Emerging and endemic arboviruses: Challenges for laboratory surveillance

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Organización Mundial de la Salud
Américas

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Emerging diseases

Microbial Threats to Health in the United States

1992, Instituto de Medicina (USA)
(*Joshua Lederberg & Robert Shope*)

- ***Emerging diseases:***
  new diseases / new pathogens (or new strains) / expansion to new territories

- ***Re-emerging diseases:***
  diseases previously “under control” but re-appear increasing the incidence

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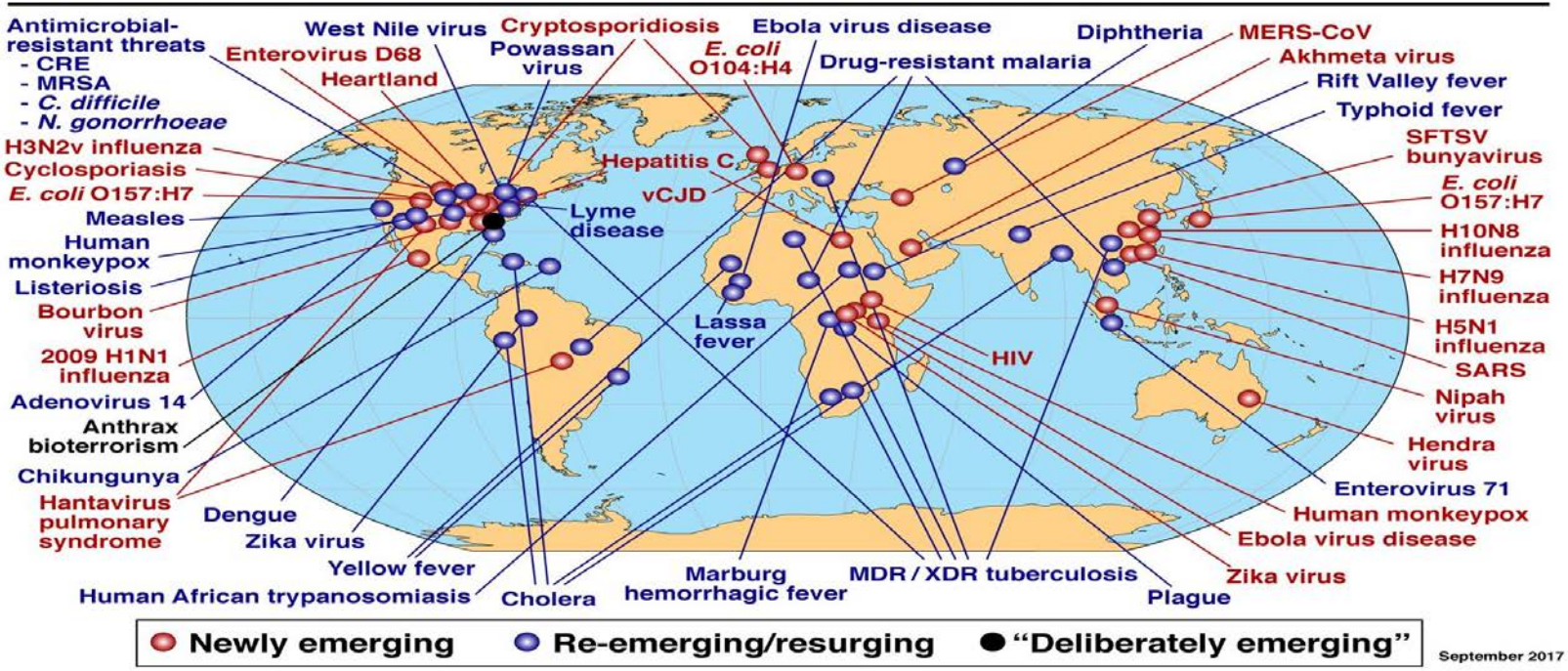
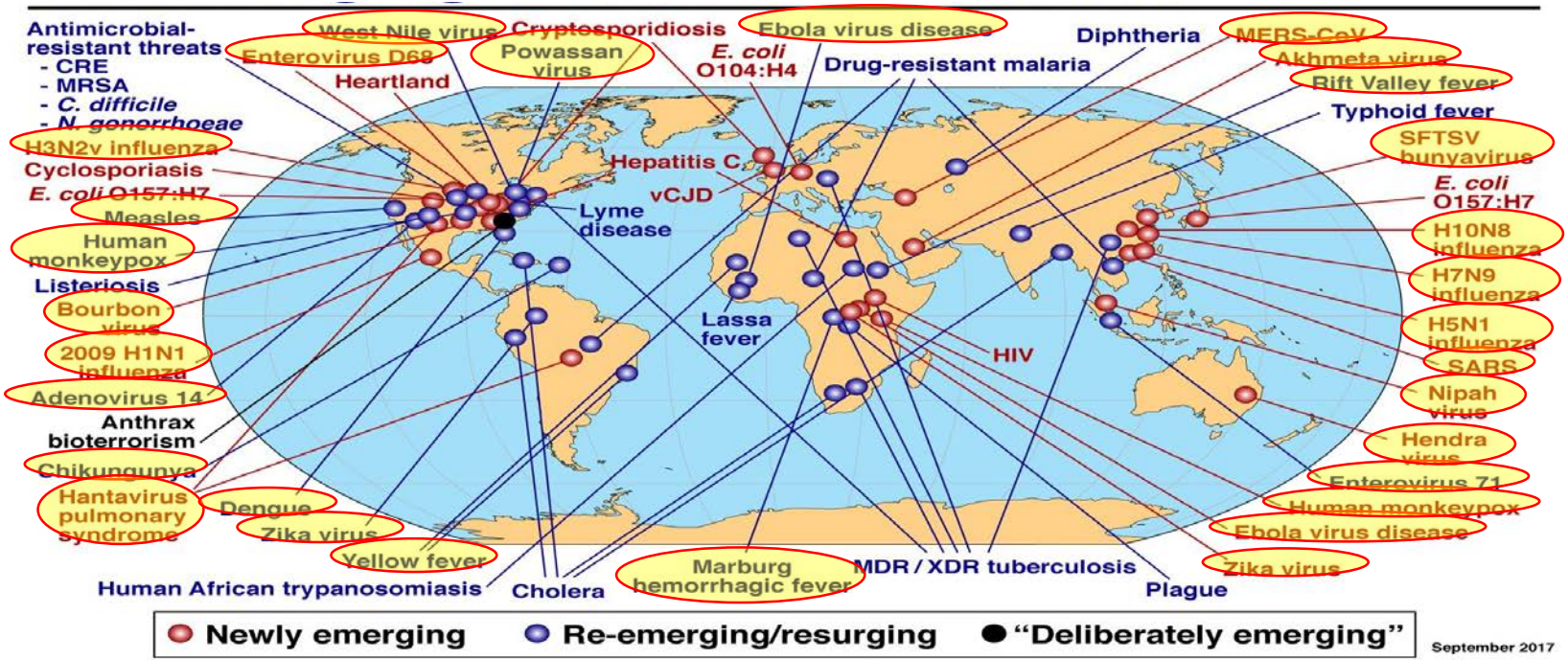
Emerging & re-emerging diseases, 1996-2017



Fonte: NIAID/NIH https://www.niaid.nih.gov/news-events/three-decades-responding-infectious-disease-outbreaks

Emerging & re-emerging diseases, 1996-2017



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Emerging Arboviruses

Pan American Health Organization
World Health Organization
Americas

Epidemiological Alert

Zika virus infection

7 May 2015

The Pan American Health Organization (PAHO) / World Health Organization (WHO) recommends its Member States establish and maintain the capacity for Zika virus infection detection, clinical management and an effective public communication strategy to reduce the presence of the mosquito that transmits this disease, particularly in areas where the vector is present.

Pan American Health Organization
World Health Organization
Americas

Epidemiological Alert

Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas

1 December 2015

Given the increase of congenital anomalies, Guillain-Barré syndrome, and other neurological and autoimmune syndromes in areas where Zika virus is circulating and their possible relation to the virus, the Pan American Health Organization / World Health Organization (PAHO/WHO) recommends its Member States establish and maintain the capacity to detect and confirm Zika virus cases, prepare healthcare facilities for the possible increase in demand at all healthcare levels and specialized care for neurological syndromes, and to strengthen antenatal care. In addition, Member States should continue efforts to reduce the presence of mosquito vectors through an effective vector control strategy and public communication.

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Epidemiological Alert

Increase of microcephaly in the northeast of Brazil

17 November 2015

Given the unusual increase in cases of microcephaly in some northeast states of Brazil, the Pan American Health Organization (PAHO) / World Health Organization (WHO) calls upon Member States to remain alert to the occurrence of similar events in their territories and to notify its occurrence through the channels established under the International Health Regulations (IHR).

Media centre

WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations

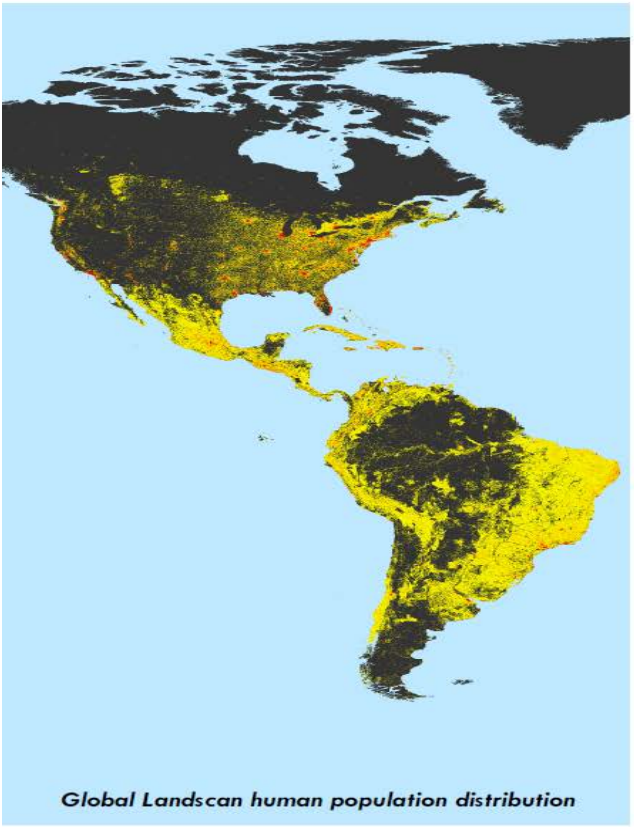
WHO statement

1 February 2016

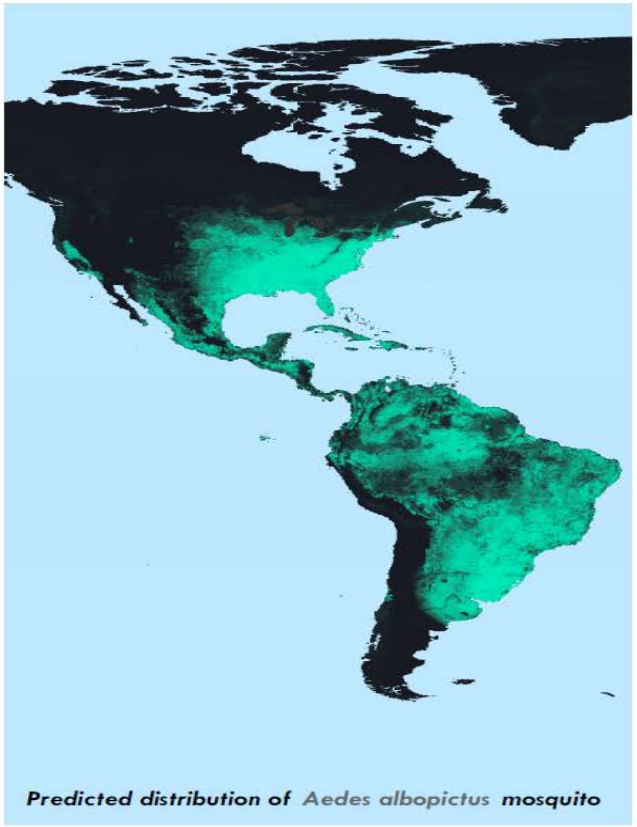
Based on this advice the Director-General declared a Public Health Emergency of International Concern (PHEIC) on 1 February 2016. The Director-General endorsed the Committee's advice and issued them as Temporary Recommendations under IHR (2005). The Director-General thanked the Committee Members and Advisors for their advice.

Population density map and Predicted distribution of the *Aedes albopictus and Aedes aegypti* mosquito

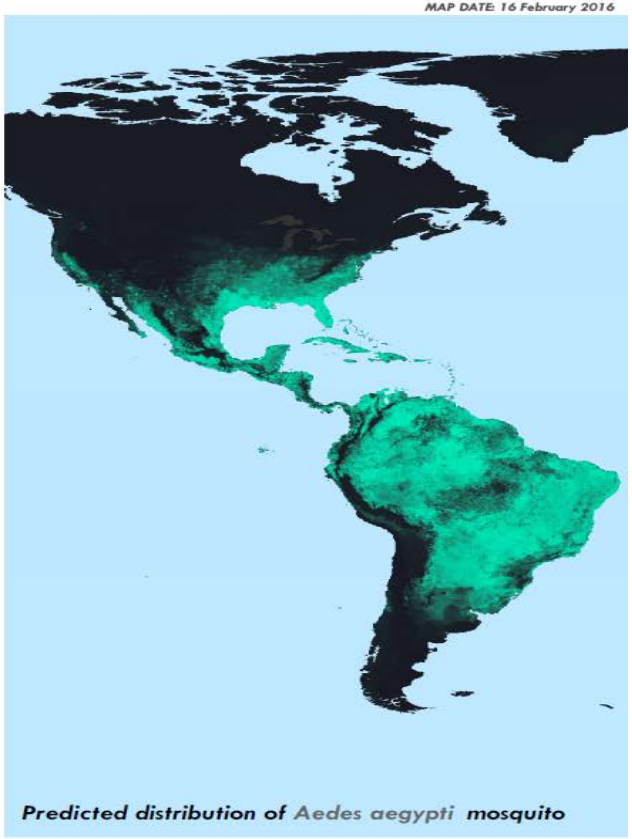
MAP DATE: 16 February 2016



Global Landscan human population distribution



Predicted distribution of Aedes albopictus mosquito



Predicted distribution of Aedes aegypti mosquito

10 POPULATION PER SQ.KM. 5,000+

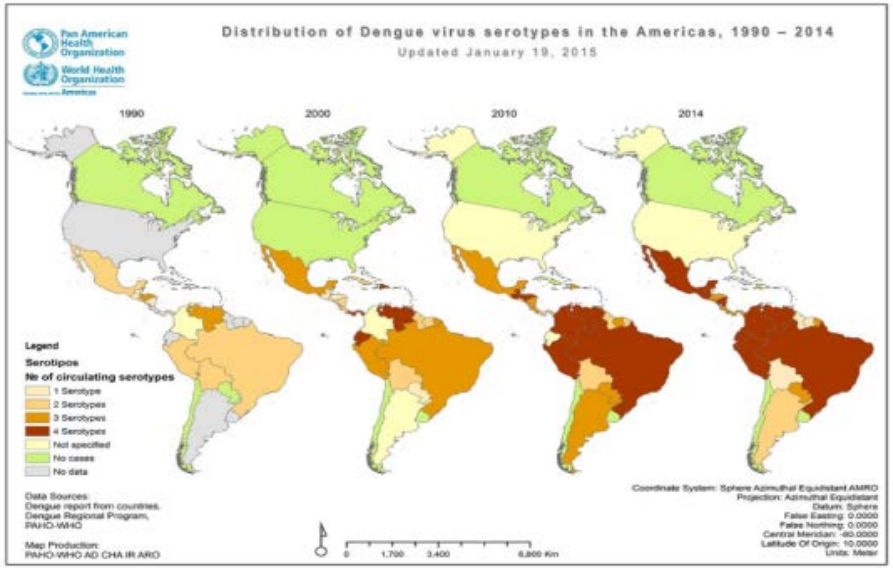
Population layer : Landscan 2010

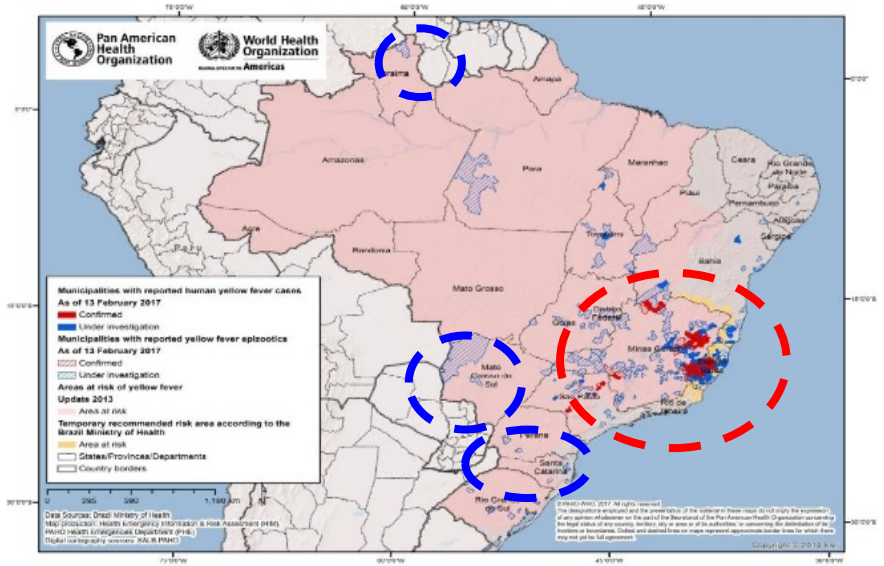
High Low

Service Layer Credits: Kraemer MUG et al. eLife

World Health Organization

(Re) Emerging

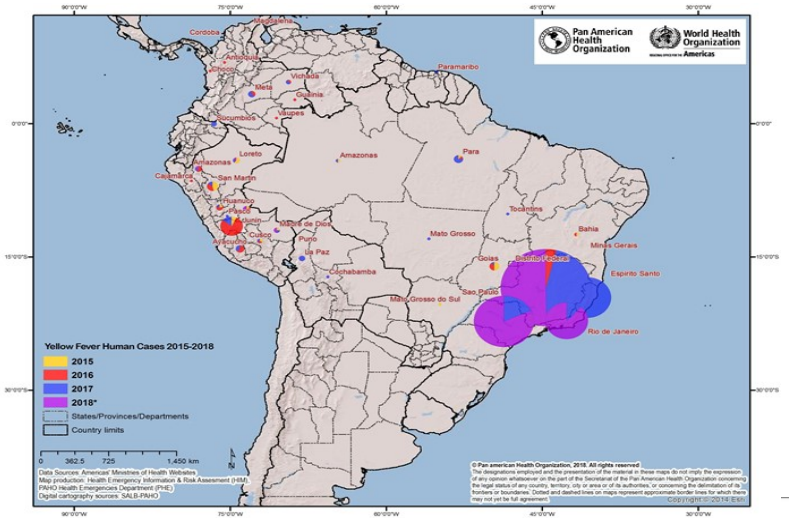




DENV
(endemic)

YFV (endemic,
re-emerging)

Yellow fever

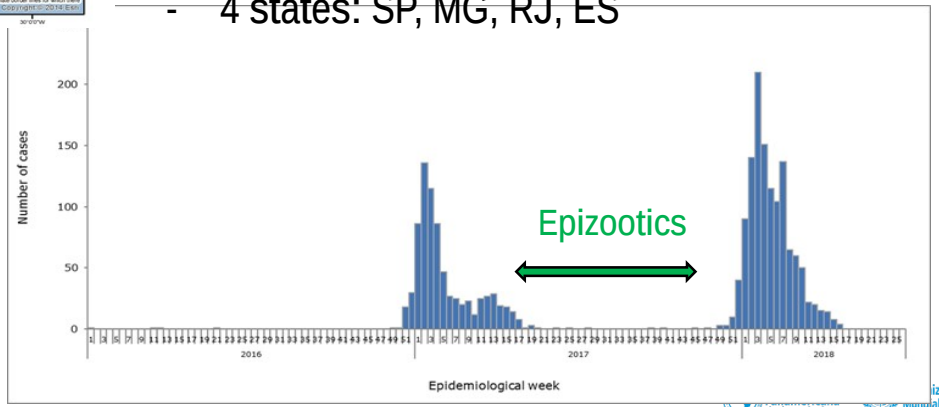


2015: 27 cases in Peru, Brazil
2016: 113 cases in Peru, Brazil, Colombia,
2017: 819 cases in Brazil, Peru, Bolivia, Ecuador, Colombia, Suriname, Fr. Guiana

South-east Brazil:

December 2016 – June 2017
- 792 confirmed cases
- 274 deaths [CFR: 34.6%]
- 4 states: SP, MG, RJ, ES

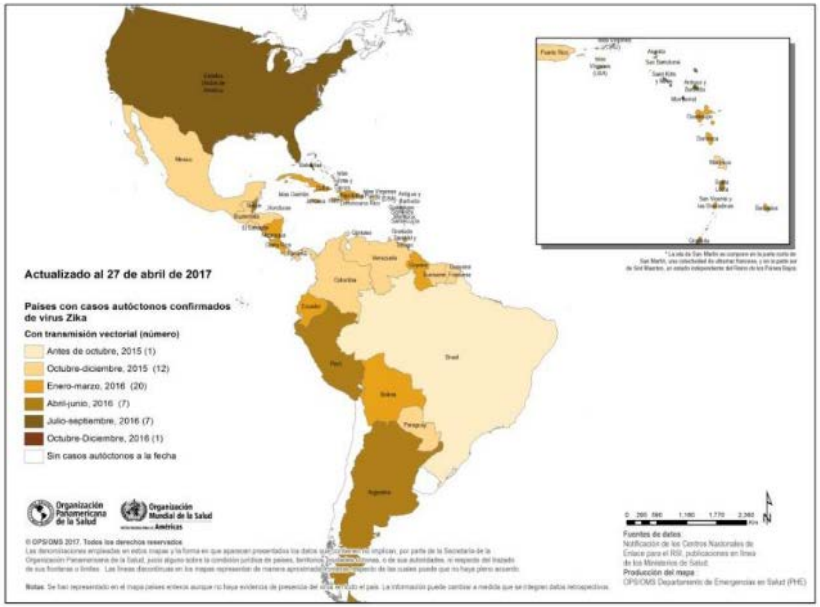
*July 2017- June 2018**
- 1266 confirmed cases
- 415 deaths [CFR: 32.8%]
- 4 states: SP, MG, RJ, ES



Distribution of confirmed yellow fever cases by epidemiological week (EW). Brazil, 2016 – 2018*

Emerging

CHIKV (Emerging, 2013)



ZIKV (Emerging, 2015)

Other arboviruses affecting humans

Virus	Family	Vector	Vertebrate hosts	Geographic distribution
Chikungunya	*Togaviridae*	Mosquitoes: Aedes and Culex spp.	Primates, birds, cattle, and rodents	Africa, Asia, Europe, Americas, Oceania
Mayaro	*Togaviridae*	Mosquitoes: Haemagogus spp.	Primates, other mammals, birds	South and Central America
Ross River	*Togaviridae*	Mosquitoes: Aedes and Culex spp.	Marsupials, other mammals, birds	Oceania and Asia
O'nyong-nyong	*Togaviridae*	Mosquitoes: Anopheles spp.	?	Africa
Sindbis	*Togaviridae*	Mosquitoes: Aedes, Culex, and Culiseta spp.	Birds	Europe, Africa, Oceania, Asia
Barmah Forest	*Togaviridae*	Mosquitoes: Aedes and Culex spp.	Birds? Marsupials, Others?	Oceania
Eastern equine encephalitis	*Togaviridae*	Mosquitoes: Culiseta, Aedes, Coquillettidia, and Culex spp.	Birds, horses, other mammals	Americas
Western equine encephalitis	*Togaviridae*	Mosquitoes: Culex, Aedes, Ochlerotatus, and Coquillettidia spp.	Birds, horses, other mammals	Americas
Venezuelan equine encephalitis	*Togaviridae*	Mosquitoes: Culex, Ochlerotatus, Anopheles, Mansonia, Psorophora, Aedes spp. and others	Horses, Rodents, Other mammals, Birds	Americas
Dengue	*Flaviviridae*	Mosquitoes: Aedes spp	Primates	Asia, Americas, Africa, Europe, Oceania

Mayer et al., Acta Tropica 2017, 166:155–163

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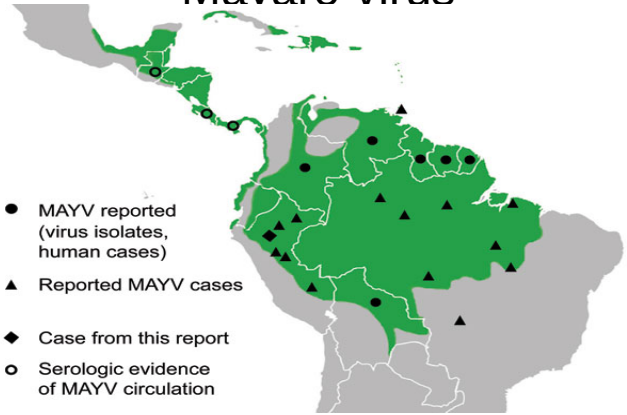
Other arboviruses affecting humans

Yellow Fever	*Flaviviridae*	Mosquitoes: Aedes and Haemogogus spp.	Primates	Europe, Oceania South America, Africa
West Nile	*Flaviviridae*	Mosquitoes: Culex spp	Birds, Horses, Other Mammals	Africa, Asia, Europe, Oceania, Americas
Japanese encephalitis	*Flaviviridae*	Mosquitoes: Culex spp	Birds, Pigs	Asia, Oceania
Murray Valley encephalitis	*Flaviviridae*	Mosquitoes: Culex spp	Birds	Oceania
Zika virus	*Flaviviridae*	Mosquitoes: Aedes spp	Primates	Africa, Asia, Oceania, Central and South America
Rocio	*Flaviviridae*	Mosquitoes: Psorophora and Aedes spp	Birds	South America
St. Louis encephalitis	*Flaviviridae*	Mosquitoes: Culex spp	Birds, Bats, Other Mammals	Americas
Kyasanur Forest disease	*Flaviviridae*	Ticks: Hemaphysalis spp.	Primates, Rodents, Other Mammals	Asia
Omsk hemorrhagic fever	*Flaviviridae*	Ticks: Dermacentor and Ixodes spp Mosquitoes:?	Rodents, Volves, Other Mammals	Europe
Tick-borne encephalitis	*Flaviviridae*	Ticks: Ixodes spp	Rodents, Goats, Sheep, Cows, Other Mammals, Birds?	Europe, Asia
Sandfly fever	*Bunyavirdae*	Sandflies: *Phlebotomus* spp.	Birds? Mammals?	Europe, Asia, Africa
Rift Valley fever	*Bunyavirdae*	Mosquitoes: Aedes, Ochlerotatus, Stegomyia, Anopheles, Culex, Neomelaniconion, Eretmapodites and others	Cows, Sheep, Camels, Goats and Other Mammals	Africa, Asia
La Crosse encephalitis	*Bunyavirdae*	Mosquitoes: Aedes spp	Rodents	North America
Crimean-Congo hemorrhagic fever	*Bunyavirdae*	Ticks: *Hyalomma* spp	Cows, Sheep, Goats, Hares and Other Mammals	Europe, Asia, Africa
Oropouche	*Bunyavirdae*	Midges: Culicoides sp	Primates? Sloths? Birds?	Central and South America
Severe febrile thrombocytopenia syndrome	*Bunyavirdae*	Ticks: Haemaphysalis sp	?	Asia
Chandipura	*Rhabdovirdae*	Sandflies: *Phlebotomus* and *Sergentomyia* spp.	Hedgehogs, Others?	Asia and Africa
Bluetongue	*Reovirdae*	Midges: Culicoides spp	Sheep, Cows, Other Mammals	Africa, Asia, Europe, Oceania, Americas (all except Antarctica)

Mayer et al., Acta Tropica 2017, 166:155–163

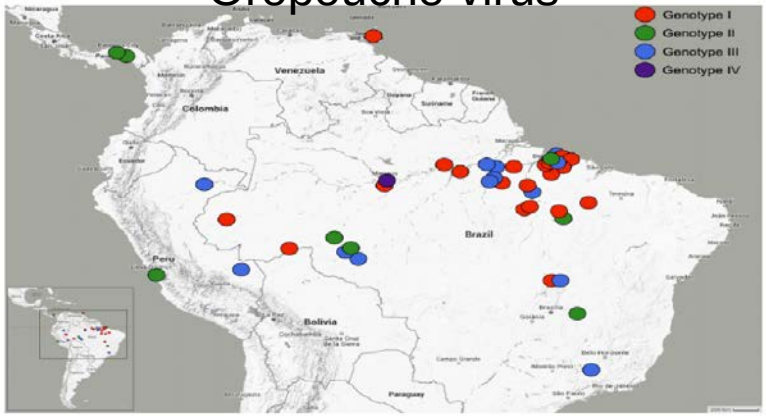
Mayaro and other arboviruses…

Mavaro virus



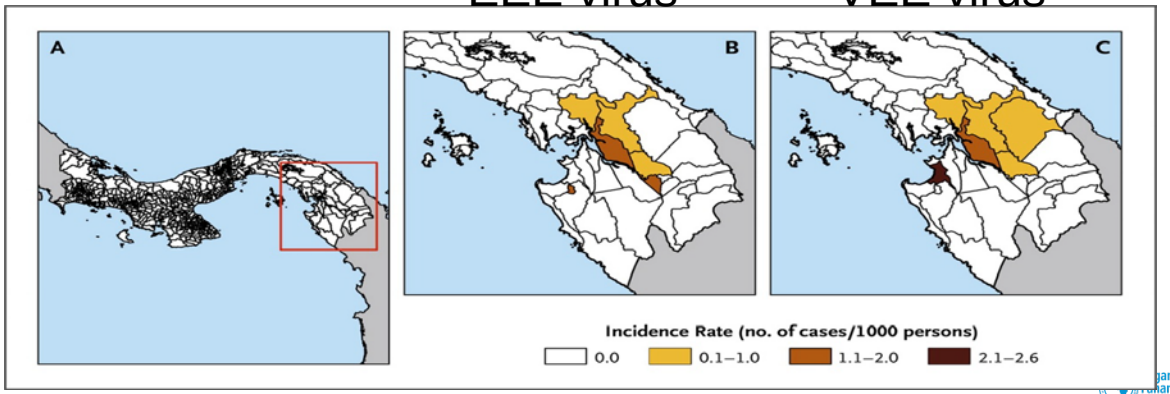
Emerg Infect Dis, 2012, 18:695-6

Oropouche virus



Am J Trop Med Hyg, 2017, 96:1019-30

EEE virus VEE virus



N Engl J Med, 2013, 369:732-744

Surveillance and early response:
Role of the laboratory

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Surveillance and early response

International Health Regulations:

- Recommends countries to maintain active surveillance of diseases and public health events.
- Urges to strengthen and respond quickly to events of international dispersion and contain any threat to public health.

Pathogens under elimination or control: viruela, poliovirus, etc…

Emerging or re-emerging pathogens (Zika, YFV, SARS, MERS, Flu…)

Early Warning System

Surveillance and early response

International Health Regulations:

- Core capacity # 8 of the IHR (2005) **obligates** WHO Member States to establish mechanisms to provide **reliable and timely identification** and characterization of infectious agents and other hazards that may cause public health emergencies of national and international interest, including sending specimens to the appropriate laboratories if necessary

Pathogens under elimination or control: viruela, poliovirus, etc…

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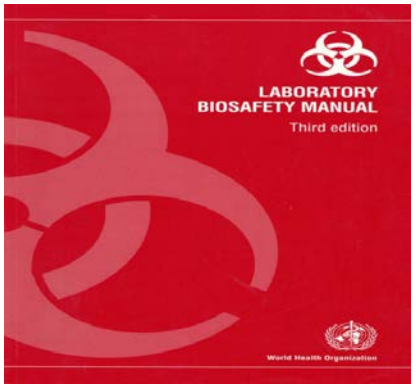
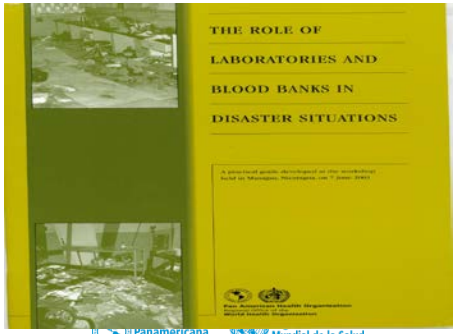
Early Warning System

IHR, Core capacity # 8 : Critical laboratory elements

1. Capacity to diagnose priority pathogens
2. Quality management
3. Management of biological risk
4. Collection and transport of samples
5. Laboratory-based surveillance
6. Laboratory networks





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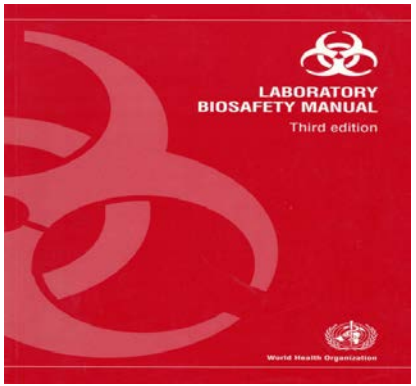

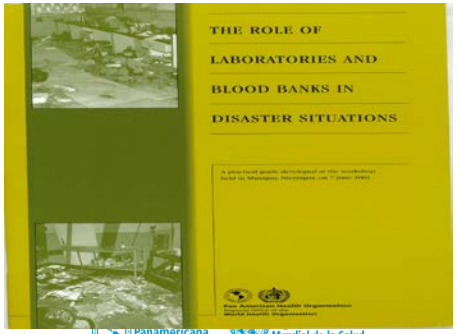

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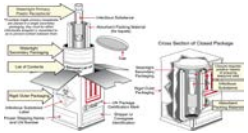
Standardization of processes

Processing



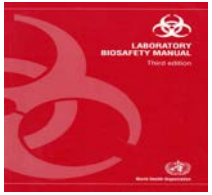
- Type of sample
- Sample conservation
- Sample transportation
- Type of test
- Equipment and Reagents
- Reference materials

Algorithms

- Sequential Vs simultaneous
- Singleplex Vs Multiplex
- Differentials

Implementation

- Training
- SoPs
- Equipment calibration
- Interpretation of results
- Limitations
- QC
- EQAP
- Biosecurity
- Biosafety
- Maintenance
- Waste disposal



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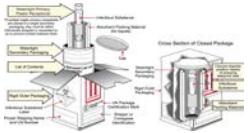

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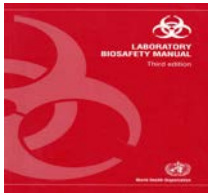

Interpretation

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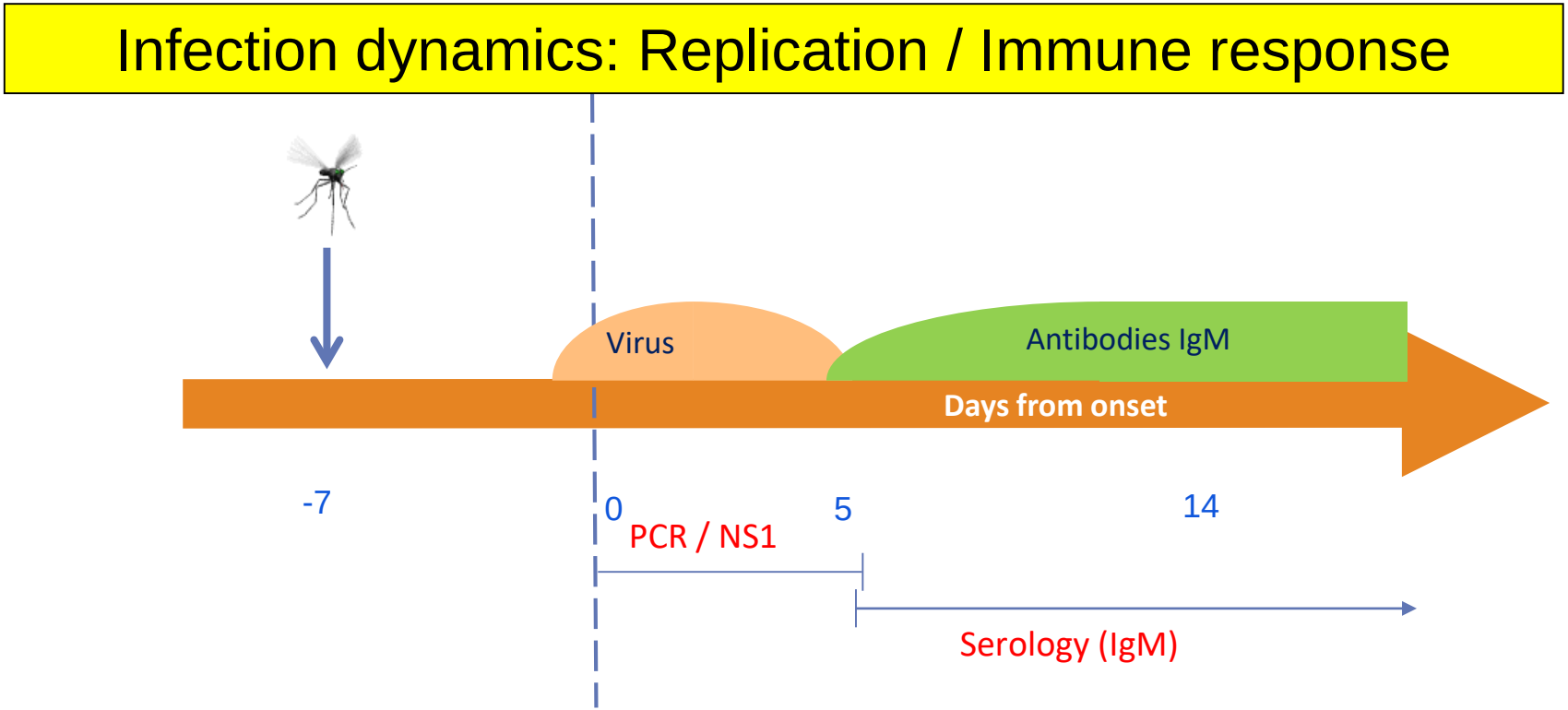
Laboratory algorithms

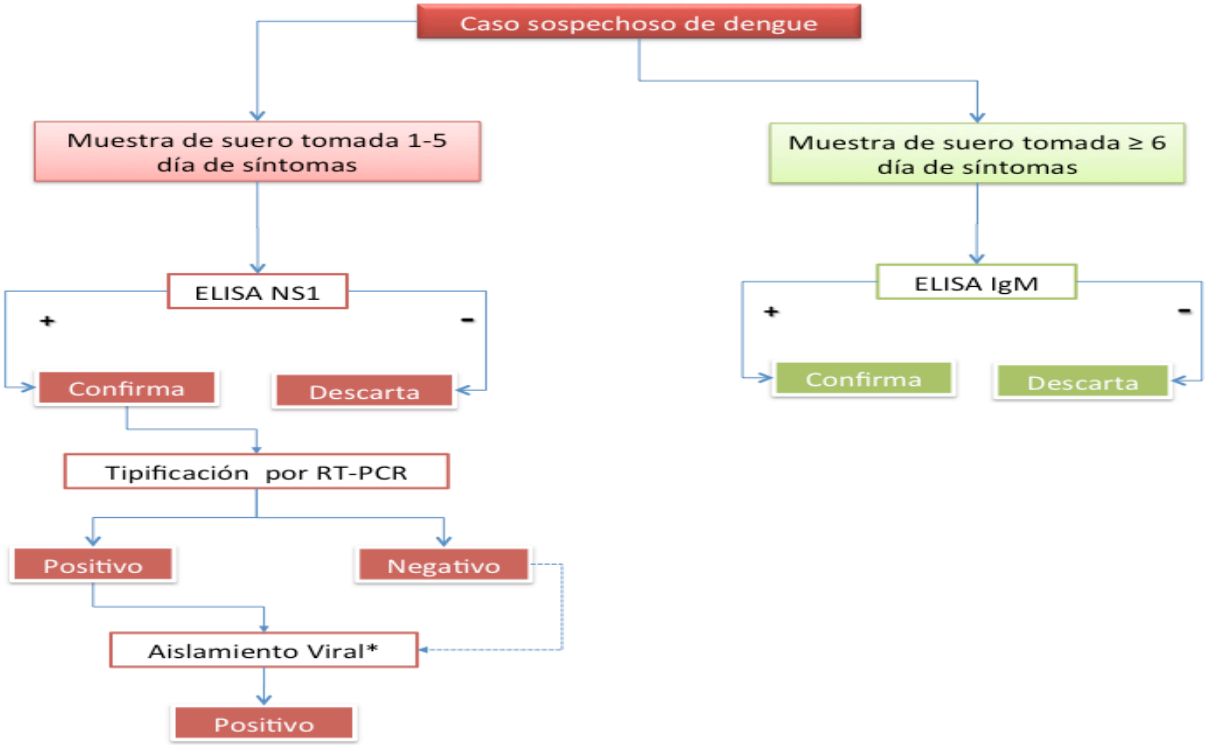


Slide adapated from Dr. Jorge Muñoz, CDC Pto. Rico

Processing algorithms

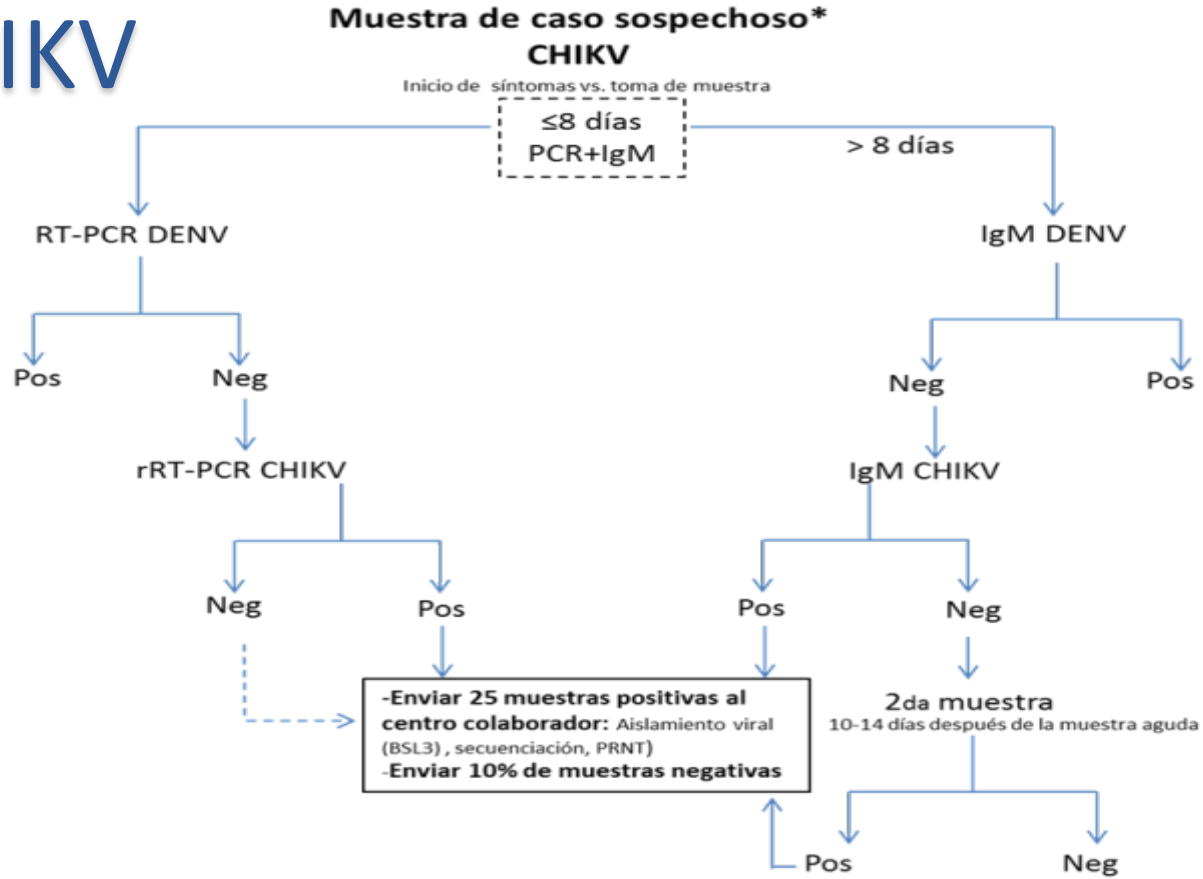
- The laboratory algorithms are NOT static and should be adjusted depending on the needs, epidemiological profile and to respond to emergencies

Dengue

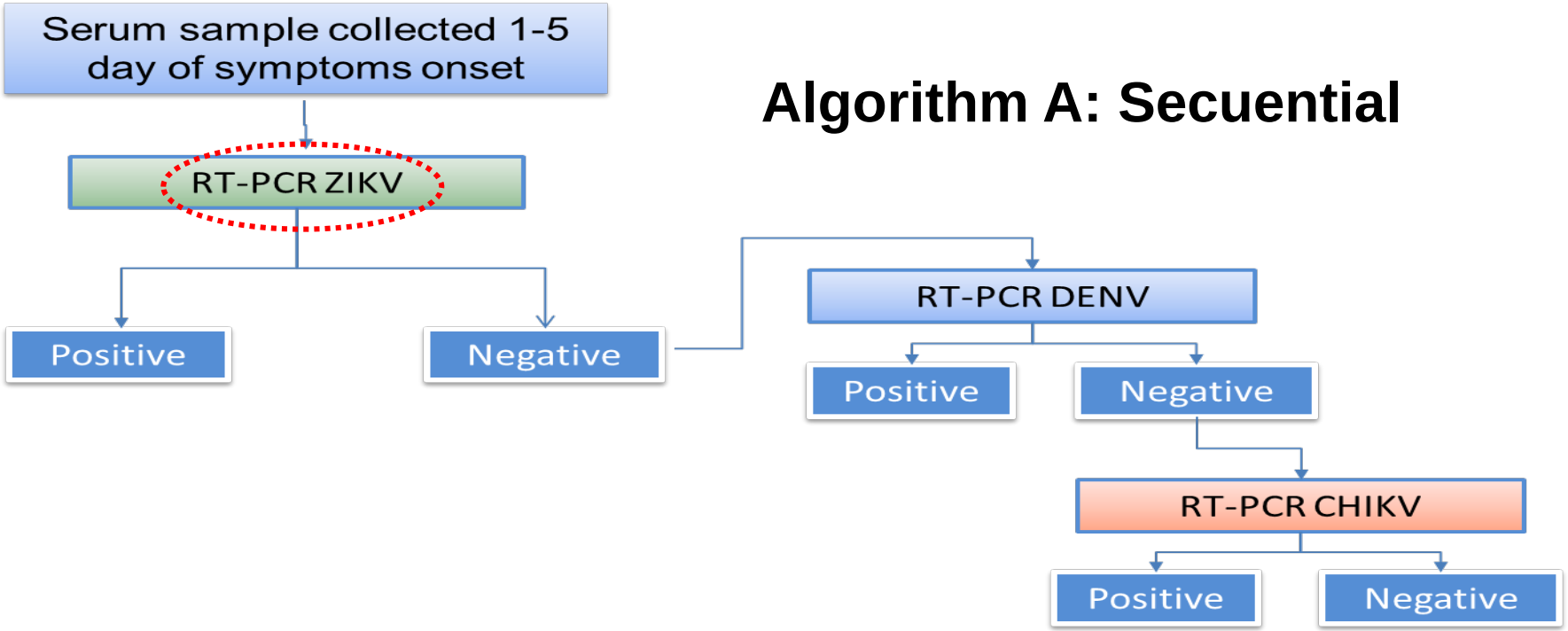


Adaptado de: Laboratorio de Arbovirus-Grupo Virología. INS Colombia

CHIKV

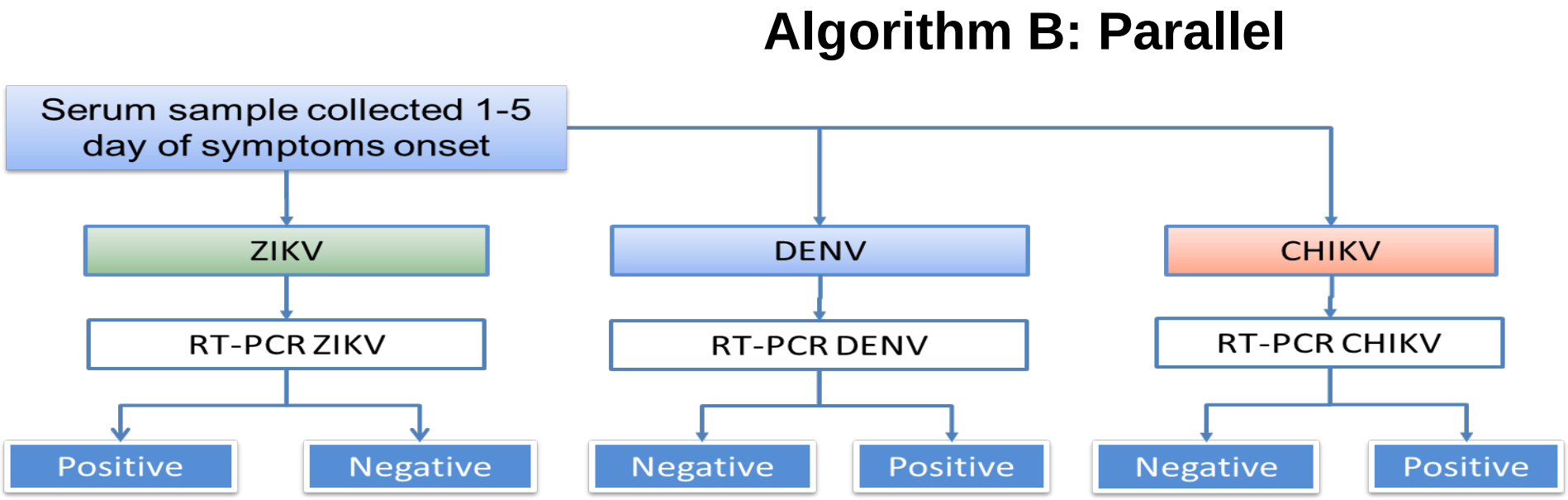

Muestra de caso sospechoso*
CHIKV
Inicio de síntomas vs. toma de muestra
≤8 días
PCR+IgM
> 8 días
RT-PCR DENV
IgM DENV
Pos
Neg
Neg
Pos
rRT-PCR CHIKV
IgM CHIKV
Neg
Pos
Pos
Neg
-Enviar 25 muestras positivas al centro colaborador: Aislamiento viral (BSL3) , secuenciación, PRNT)
-Enviar 10% de muestras negativas
2da muestra
10-14 días después de la muestra aguda
Pos
Neg

Algorithm for *integrated* surveillance

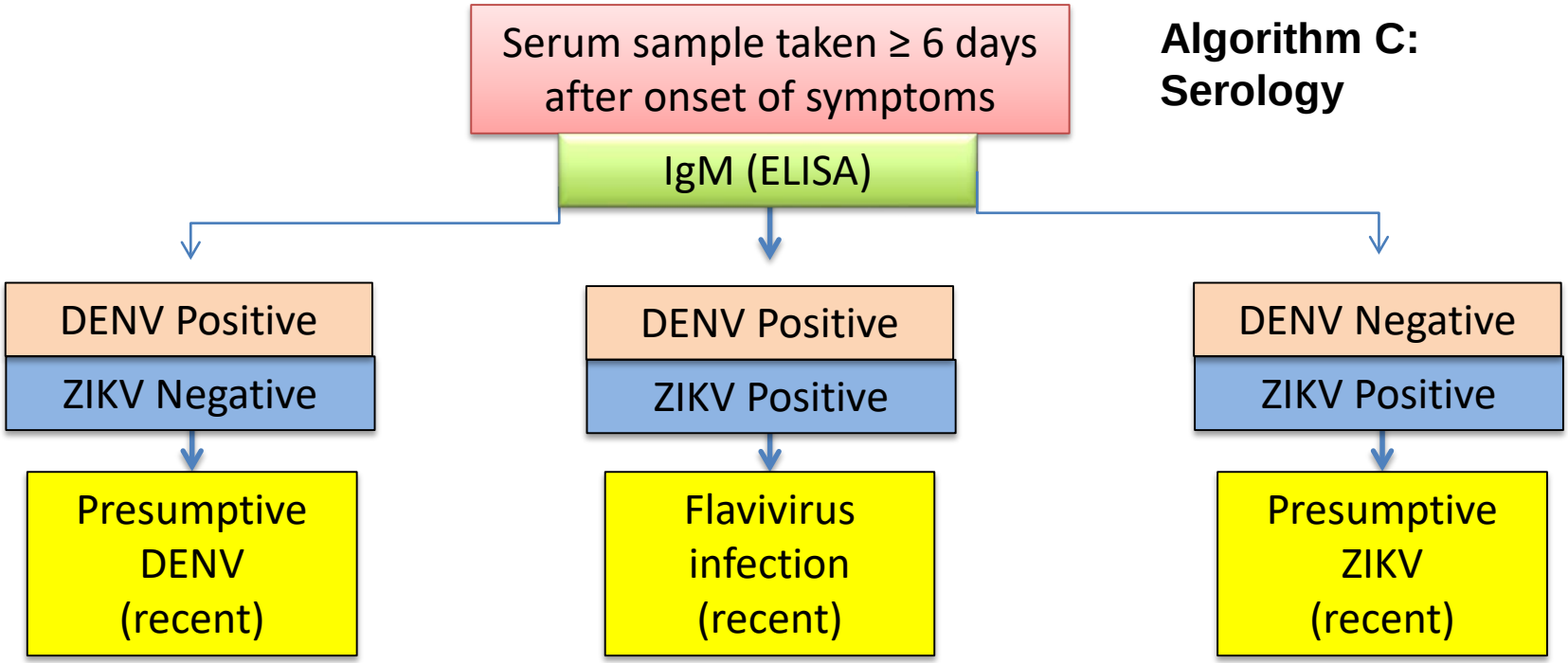


Algorithm A: Secuential

Algorithm for *integrated* surveillance



Algorithm for *integrated* (serological) surveillance

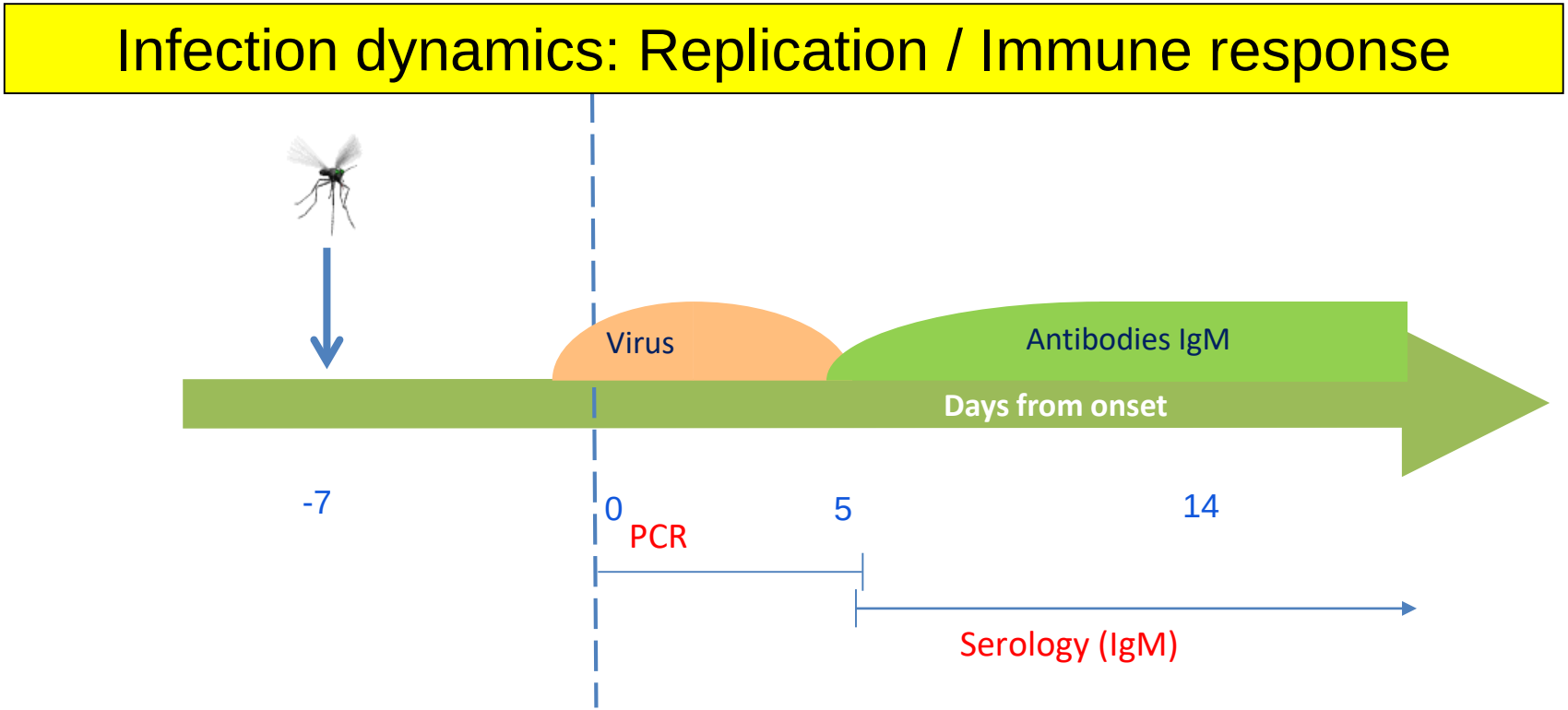


Processing algorithms

- The laboratory algorithms are NOT static and should be adjusted depending on the needs, epidemiological profile and to respond to emergencies

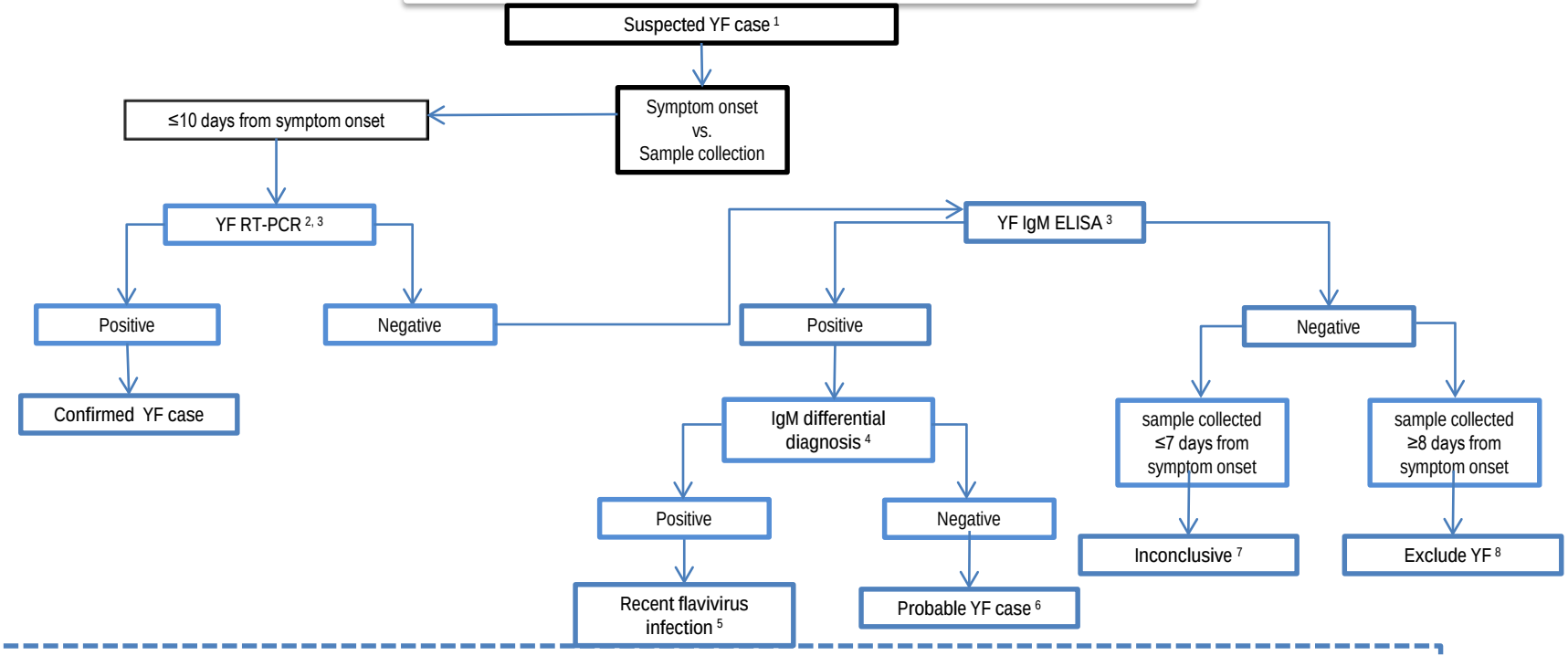
Take into account new findings, biological evidence and performance of new assays

Laboratory algorithms



Slide adapated from Dr. Jorge Muñoz, CDC Pto. Rico

Algorithm for laboratory confirmation of yellow fever (YF) cases



[1] No YF vaccination within 30 days or unknown YF vaccination history.
[2] Laboratories that only have the capacity to perform RT-PCR or IgM ELISA should test samples with the available technique. Results should be interpreted according to the algorithm.
[3] RT-PCR sensitivity is higher in the first 10 days from symptom onset. However, detection beyond 10 days has been reported, in particular in severe (and fatal) cases.
[4] Must include dengue virus as well as other flaviviruses depending on the epidemiological situation of the area/country.
[5] Consider performing PRNT in a reference laboratory. This result does not rule out yellow fever. Thus, in areas where no YF circulation has been described recently, this should prompt an investigation.
[6] A positive IgM test in a single sample is not confirmatory. Additional clinical and epidemiological criteria must be used for the final interpretation of the case, in particular in areas where no YF circulation has been described recently.
[7] A second sample should be requested and tested according to the algorithm.
[8] Cases should be investigated and clinical differential diagnosis performed.

Processing algorithms

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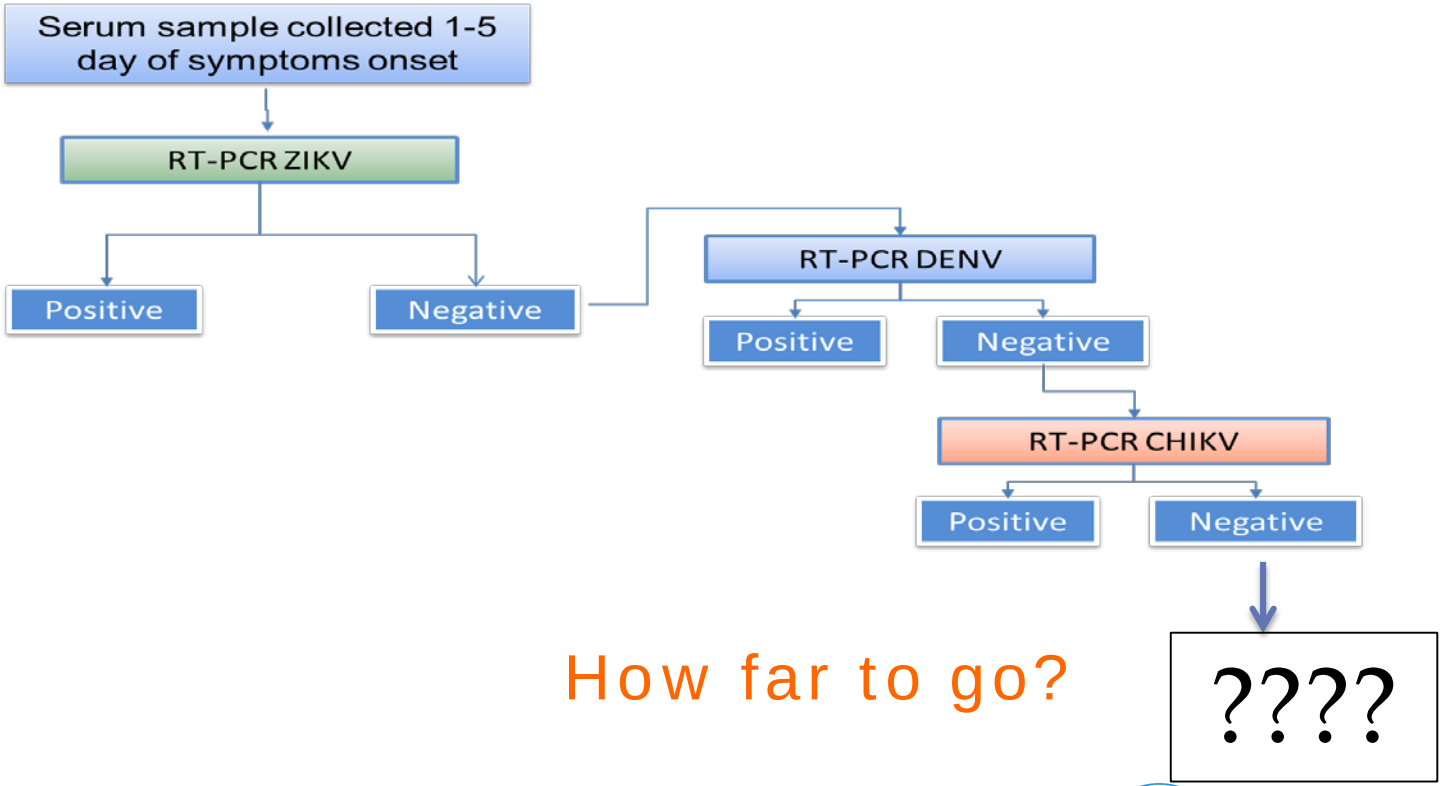
For early detection of emerging agents,

the **negative** samples are as important as the positive ones

Algorithms to detect emerging arboviruses...



How far to go?

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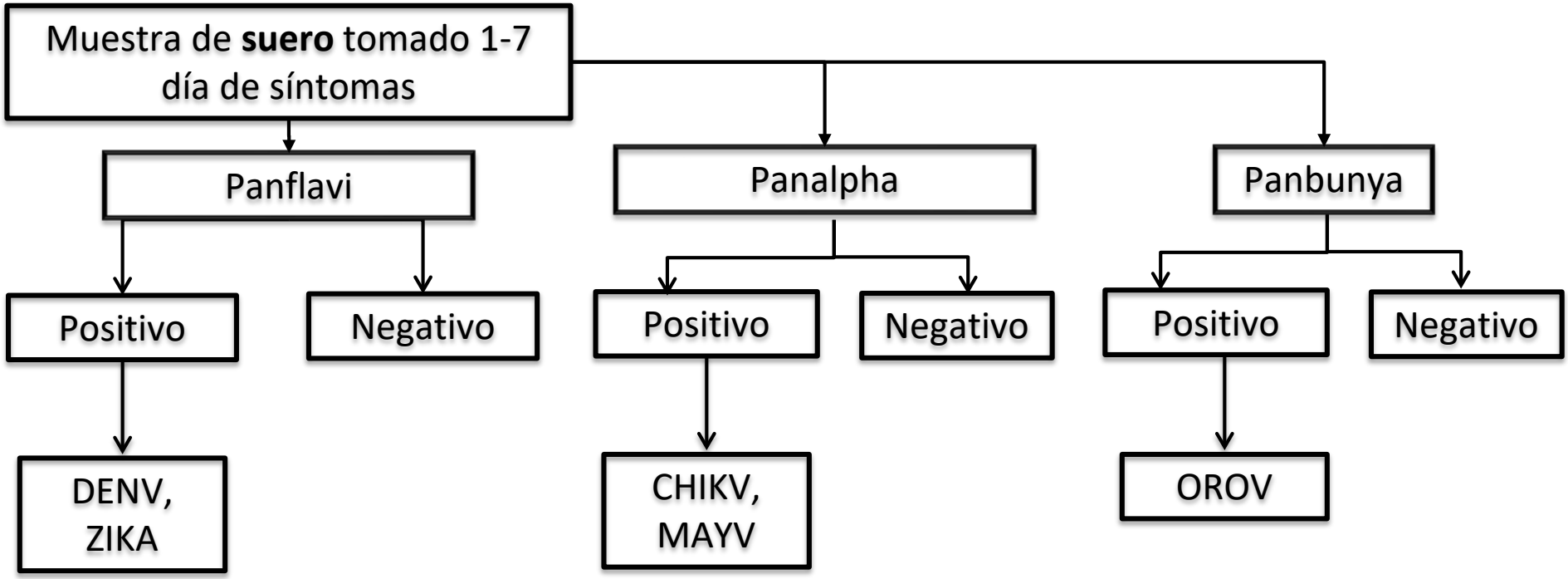
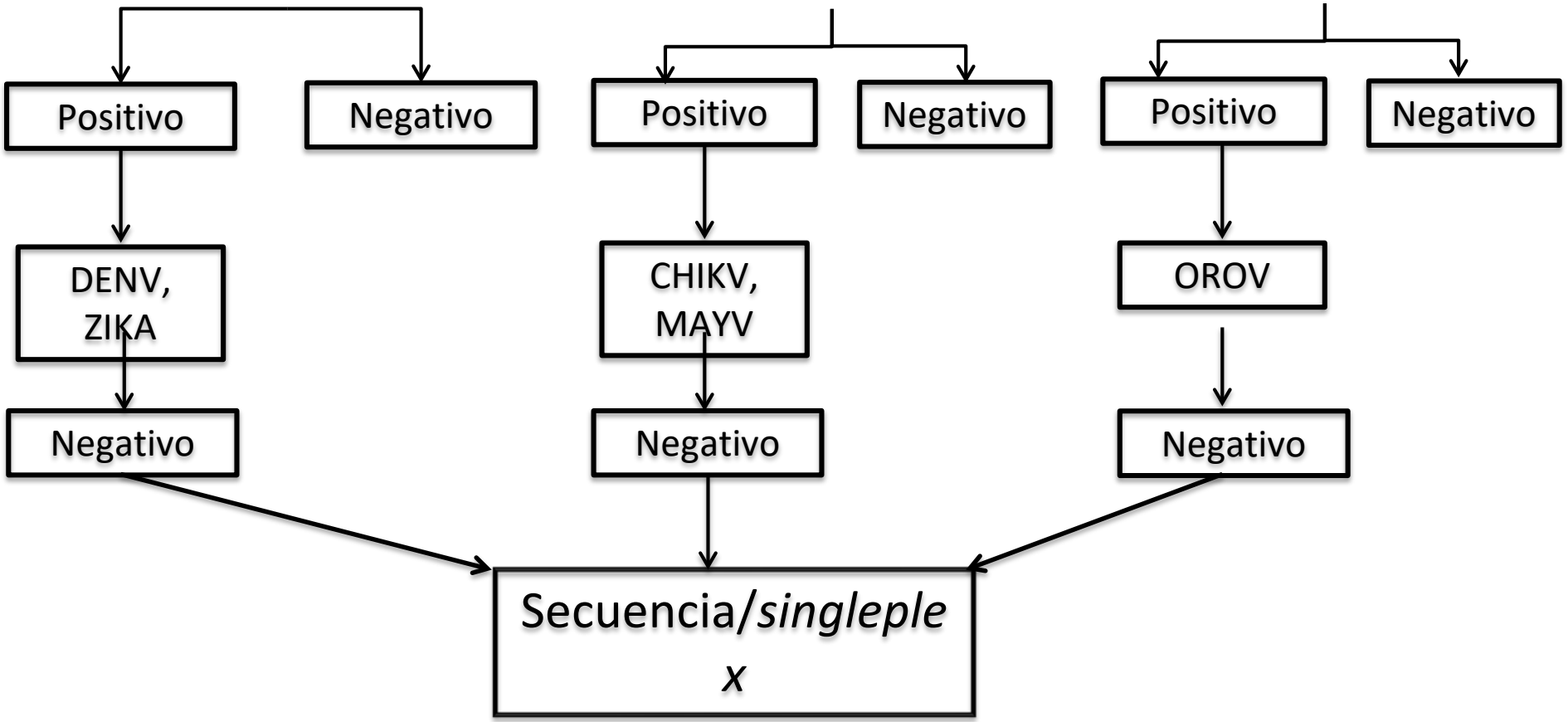
Algorithms to detect emerging arboviruses...

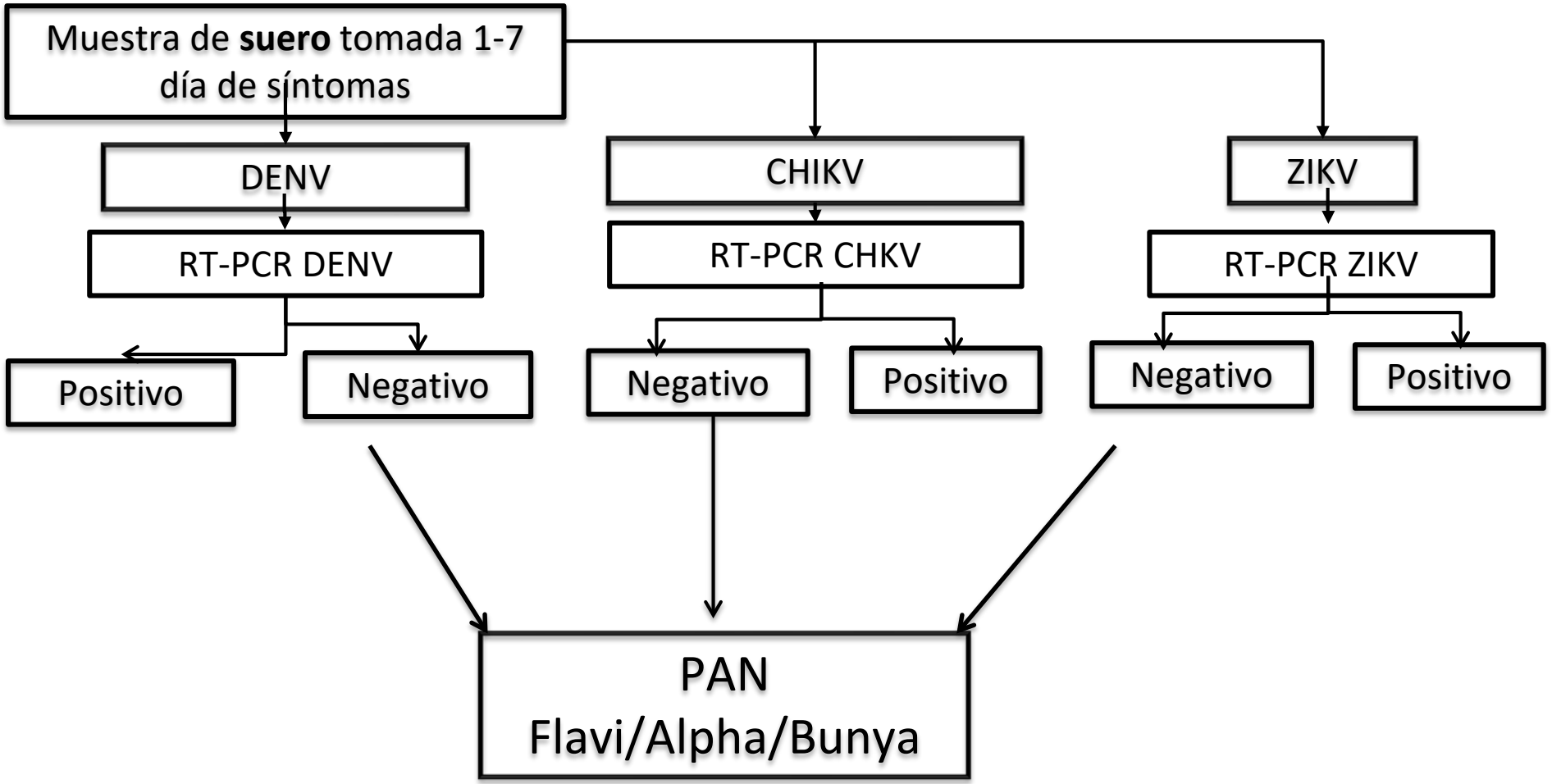
- Additional assays…(*singleplex*?)
- Generic assays
  - *Panflavivirus*
  - *Panalphavirus*
  - *Panbunyavirus*

“Generic” algorithms (1)

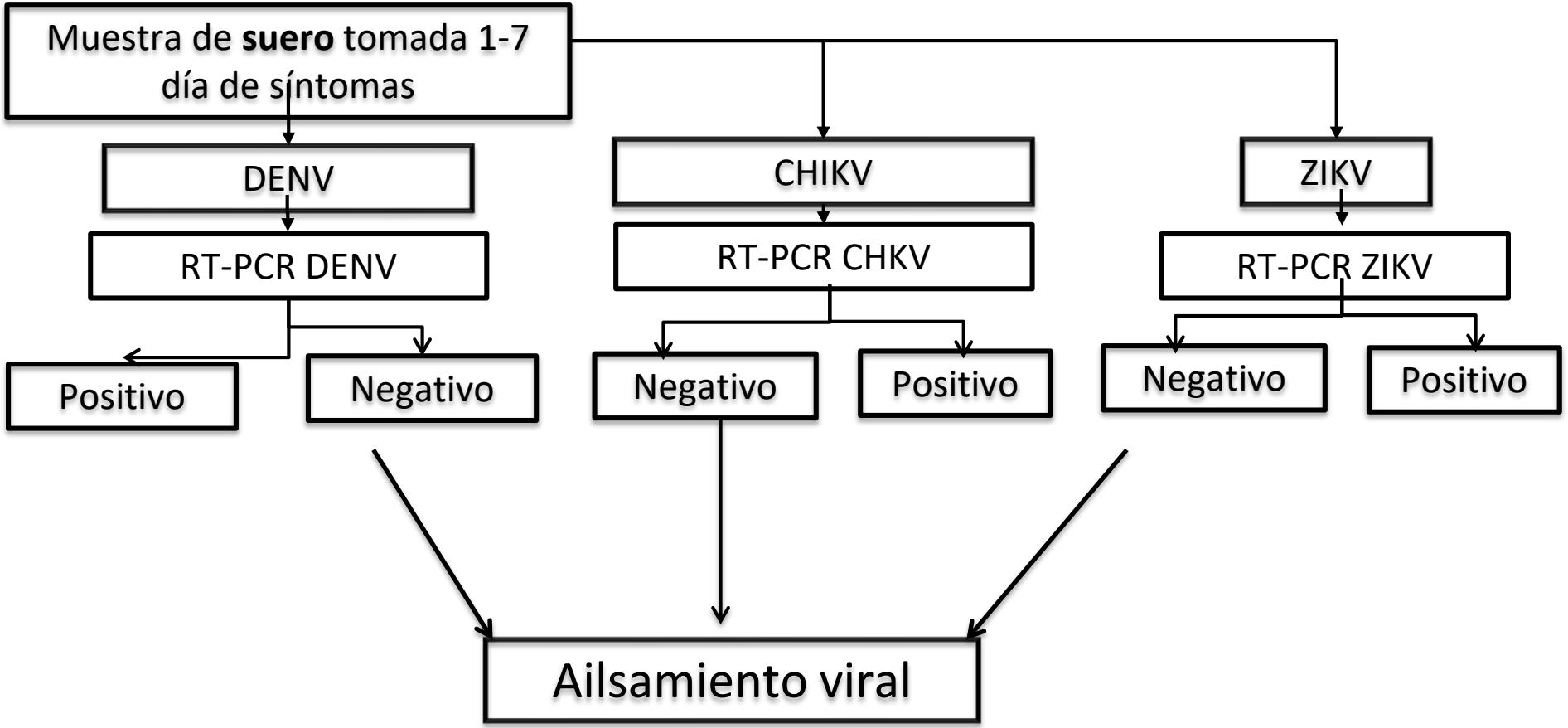



Positivo
Negativo
Positivo
Negativo
Positivo
Negativo
DENV,
ZIKA
CHIKV,
MAYV
OROV
Negativo
Negativo
Negativo
Secuencia/*singleple*
x

“Generic” algorithms (2)



“Generic” algorithms (3)

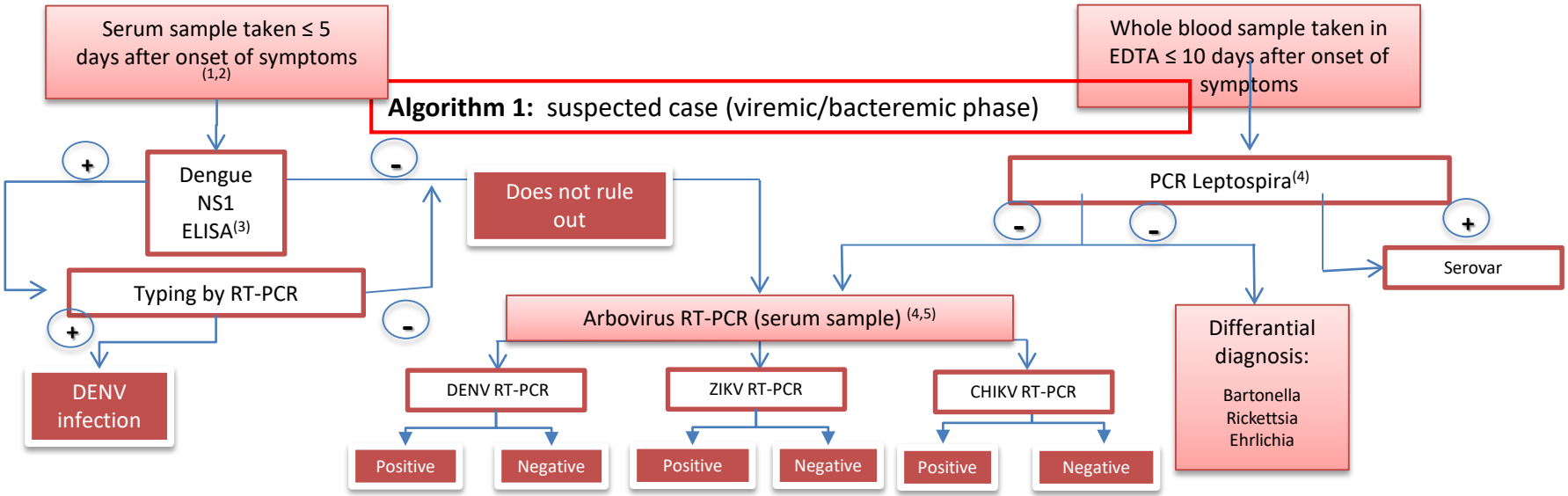


Processing algorithms

- The laboratory algorithms are NOT static and should be adjusted depending on the needs, epidemiological profile and to respond to emergencies

In case of emergencies due to natural disasters, the differential diagnosis must be considered with other types of agents

Algorithm for the differential diagnosis of arbovirus and leptospira infection in areas of documented co-circulation and post-emergency areas at risk



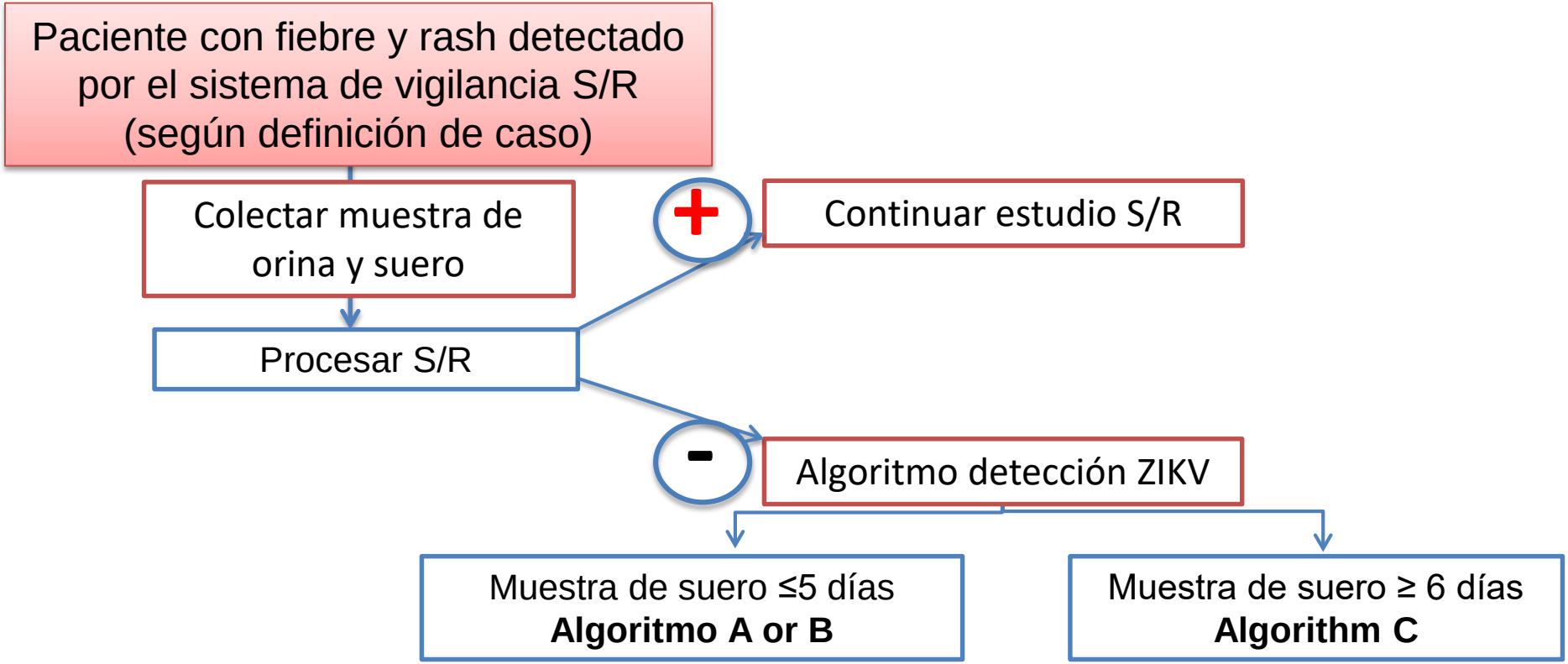
(1) Perform a leptosirosa IgM ELISA with this serum sample and a second sample collected at least 14 days after the first to test for seroconversion
(2) A minimum sample volume of 5ml should be collected to obtain at least 1ml of serum for arboviruses testing and 1ml of serum for leptospira testing
(3) Sensitivity can vary depending on the serotype
(4) Molecular detection can be performed sequentially (*singleplex*, starting with the most probable agent according to clinical criteria) or in parallel (*multiplex*)
(5) ZIKV can also be detected by RT-PCR in urine from day 1 to day 15 (on average)

Processing algorithms

- The laboratory algorithms are NOT static and should be adjusted depending on the needs, epidemiological profile and to respond to emergencies

For the differential diagnosis of other pathologies considered in the IHR and that are in the process of elimination: Measles vs Zika

Proposed algorithm for Zika surveillance integrated to Measles



Comentarios finales

- Adequate surveillance allows monitoring endemic pathogens
- Efficient mechanisms are required to identify new events, new agents (viruses), or new variants with pandemic potential.

SURVEILLANCE OF UNUSUAL CASES

Comentarios finales

- The laboratory is critical to confirm (or rule out) new agents: Zika, Mayaro, Oropouche, EEV, West Nile ...

- LSPs must be prepared to detect and report new agents in a timely manner (mandatory notification within 24 hours, RSI)

- However, the detection capacity does not refer only to the installed capacity; It implies the possibility of having access to a laboratory that has the capacity (Networking!)

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Comentarios finales

- A good laboratory diagnosis depends on a good sample and a well recognized case ...
- Surveillance results should not be used / expected to make medical decisions! (the clinical diagnosis should be prioritized!)
- Articulation of the laboratory with the epidemiology and clinical components is essential to ensure an appropriate response to the IHR

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Thank you!

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PAHO/PHE