– Pre-existing flavi antibody decreases initial ZIKV immune response

--- Antibody Dependent Enhancement

Zika antibody enhances flavi infection

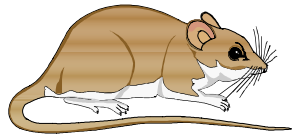
DNA Vaccine Approach



DNA Vaccine Utilized To Protect Against ZIKV Testes Damage in Mice (Griffin BD et al 2017)

Antibody and Monoclonal / Polyclonal Based Therapeutics:

--- Neutralizing human antibodies to ZIKV replication and maternal-fetal transmission & disease in mice (Sapparapu et al 2016, Nature)



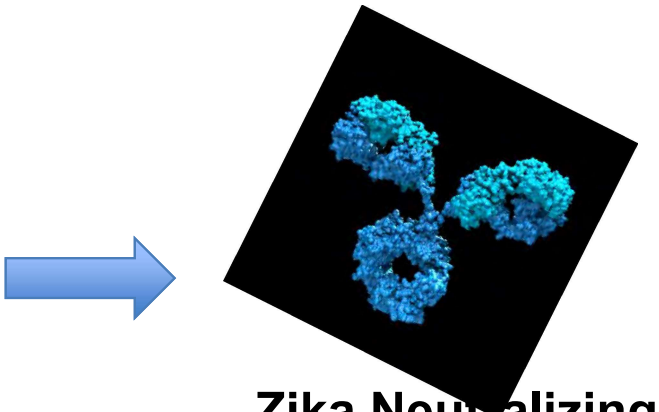
Broadly reactive mAb panel from subjects previously infected, cloned hybidomas , possible therapeutic and vaccine design insights

Genetic Engineering of Bovines For Generating Therapeutic Antibodies

Tranchromosomal Cows:
- > 30 litres of conc ab
- SAB Biotherapeutics

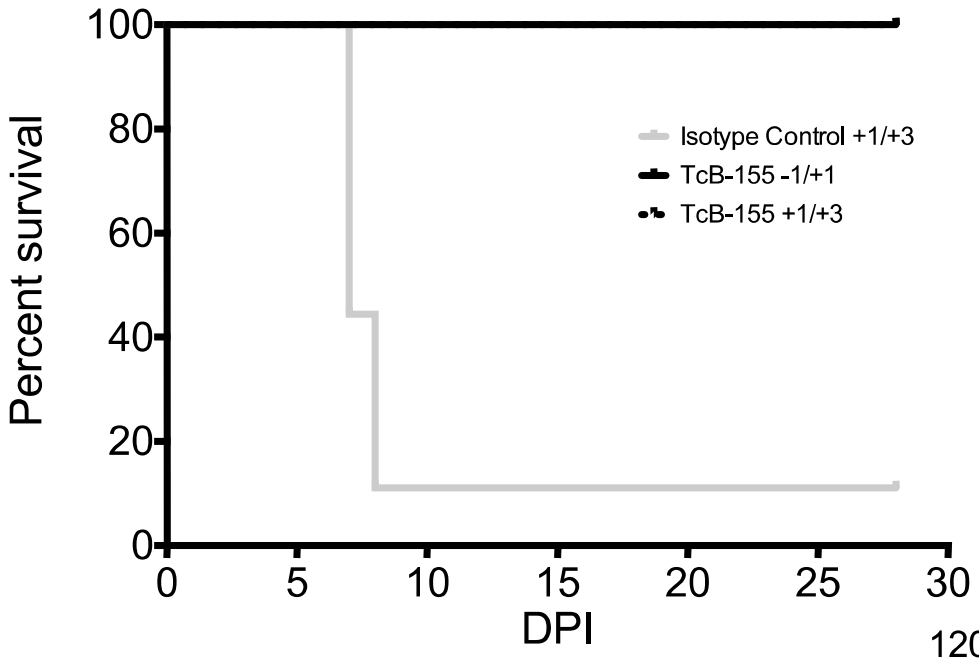
Trans-Chromosomal Bovine Antibodies

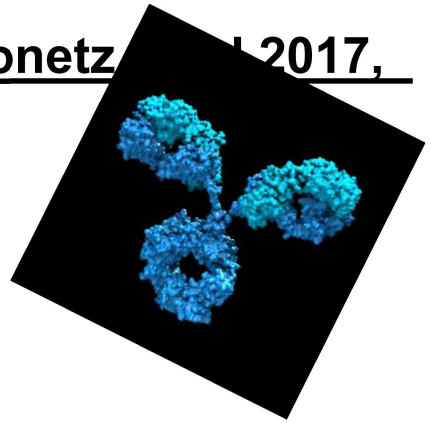
- Ideal for rapid large scale production
- SAB Biotherapeutics has developed humanized cattle
- The bovine immunoglobulin genes have been knocked out and replace with fully human germ line antibody sequences
- Allows for hyper-immunization, and production of fully human polyclonal antibody to emerging pathogens.



Zika Neutralizing Polyclonal Antibody

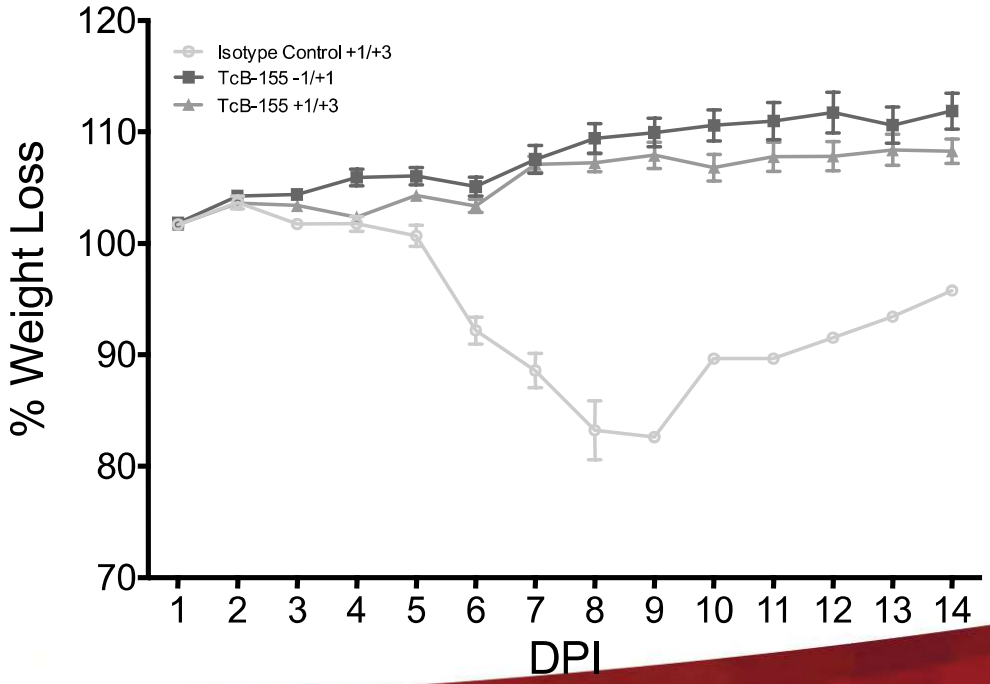
Transchrom Bovine Ab Results in Mouse Model, Stein, Safronetz 2017,





100% Protection 1 Day Post Infection from lethal Zika infection in IFN$^{-/-}$ mice, reduced Viremia, No virus detected in brain, testes etc. after bovine ZIKA polyclonal Ab dose

Significant weight loss in Isotype control treated mice



Persistence of ZIKV in Seminal Fluid

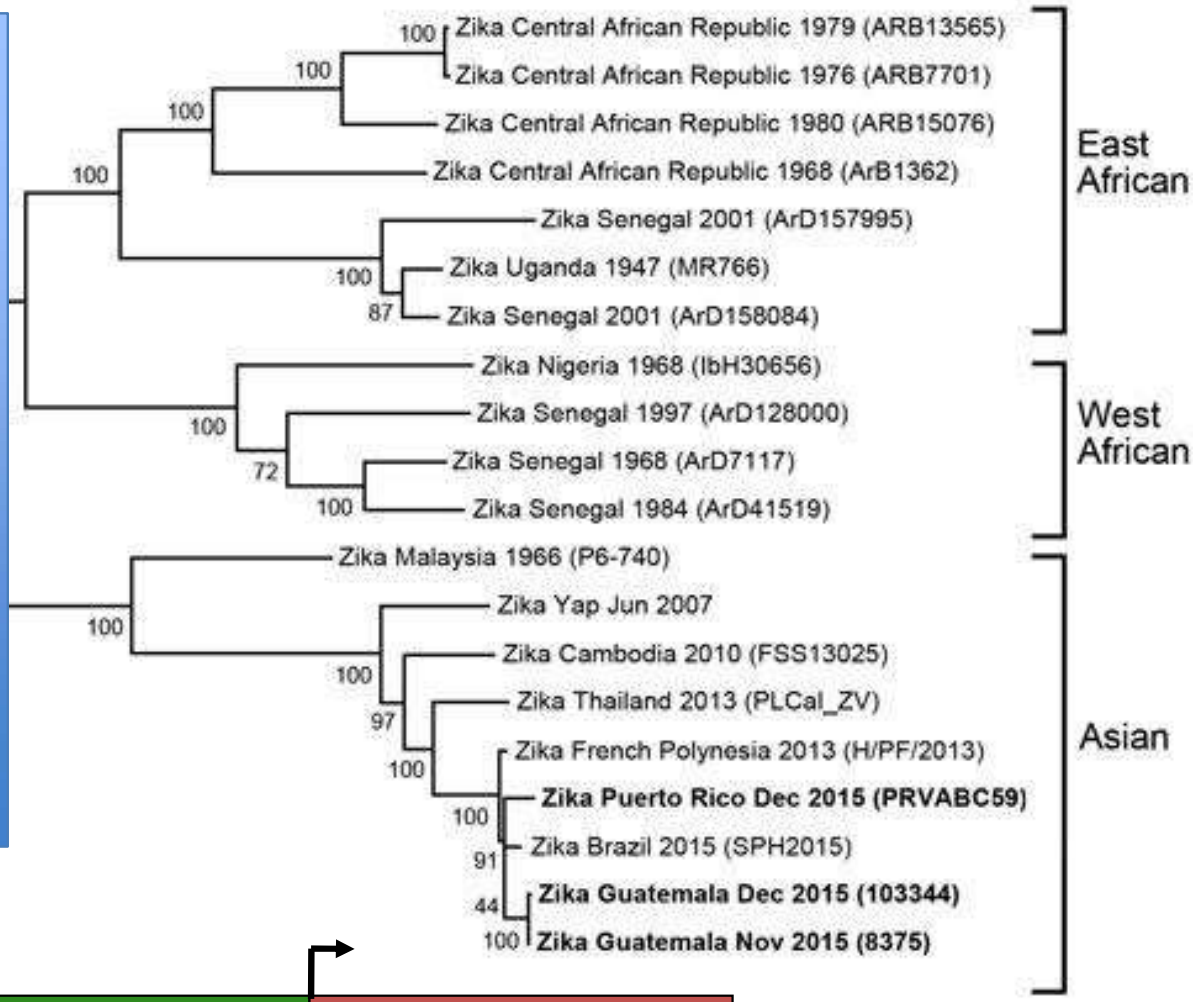
- CDC preliminary studies (CDC-PR, 2017) –
- Significant but limited lingering of virus, **majority of infections** result in 1-**3** month semen persistence.
- However there is evidence of 6 month persistence in rare cases which has guided current public health recommendations.
- UK Study (EID publication) with similar results ---

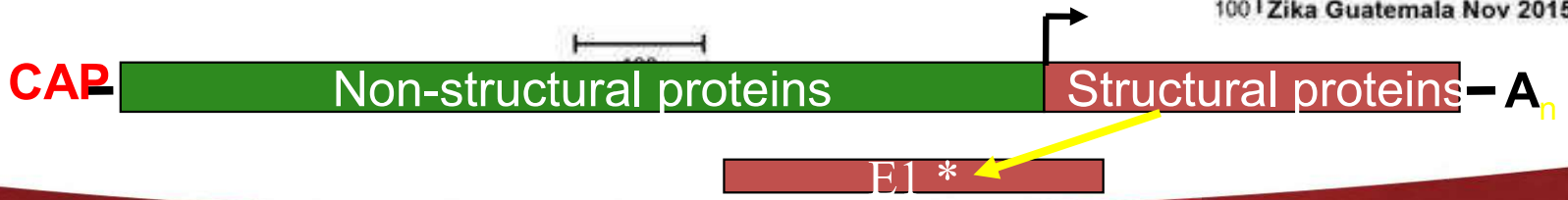
Arbovirus Mutation / Evolution Can Lead To Increased Transmission, Expansion, etc.

West Nile Virus 1999 – 2002 Genotypic Changes Led to Increased Transmission & Adaption

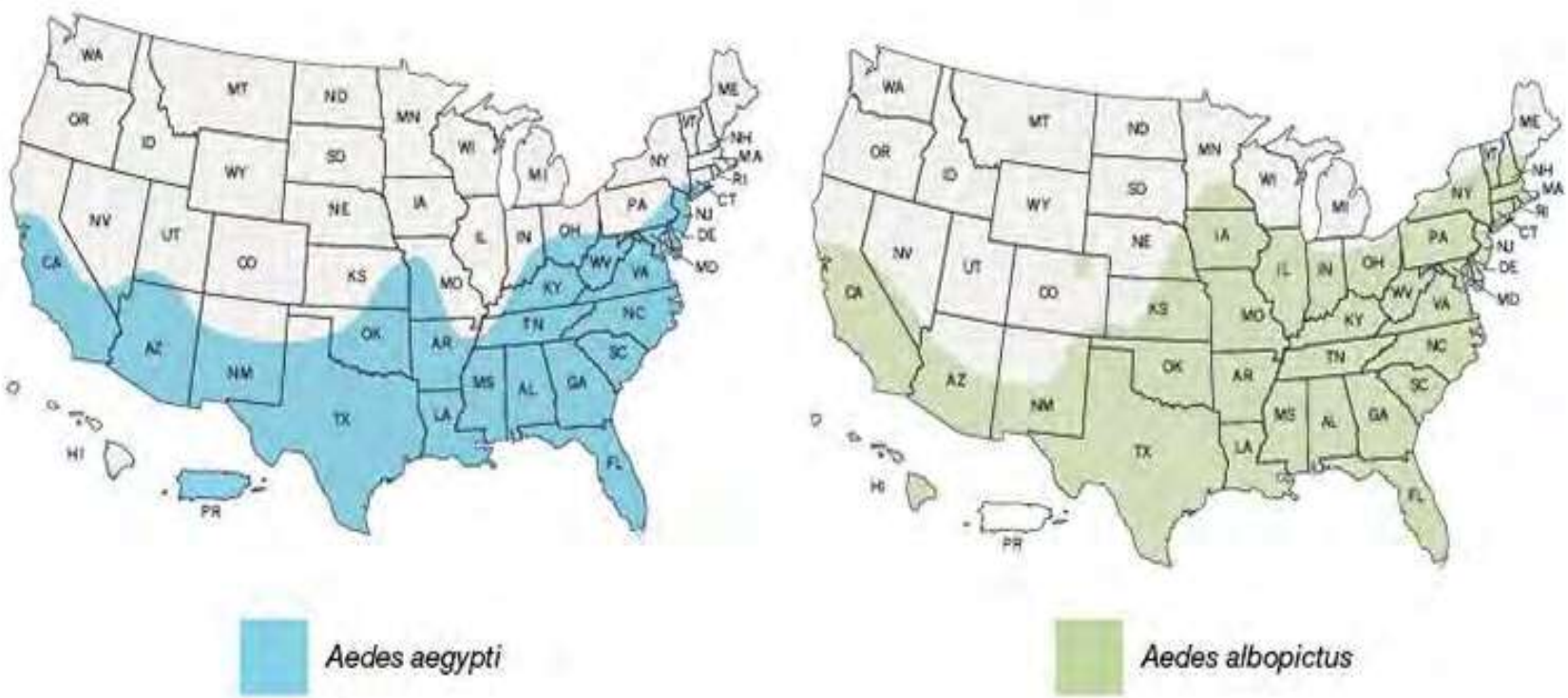
Chikungunya E protein mutation (s) Increased viral transmission by *Aedes. Albopictus*

(*Albopictus* is found in more northerly regions than *Aedes aegypti* (Eg. Europe, North East US, Canada ?)



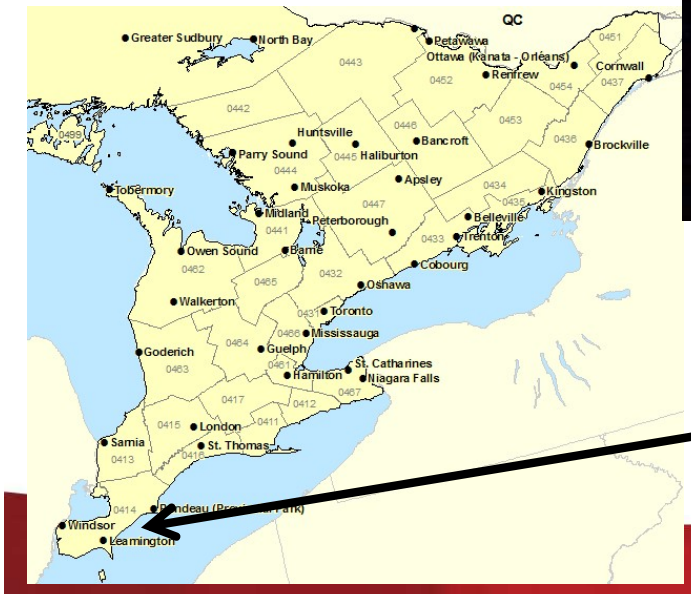


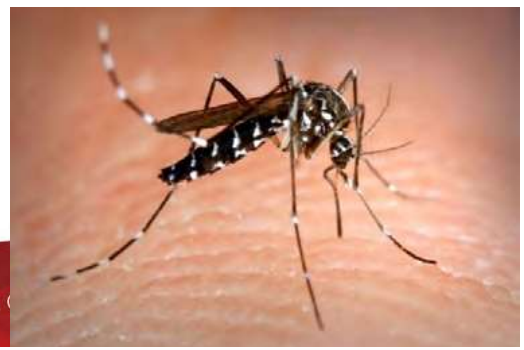
Distribution of Primary ZIKV Vectors in USA – Expansion to Canada ?



Possible adaption of vectors to different climates, and/or viral adaption to "new" mosquitoes ?

Surveillance for *Aedes Aegypti* and *Aedes Albopictus* In Canada
Mosquitoes found in Windsor, Ontario in 2016 !
Risk for Establishment is low, however, continual monitoring is warranted.

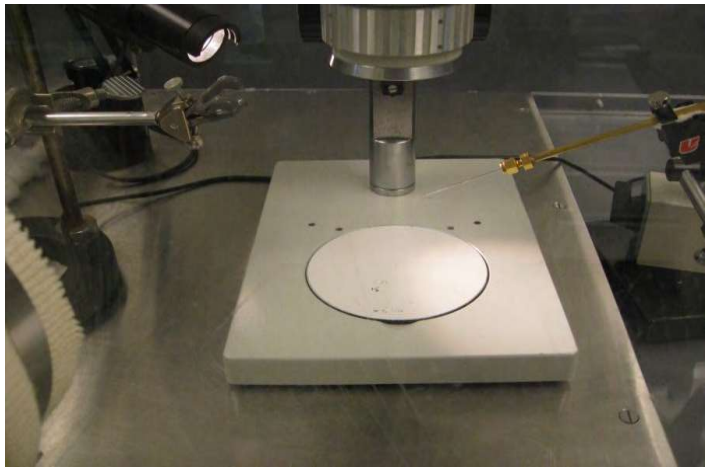




Vector Competence Studies on Canadian Mosquitos (*Aedes vexans, etc*) Lindsay et al.

Oral infection

Infection through needle inoculation



Collection of saliva to assess transmission ?!

Orally Infected Mosquitoes with Two Strains of ZIKV, Winnipeg, MB, Summer 2016

Species	Number tested	No. infected (% infected)	No. disseminated (% dissem.)	Min. No Saliva Pos. (%)
Ae. vexans	131	4 (3.2)	2 (1.5)	2* (1.5)
Oc. euedes	7	1 (14.3)	0	0
Oc. fitchii	10	0	0	0
Oc. sticticus	29	0	0	0
Cx. tarsalis	11	0	0	0
Cq. perturbans	43	0	0	0

** Live ZIKV isolated from these saliva samples*

Conclusions on Canadian Vector Competence For ZIKV, Lindsay R et al

- To-date, mosquitoes from southern Manitoba have demonstrated poor competence as vectors for ZIKV
- ZIKV multiplied in the bodies of many of the species that were inoculated
- Small numbers of *Ae. vexans* successfully transmitted ZIKV under laboratory conditions
- There was no significant difference in rates of transmission between the two strains of ZIKV
- Further studies are required to determine whether climatic conditions in Canada are permissive for local transmission of ZIKV

Vector control strategies for Zika virus and other arboviruses

Main components include:

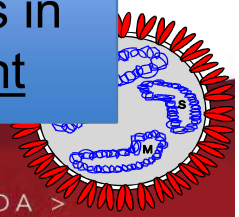
1. Entomological surveillance
2. Vector control options
   - Measures targeting aquatic stages
   - Measures targeting adult mosquitoes
3. Personal protective measures

Other Mosquito Pathogens

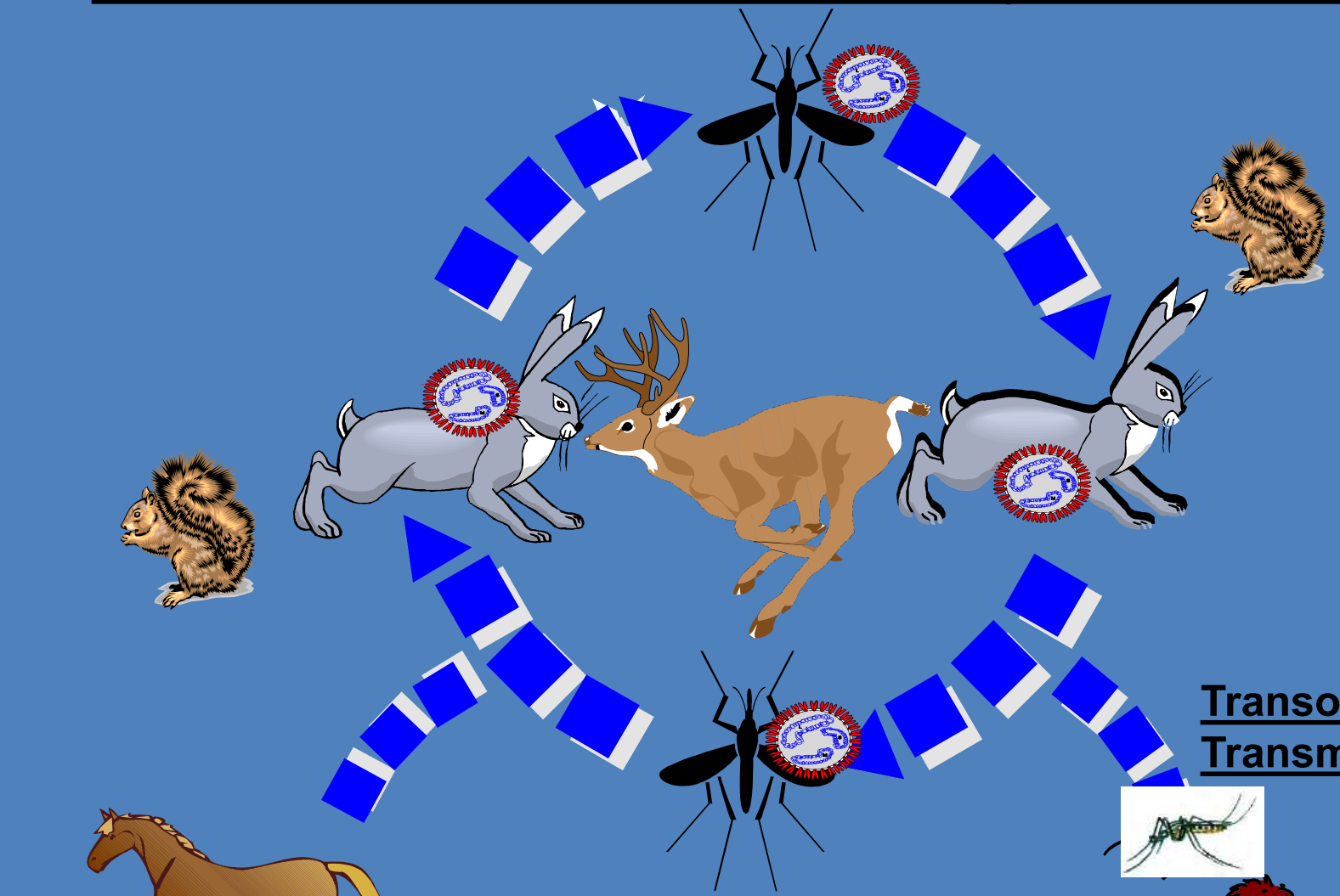
Mosquito Transmitted Arboviruses Isolated in Canada

Virus	Antigenic group	Disease in humans/animals
Eastern equine encephalitis	Alphavirus	+ humans, + animals
Western equine encephalitis	Alphavirus	+ humans, + animals
St. Louis encephalitis	Flavivirus	+ humans, - animals
West Nile	Flavivirus	+ humans, + animals
California encephalitis	California-Bunya	+ humans, - animals
Snowshoe hare (SSH)	California-Bunya	+ humans, + animals
Jamestown Canyon	California-Bunya	+ humans, + animals
Trivittatus	California-Bunya	- humans, - animals

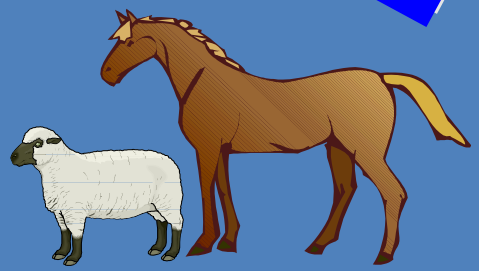
Seasonal trends are key: Most infections occur late in the summer when virus levels are peaking
However, some arbos such as California serogroup cause infections in late spring – should be part of differential when mosquitoes present



Bunyaviruses -- California Serogroup (Jamestown Canyon and Snowshoe Hare virus Transmission Cycles (Canada wide !)



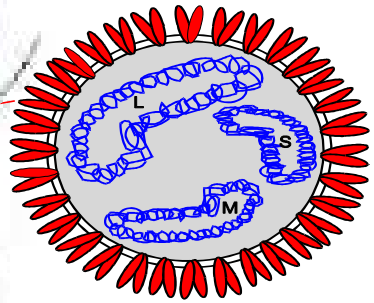
Transovarial Transmission



Incidental hosts
Febrile and Neurological Disease

Snowshoe hare virus (SSHV), Jamestown Canyon Virus (JCV)

CSG Neurological/Encephalitic Cases With Detailed Clinical Information And Complete Diagnostic Confirmation



Yukon

Northwest Territories

Nunavut

British Columbia

Alberta

Saskatchewan

Manitoba

HUDSON BAY

Ontario

Quebec

Newfoundland and Labrador

Prince

Nova Scotia

New Brunsw

2008-2015
>200 Probable Cases of JC & SSH

MB 2011 SSH Case

BC & AB 2011-13 cases Confirmed JC encephalitis

Montana JC Case May 2009

QC 2011 & 2014 cases of confirmed JC virus Encephalitis

NS 2006 & 2014 Confirmed cases SSH & JC virus Encephalitis

JC

PUBLIC HEALTH AGE

Case History (Webster D et al 2017):

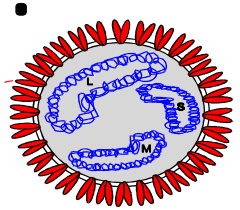
On July 23, 2015 a 73 year old male from Grand Manan Island, New Brunswick developed symptoms of fatigue, nausea, fever.

Several days later febrile illness progressed to delirium and increasing confusion- encephalitis
Condition further declined – post encephalitic dementia in Jan

Herpes, Bartonella, Borrelia. Anaplasma, Coxiella etc. negative (frequent outdoor activities)
Case for "VZ Swap Team, & Dr. Duncan Webster"

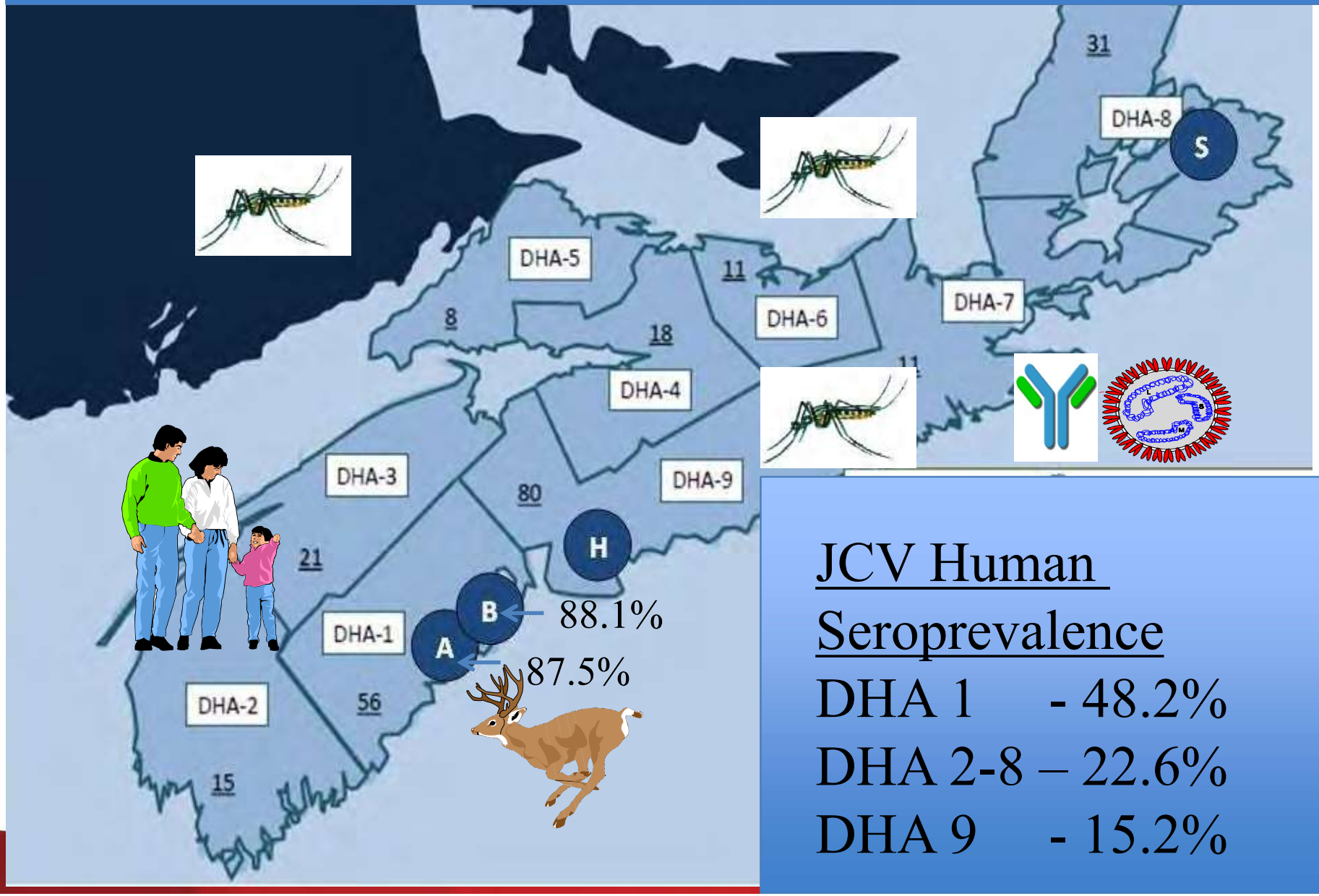
Mosquito-borne disease threats: Atlantic Canada



- Sporadic activity limited to enzootic cycles of transmission of
  - **West Nile virus** (infected birds, horses in early 2000's, no humans)
  - **Eastern equine encephalitis virus** (horses, no human cases)
- Greater seasonal exposure to other arboviruses like **Snowshoe hare virus (SSH), Jamestown canyon virus (JCV)** and other California serogroup viruses
  - Wide range of vectors, high infection prevalence and typically high rates of human exposure, most infections asymptomatic or only mild course of disease but neuroinvasive cases do occur

JCV Serosurvey of NS residents and deer
(Patriquin G, Drebot M, .. Hatchette T et al. 2017

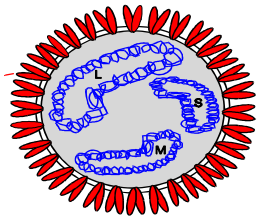


JCV Human Seroprevalence

DHA 1 - 48.2%

DHA 2-8 – 22.6%

DHA 9 - 15.2%



Acute Serum Sample Tested For CSG (JCV & SSH) IgM:
ELISA negative - equiv

However PRNT – IgG positive!

2nd serum sample IgM equivocal

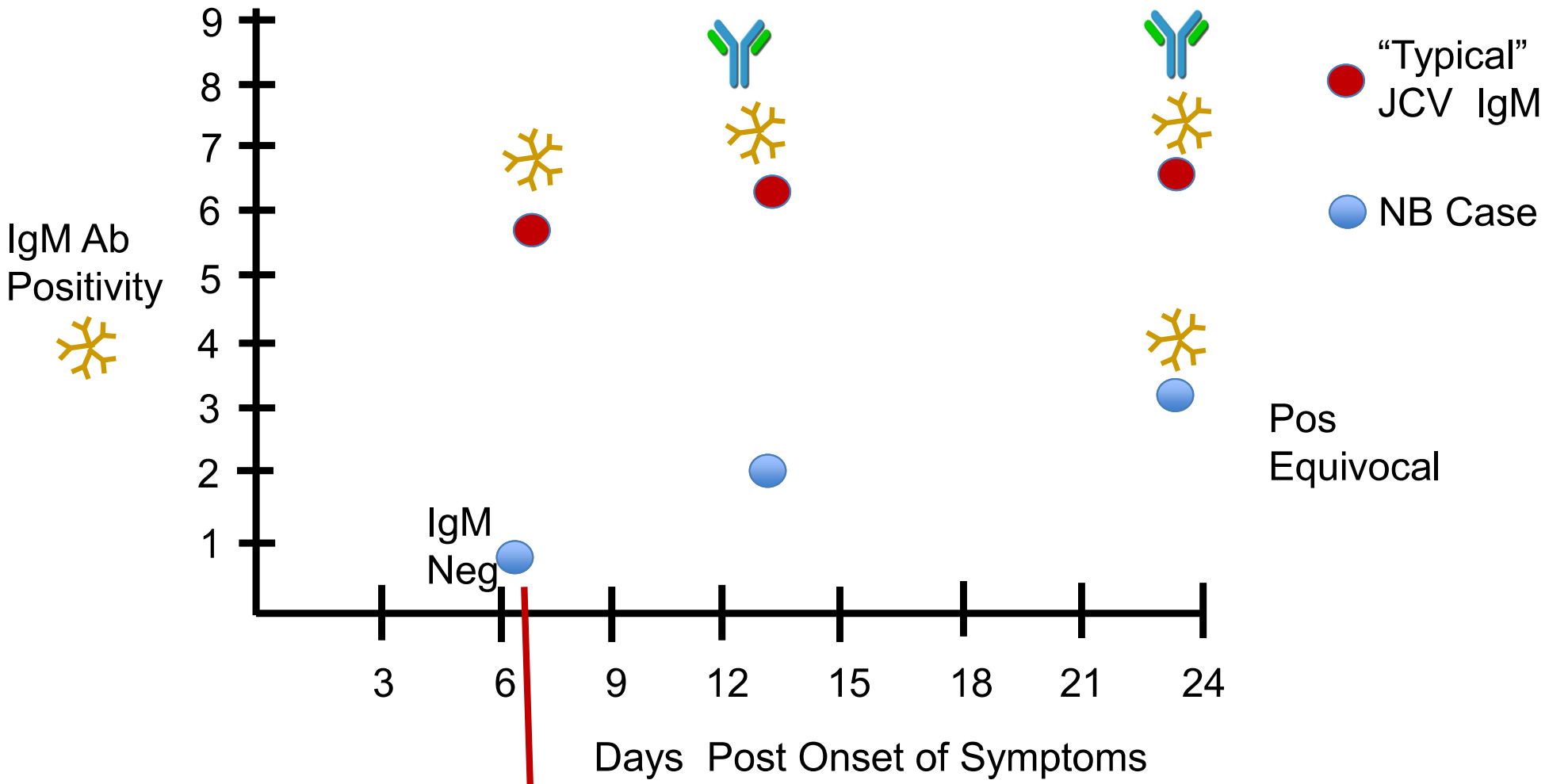
Diagnostic 4 fold rise in neut IgG

4 weeks PO IgM pos!, neut IgG +

Impaired IgM induction, high neut / IgG titres to 2 CSGs

Secondary CSG Exposures & Antigenic Sin !?

IgM Dynamics of CSG Case NB Native, Sepsis Case in MN, WNV case



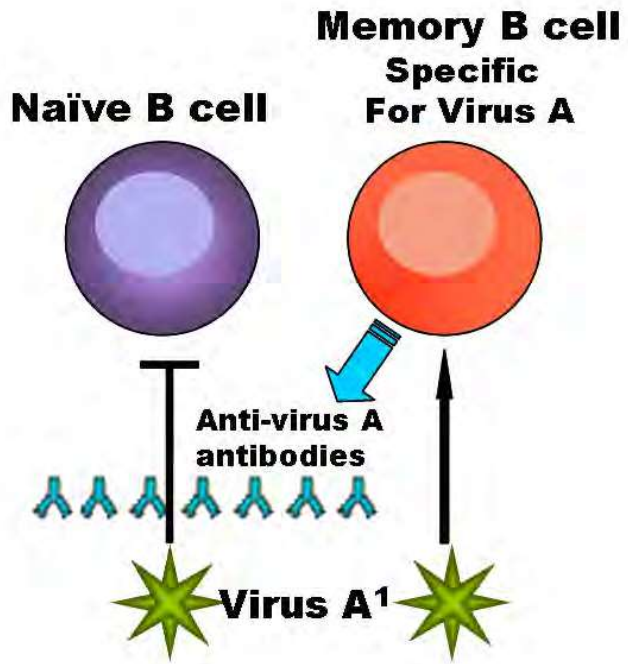
NB Case

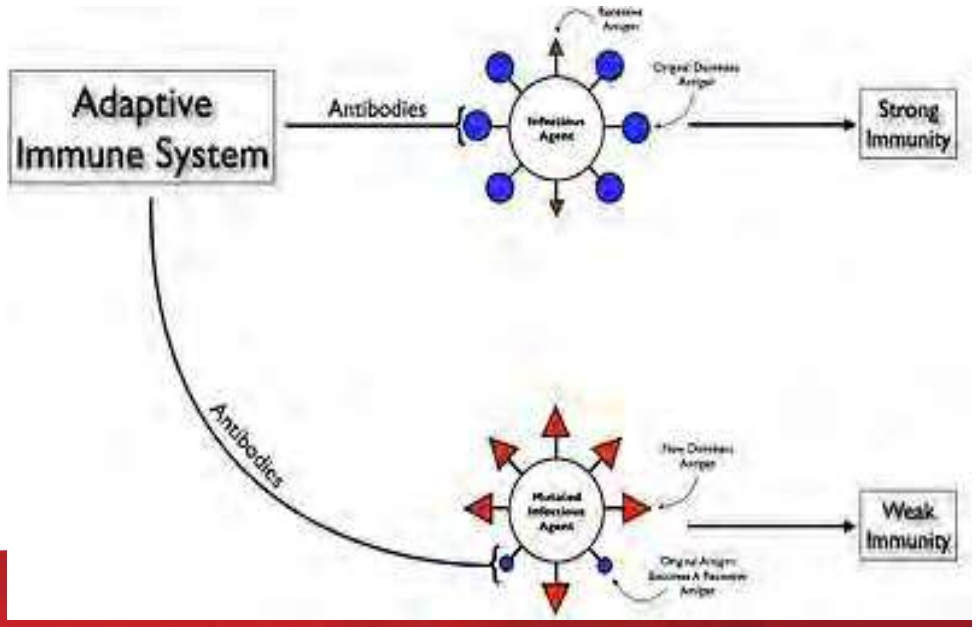
JCV IgG / Neut titres	40!	160	320!	IgG / Neut
SSH IgG / Neut titres	20!	320	320!	

IgM production delay and Original Antigenic Sin as seen in Dengue & Zika flaviviruses.

When similar virus co circulate at high levels previous exposures or co infections can occur that may confound serological test Interpretations
(**Previous Canadian serosurveys indicated 9-10% previous Den exposures**)

May also cause issues involving Increased Disease Severity and reduced Vaccine efficacy !





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West Nile	Flavivirus	+ humans, + animals
California encephalitis	California-Bunya	+ humans, - animals
Snowshoe hare (SSH)	California-Bunya	+ humans, + animals
Jamestown Canyon	California-Bunya	+ humans, + animals
Trivittatus	California-Bunya	- humans, - animals
Cache Valley	Bunyamwera	+ humans, + animals
Northway	Bunyamwera	- humans, - animals
Turlock		- humans, - animals

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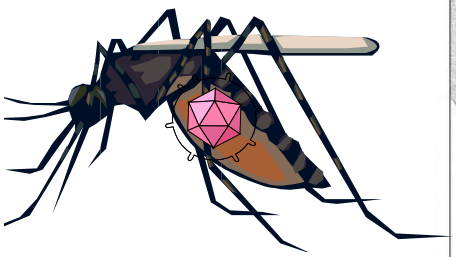
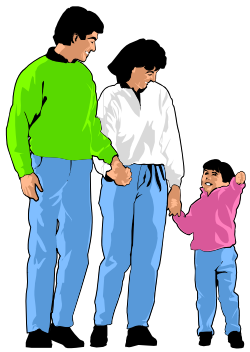
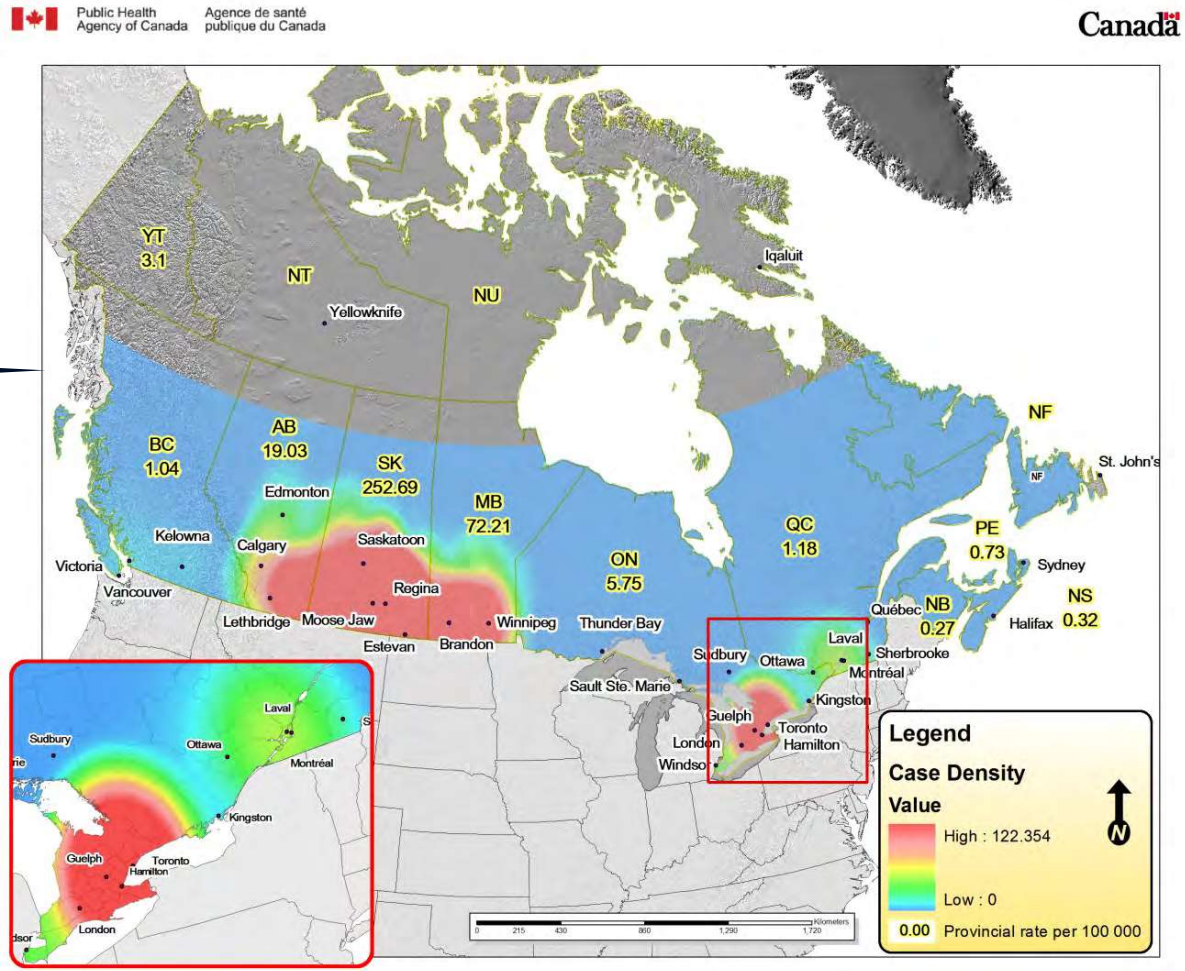
West Nile Virus continues to be our most important domestic arbovirus in Canada, North America

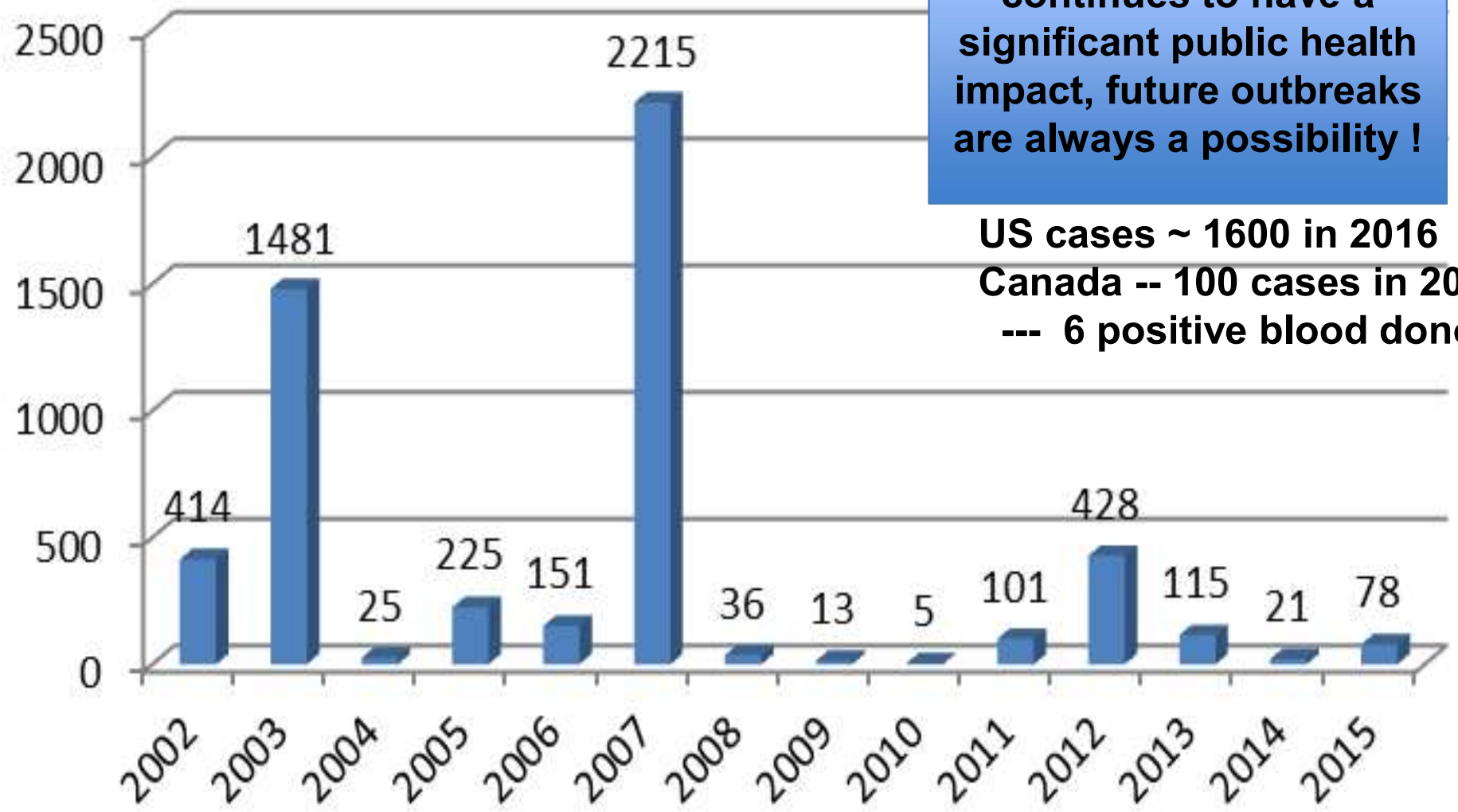
Average Case Density Value per 100,000 population of West Nile virus disease , by provinces and territories in Canada: 2002-2013







No. of WNV human cases: 2002-15



West Nile virus continues to have a significant public health impact, future outbreaks are always a possibility !

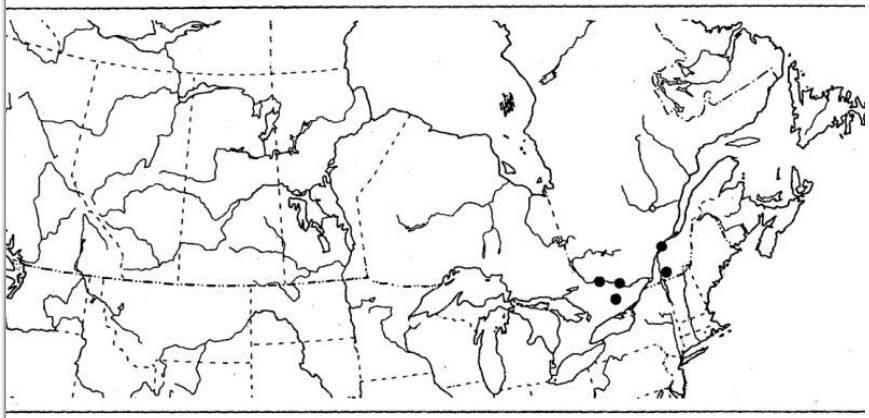
US cases ~ 1600 in 2016
Canada -- 100 cases in 2016
--- 6 positive blood donors

Culiseta melanura distribution and Eastern Equine Encephalitis Virus

First Non-Imported Case in Canada September, 2016 !!

13 year old, Encephalitis case, Ont high titres in serum, PRNT pos CSF

Prior to 2016 livestock cases (horses, emu) but no human cases in Canada



Collection localities for *Culiseta melanura* in Canada: • specimens

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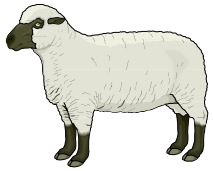
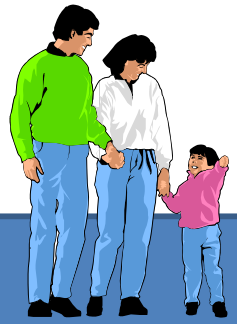
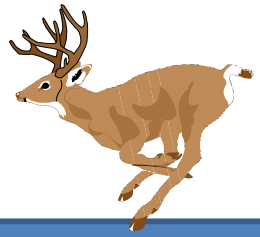

Vector - borne / mosquito borne zoonotic diseases continue to be of importance as public health issues for both travelling and non-travelling Canadians.

Mosquito associated pathogens continue to emerge and increase in frequency both in Canada and Internationally and need to part of physicians / health care provider's differential.

National and Global Partnerships Using a "One Health" Approach Are Key For Identifying, Monitoring and Characterizing These Pathogens and Assessing The Risk for Both Preparedness & Response

Questions ?