

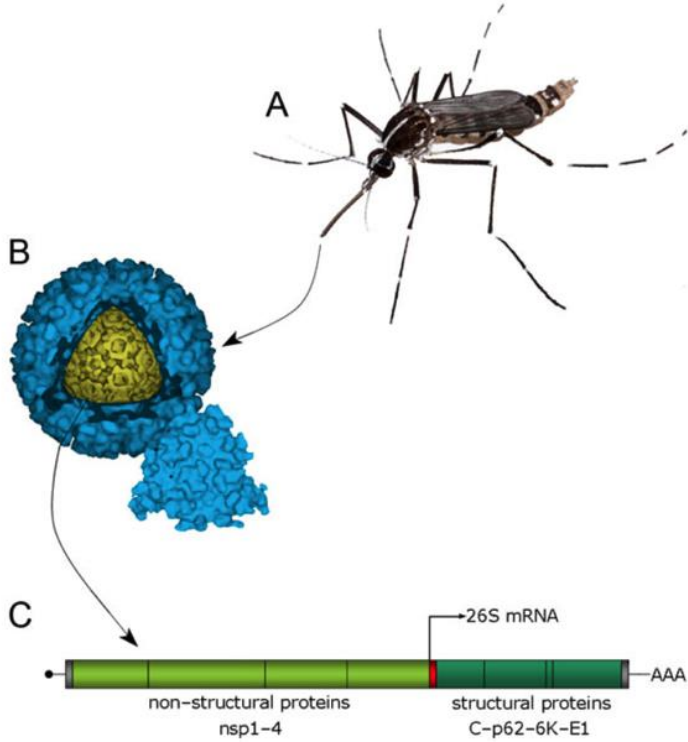
How basic research informed the development of a chikungunya virus vaccine

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Alphaviruses



- Sole genus within Togaviridae family
- Small, enveloped particle containing a single stranded RNA genome of positive polarity.
- Chikungunya, Semliki Forest, Ross River viruses
- CHIKV causes an arthritic disease with severe joint pain in recurrent outbreaks in tropical regions
- Transmitted by *Aedes* mosquitoes

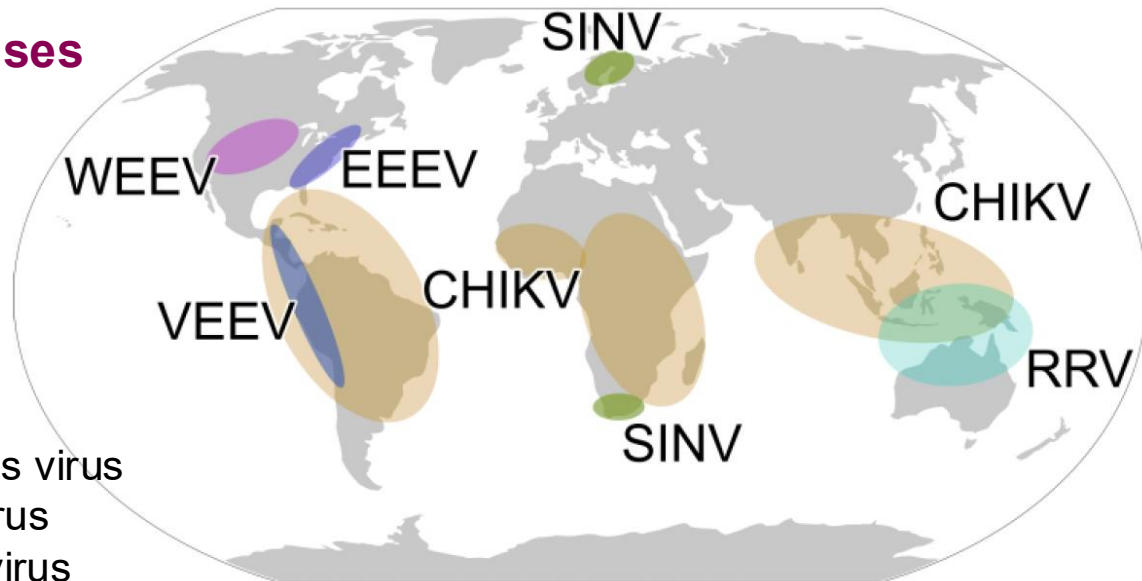
Global distribution of alphaviruses

Old World

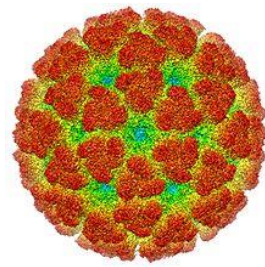
CHIKV, chikungunya virus
SINV, Sindbis virus
RRV, Ross River virus

New World

VEEV, Venezuelan equine encephalitis virus
EEEV, Eastern equine encephalitis virus
WEEV, Western equine encephalitis virus



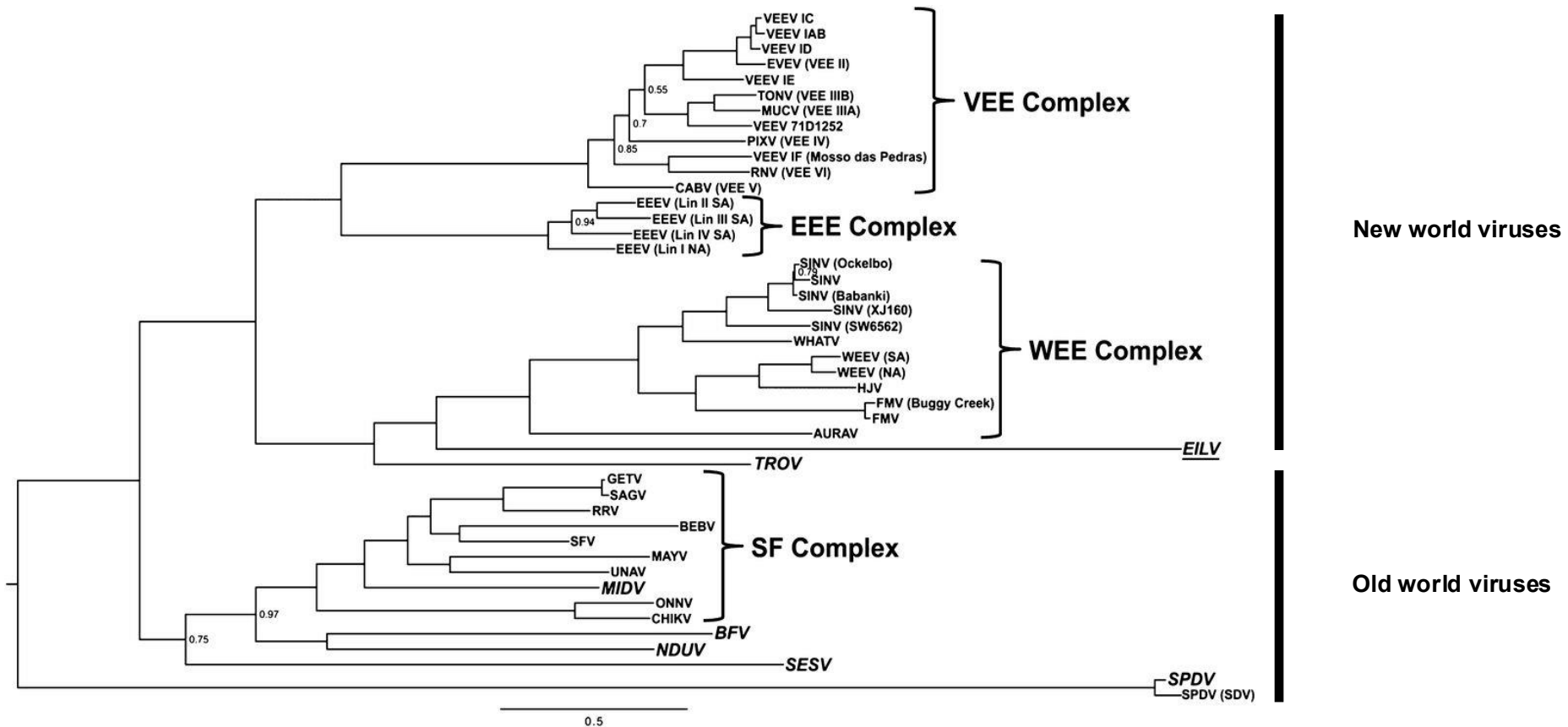
Alphaviruses phylogeny: The Old and the New



Marine origin

Introduced into the New World and Australasia and from there into the Old World

Multiple introduction events likely



Infection and pathogenesis of arthritic alphaviruses (eg chikungunya)

Following a bite from an infected mosquito, arthritogenic alphaviruses replicate locally in skin cells - fibroblasts, keratinocytes, epithelial and endothelial cells, also macrophages.

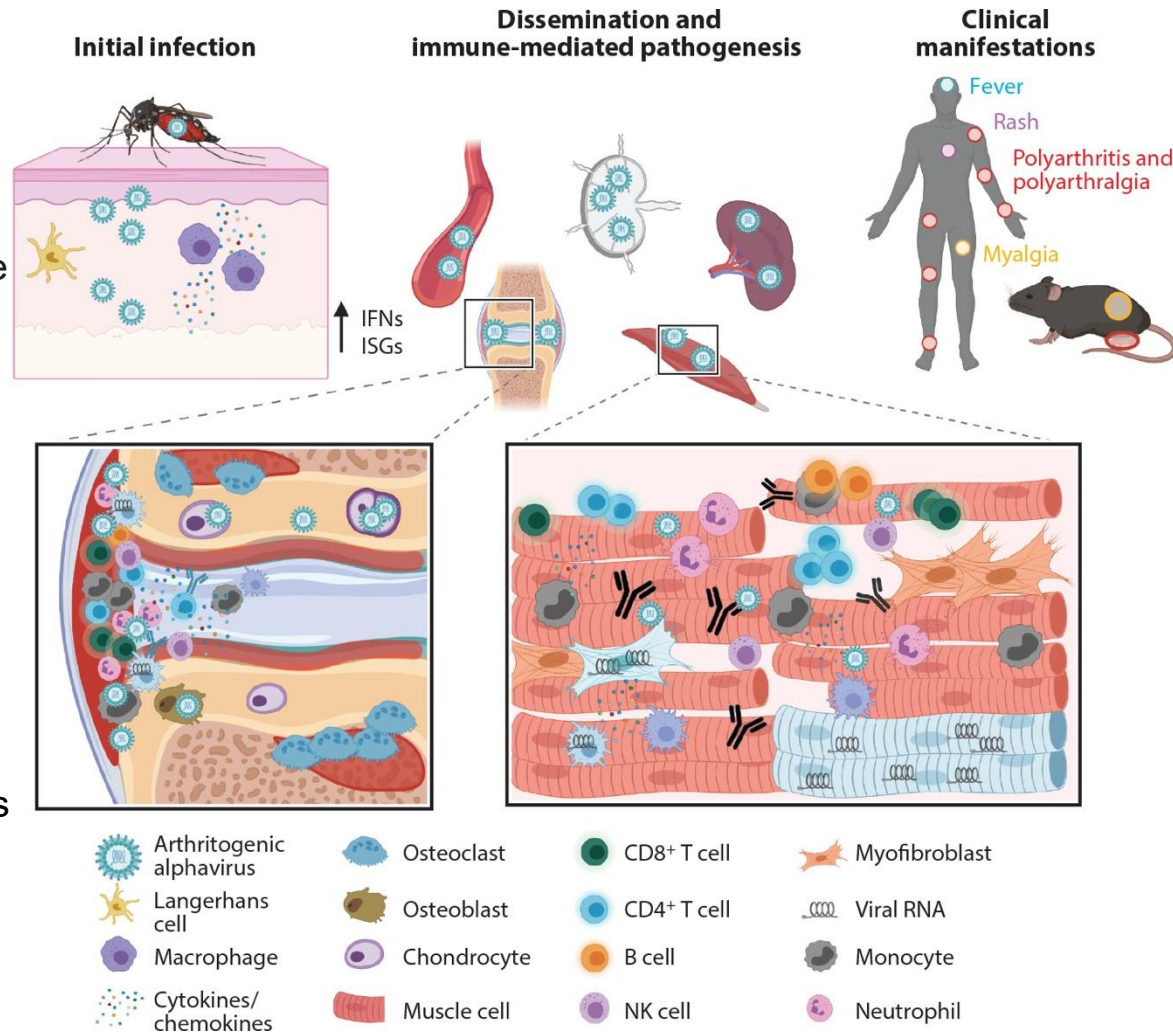
Cellular infection results in induction of type I interferons and expression of ISGs.

Virus travels to the lymph node or through the bloodstream to disseminate to peripheral organs, where it replicates to high titers in the joint-associated and musculoskeletal tissues.

Infection of osteoblasts promotes osteoclastogenesis and bone erosion

Proinflammatory cytokines and chemokines are released and recruit cells that are essential to control infection but also mediate damage including synovitis, bone reabsorption, and muscle fiber destruction.

Macrophages, myofibroblasts, and muscle cells can survive infection and harbor viral RNA many weeks after acute infection.



Chikungunya virus and disease

Symptoms usually begin 3-7 days after bite from infected mosquito

Acute phase (rash, fever, joint pain) typically resolves in 7-10 days

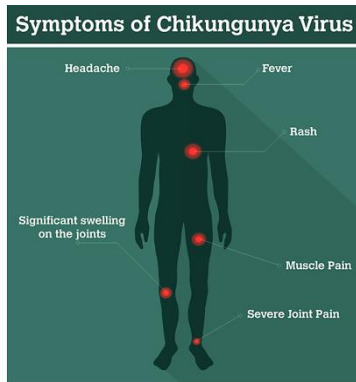


Figure 4: Chikungunya fever symptoms. A and B: Rash characterized by raised, spotted lesions. C: Joint pain with the presence of swelling



Chronic phase: arthralgia, fibromyalgia, fatigue
 Can persist for months to years
 Can severely impact quality of life



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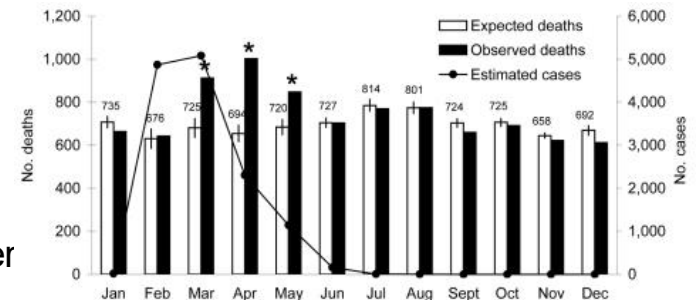
Chikungunya-attributable deaths: A neglected outcome of a neglected disease

Antonio S. Lima Neto, Geziel S. Sousa, Osmar J. Nascimento, Marcia C. Castro

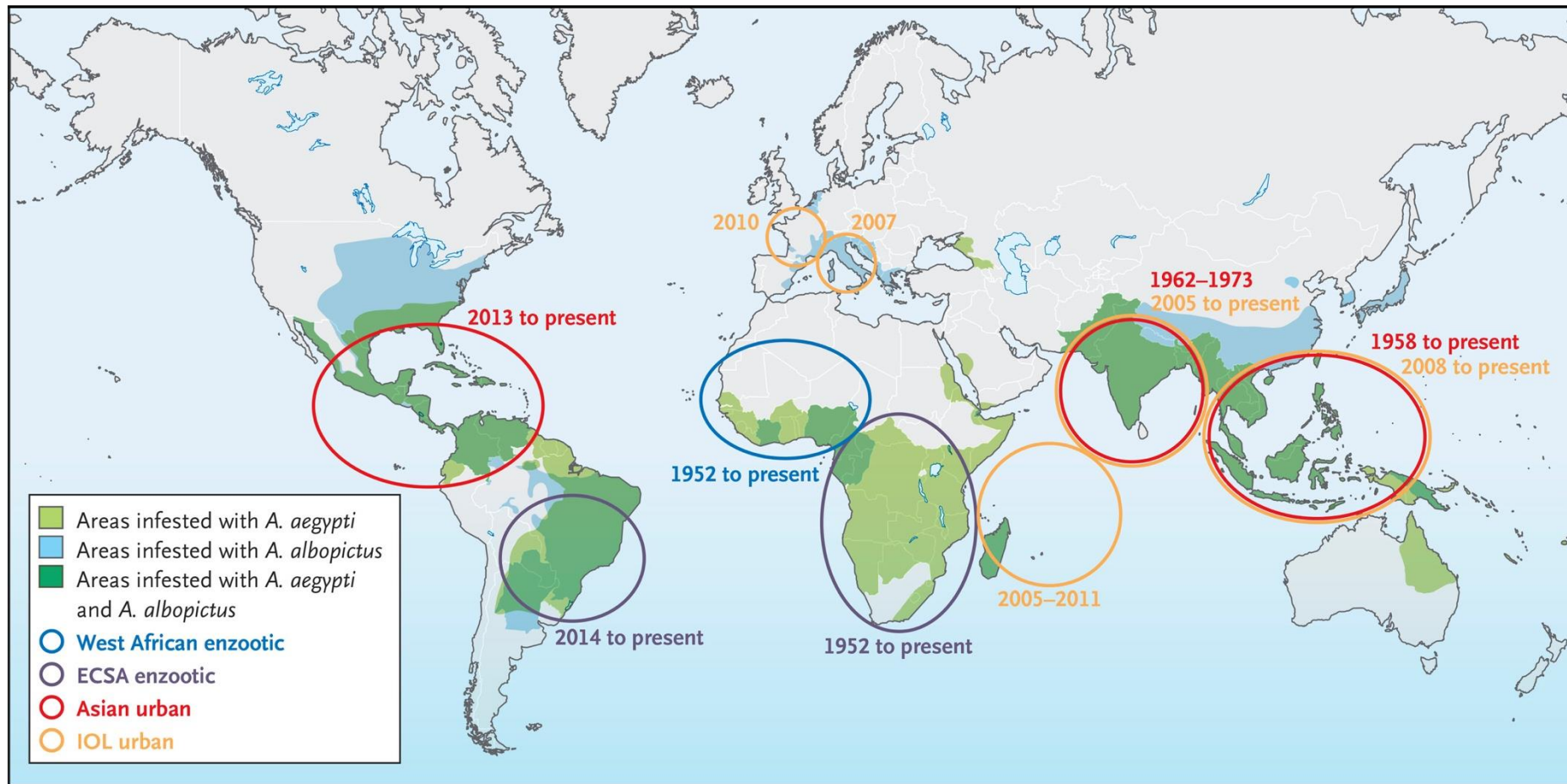
Published: September 12, 2019 • <https://doi.org/10.1371/journal.pntd.0007575>

Have deaths due to chikungunya infection been underestimated?

Data from Beeson et al., 2008. "Chikungunya Fever Mauritius, 2006"



Global spread of chikungunya virus Weaver and Lecuit, NEJM 2015



Annual disease burden of **106,000 DALYS** (Disability-Adjusted Life Year)

Puntasecca CJ, et al PLoS Negl Trop Dis. 2021

Chikungunya virus transmission

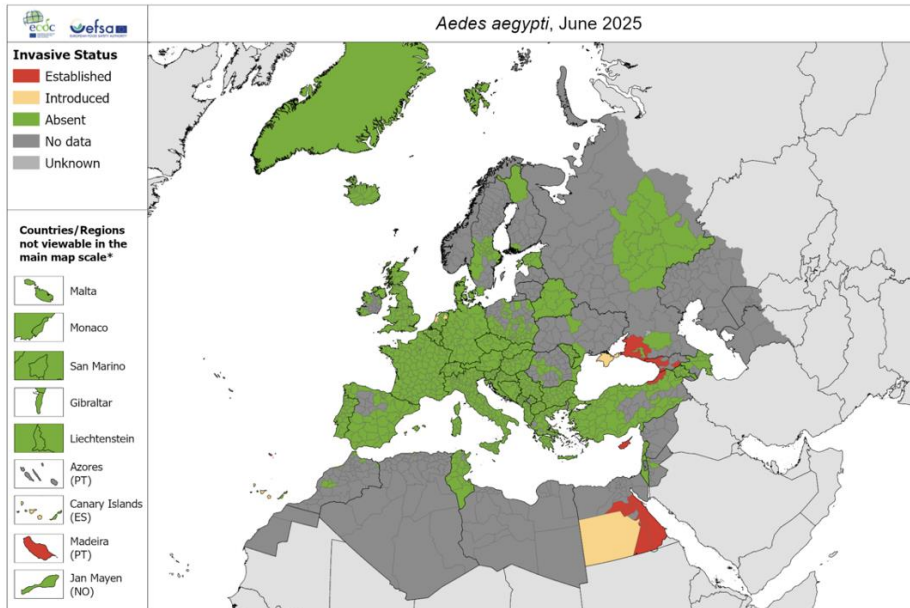
Mainly *Aedes aegypti* and *Aedes albopictus* mosquitoes, by bloodfeeding

Habitats likely to expand in future

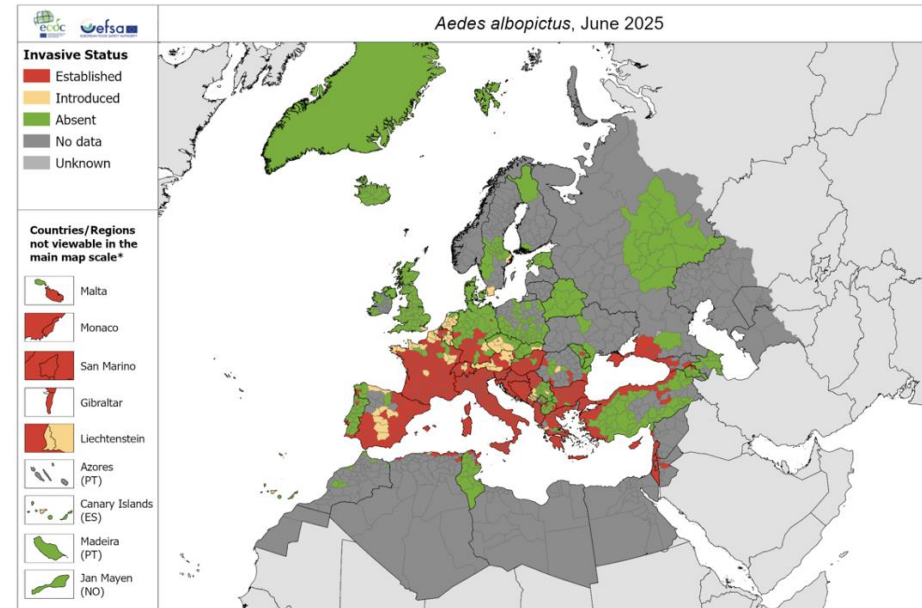


Current distribution of Aedes mosquitoes

Aedes aegypti, June 2025



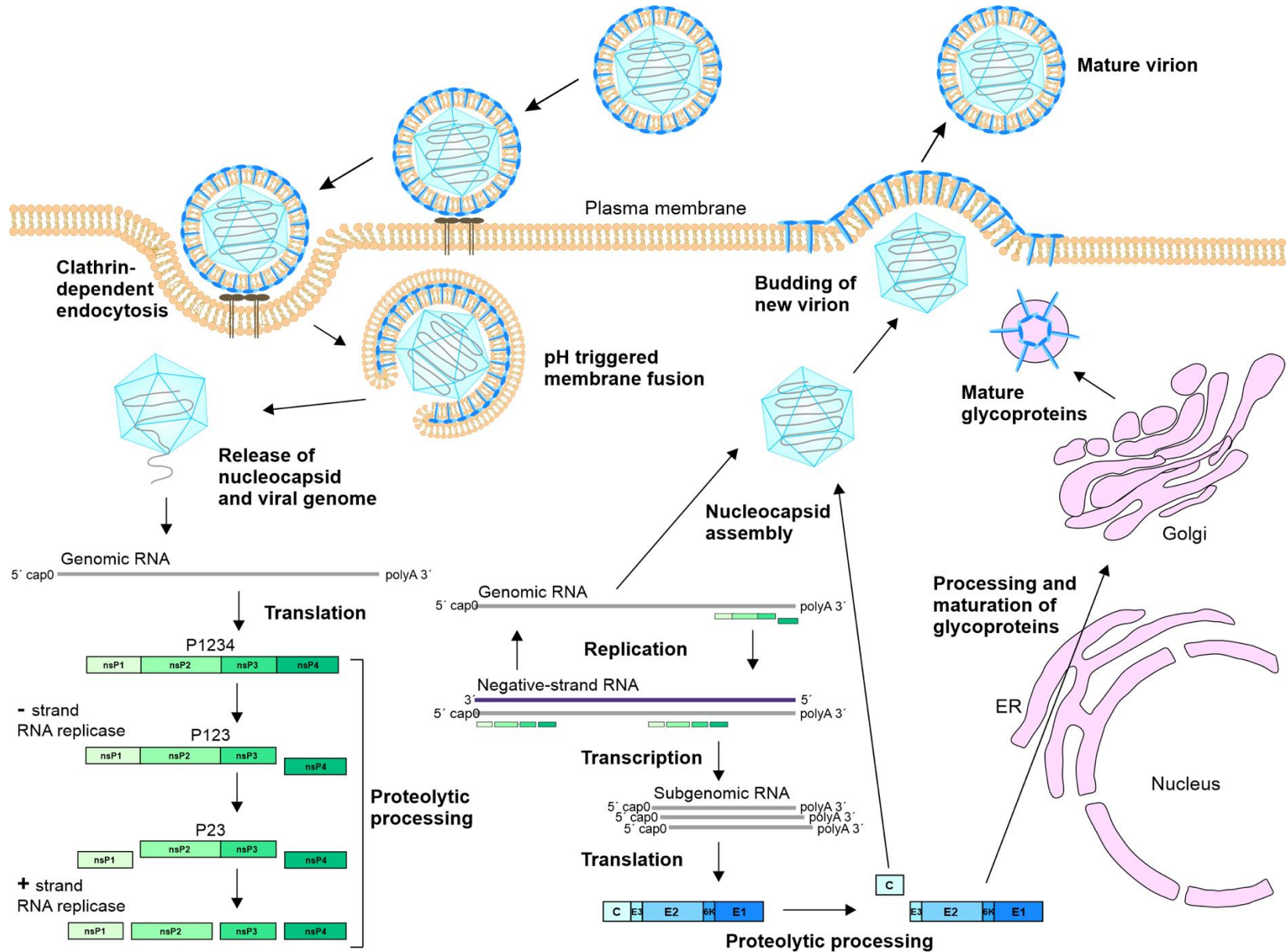
Aedes albopictus, June 2025



ECDC and EFSA, map produced on 15 Sep 2025. Data presented in this map are collected by the VectorNet project. Maps are validated by external experts prior to publication. Please note that the depicted data do not reflect the official views of the countries. * Countries/Regions are displayed at different scales to facilitate their visualisation. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Administrative boundaries © EuroGeographics, UNFPA.

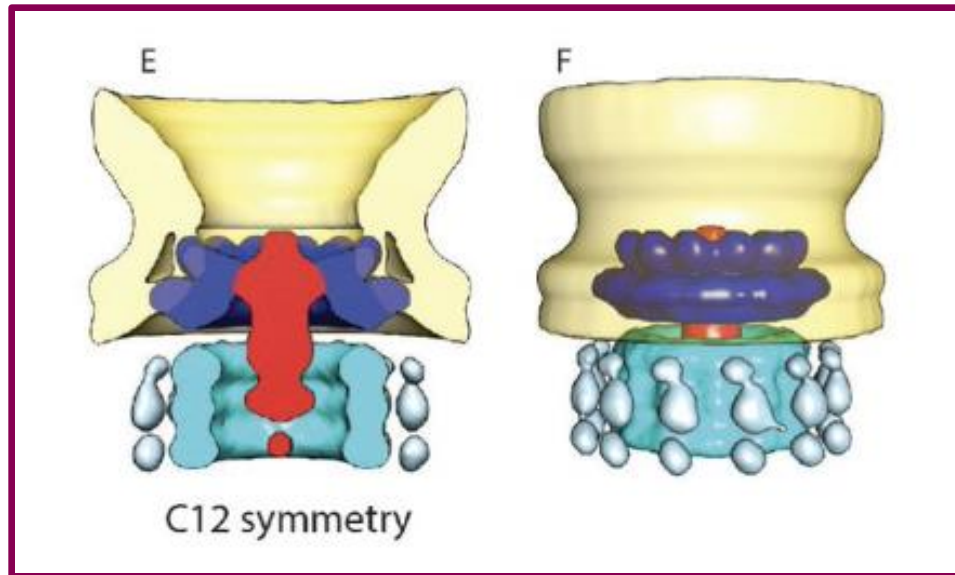
ECDC and EFSA, map produced on 15 Sep 2025. Data presented in this map are collected by the VectorNet project. Maps are validated by external experts prior to publication. Please note that the depicted data do not reflect the official views of the countries. * Countries/Regions are displayed at different scales to facilitate their visualisation. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Administrative boundaries © EuroGeographics, UNFPA.

Alphavirus intracellular life cycle



Alphavirus replication

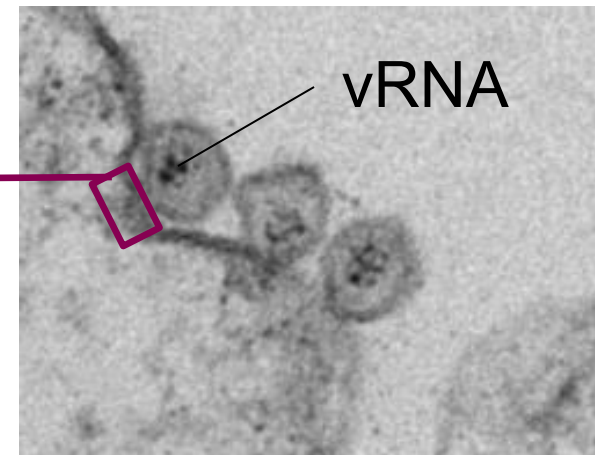
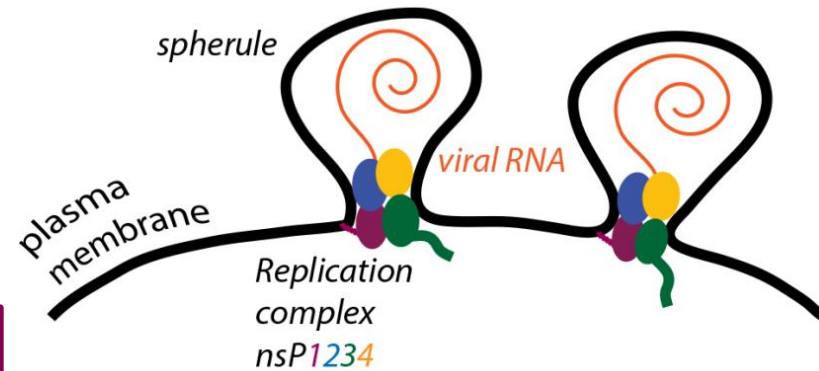
Replication complexes/spherules are formed at the plasma membrane



nsP1

nsP2, nsP4

nsP3



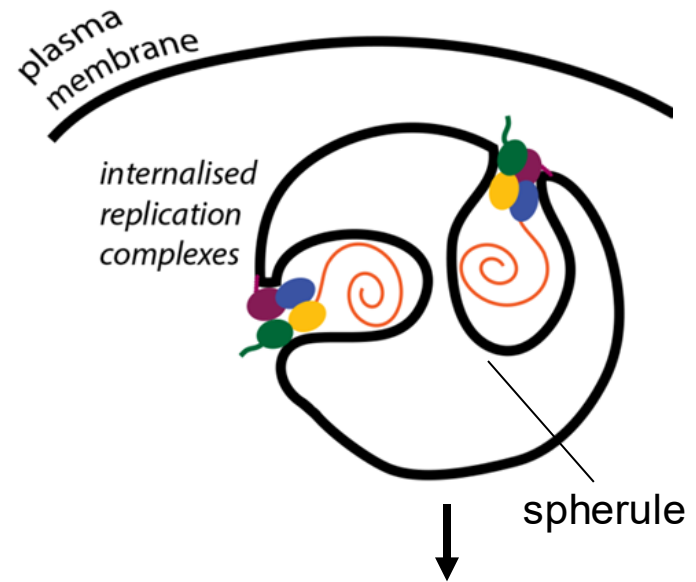
Diameter: ~ 60 nm

Alphavirus replication

Replication complexes/spherules are formed at the plasma membrane

and are then internalised:
modified endosomes/“cytopathic vacuoles”

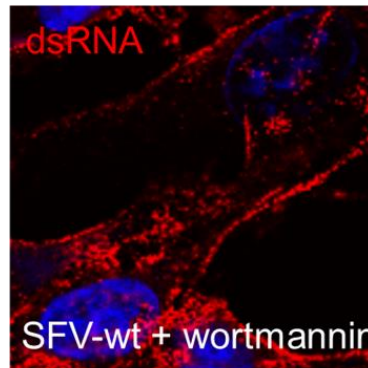
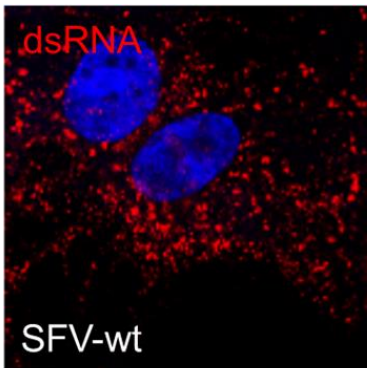
Internalisation dependent on host Akt pathway



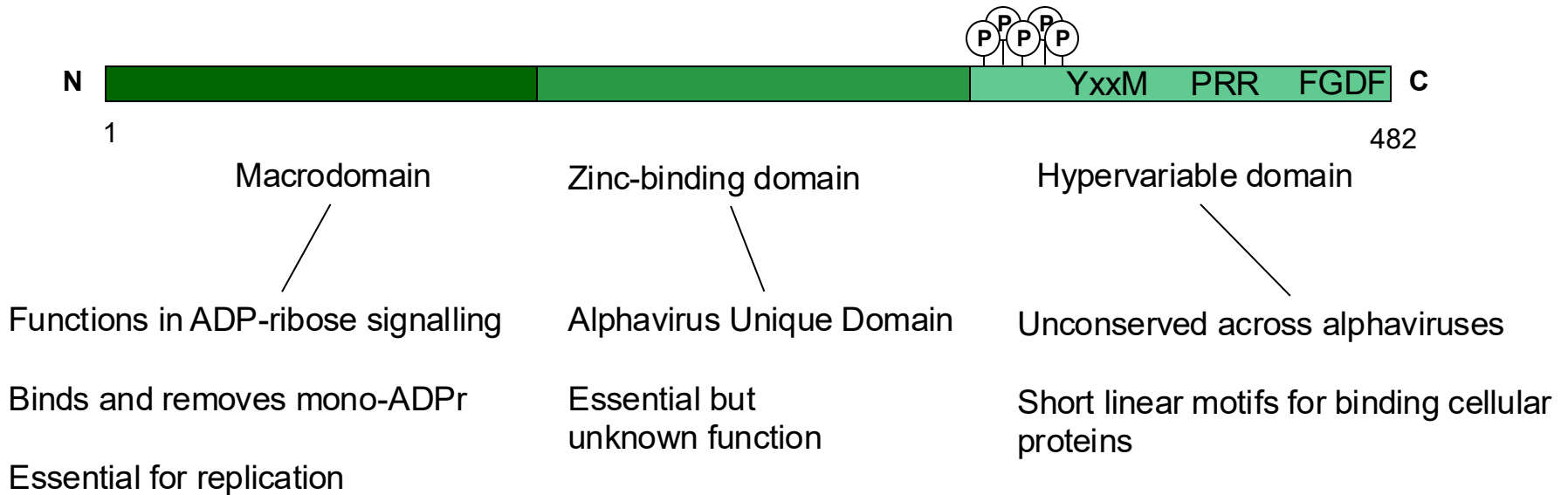
CPV



200 nm



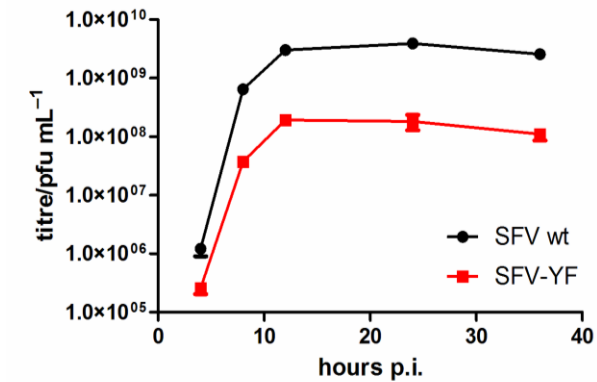
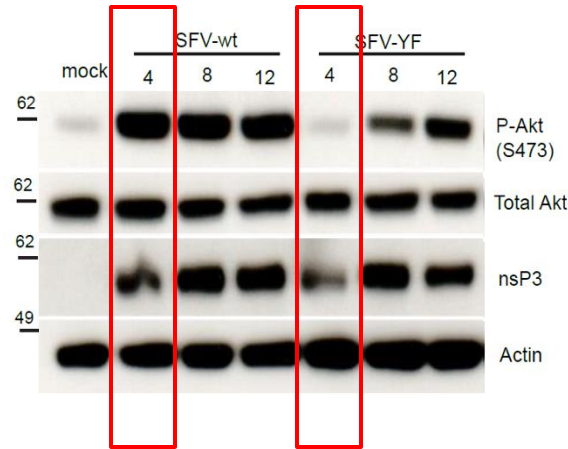
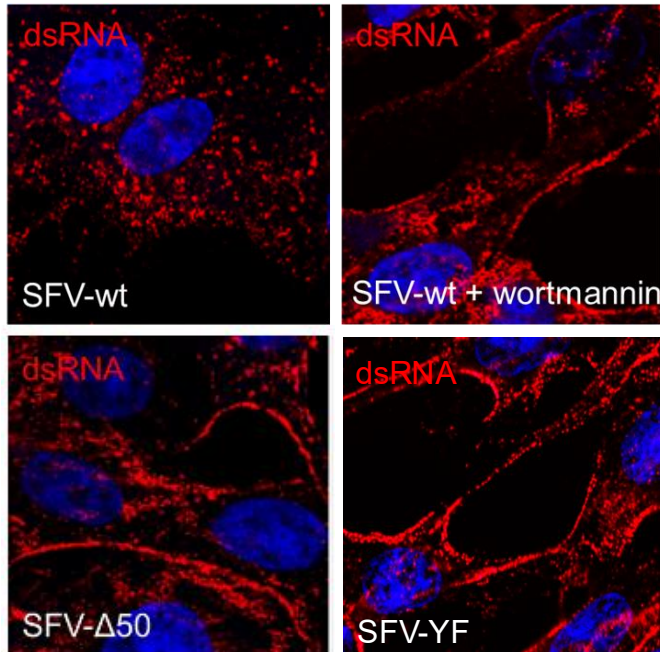
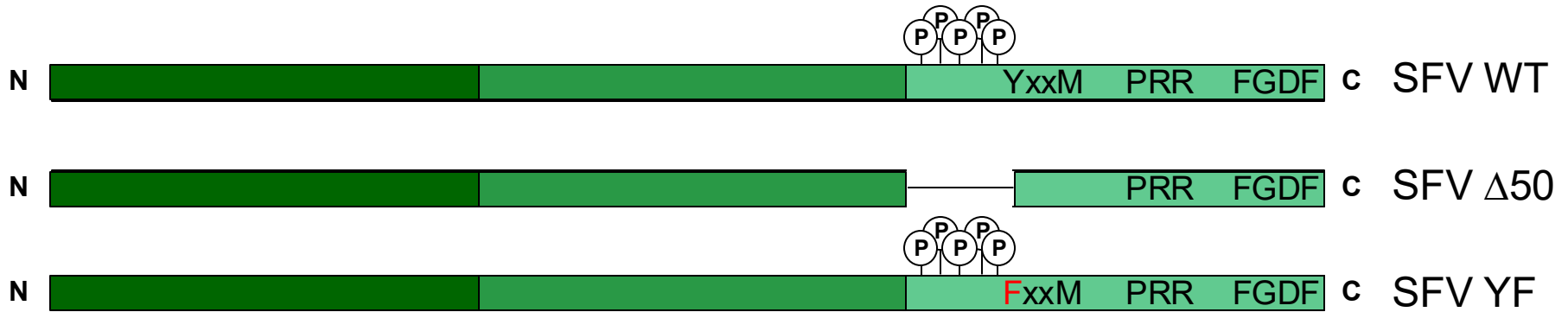
Non-structural protein 3 nsP3



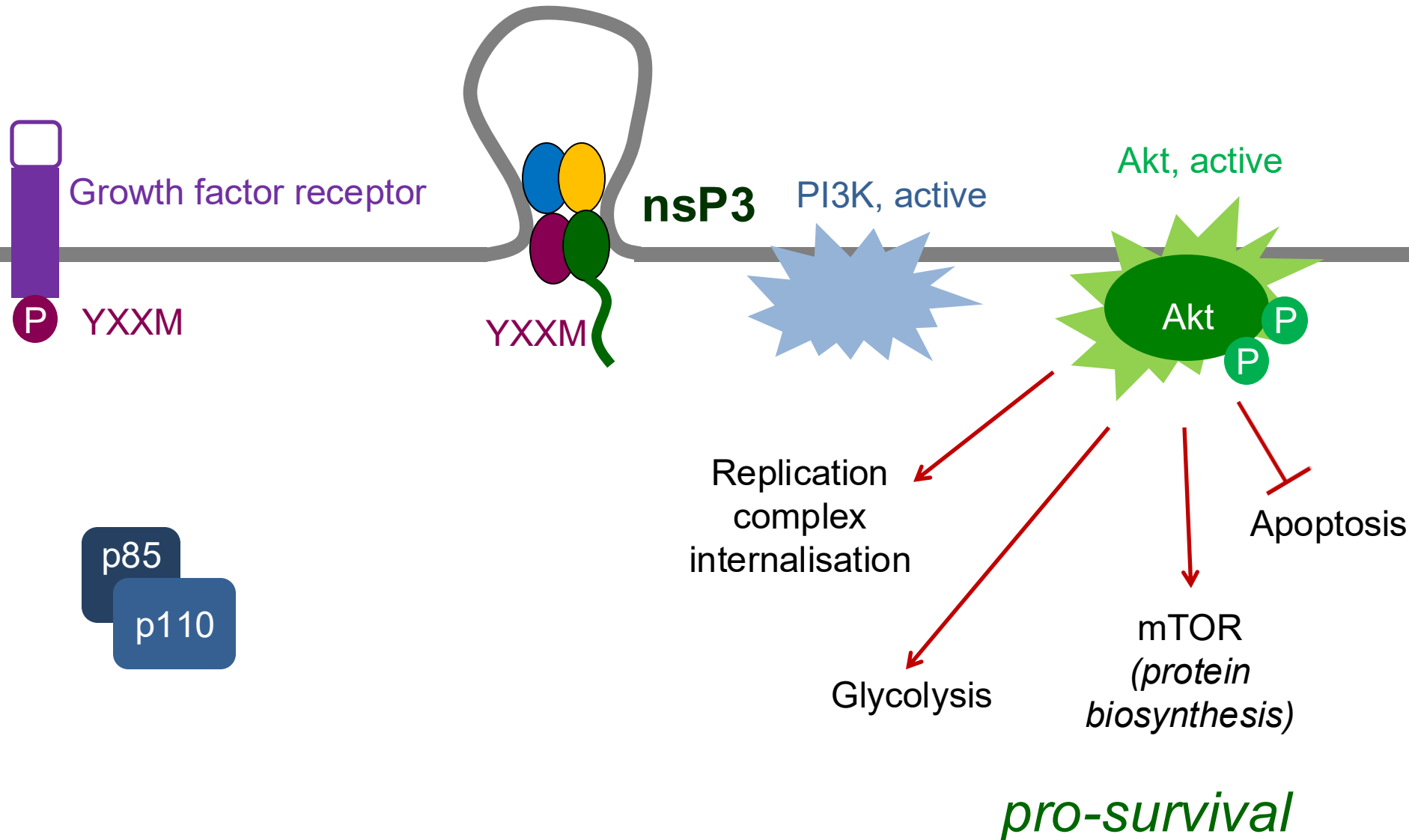
Previously known as the 'enigmatic' nsP since no single function was known

Now mainly thought of as a hub for host cell protein interactions

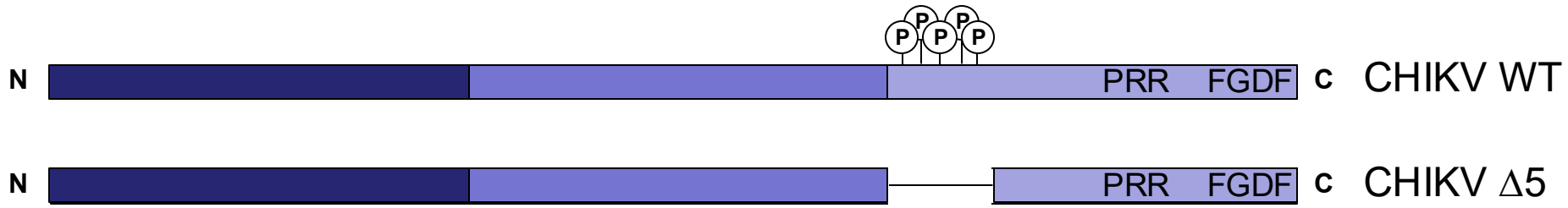
SFV infection activates cellular Akt pathway for efficient replication



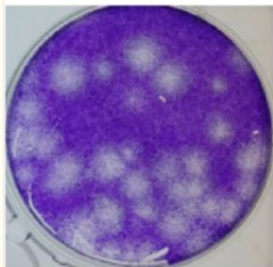
The YXXM motif in SFV nsP3 mediates Akt activation



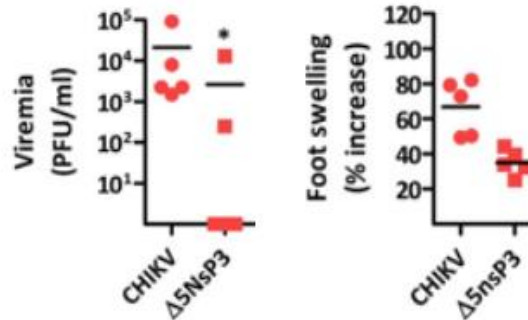
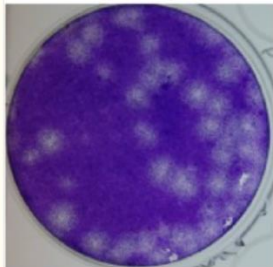
Based on SFV- Δ 50, a similar mutation was generated in CHIKV



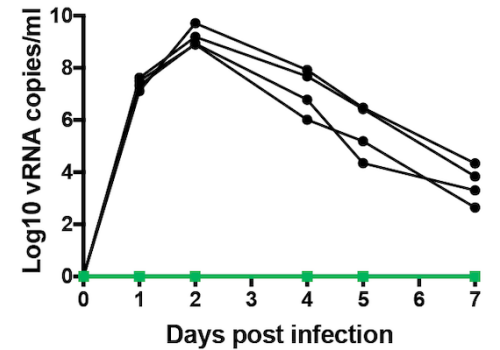
WT



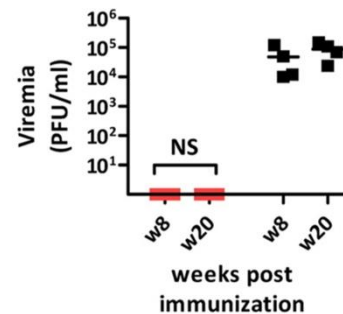
Δ 5



Challenge with WT CHIKV



Challenge with WT CHIKV

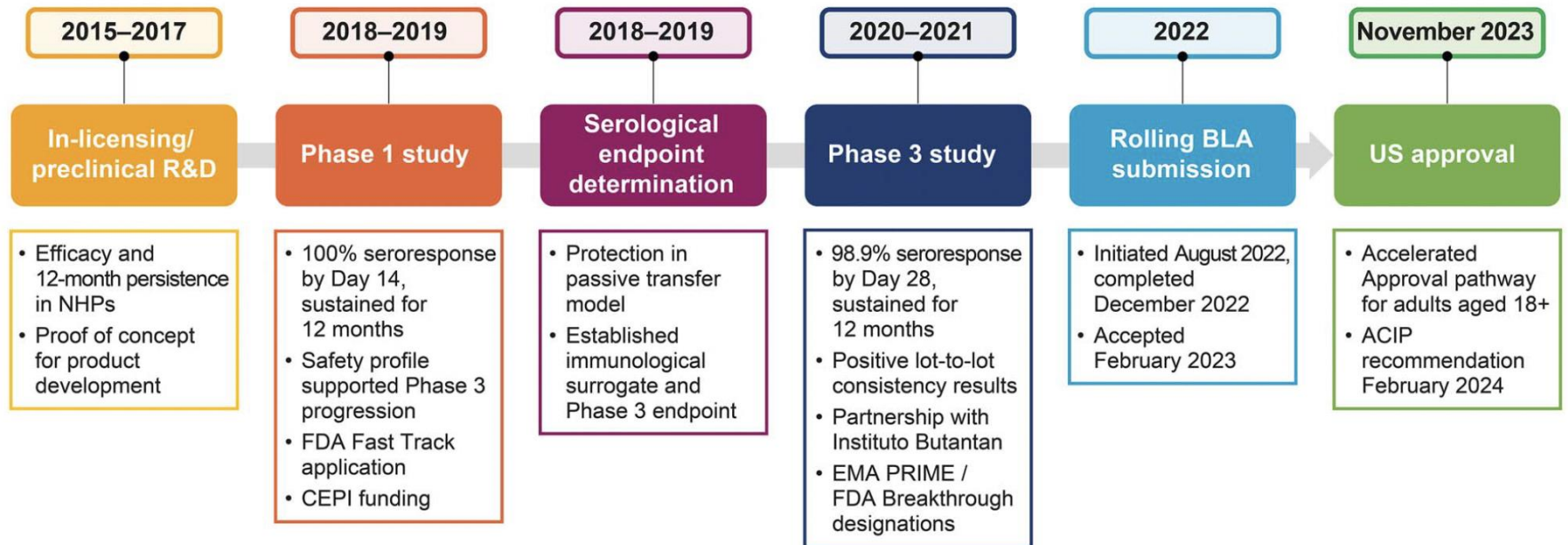


— PBS
— Δ 5nsP3

CHIK Δ 5 developed into a live-attenuated vaccine by

CHIKV- Δ 5 (now VLA1553) was developed by Valneva into a live attenuated viral particle vaccine

VLA1553 development pathway Chen et al., J Travel Med, 2024



September 30, 2025 - Valneva reports 95% seroresponse 4 years after single shot of IXCHIQ (antibody persistence is planned to be collected up to 10 years after vaccination).

Some adverse effects in elderly patients have dampened optimism

Här tar forskarna sitt eget vaccin

De är bland de första i Sverige som vaccinerar sig mot *chikungunya-viruset* – ett vaccin som är resultatet av en upptäckt från deras eget laboratorium.

Text: **Catarina Thepper** Foto: **Fredrik Persson**

VI BESTÄMDE OSS, hela forskargruppen, för att gå och ta vaccinet tillsammans, lite som en happening. Det var en speciell upplevelse, säger Gerald McInerney, professor i molekylär virologi vid Institutionen för mikrobiologi, tumör och cellbiologi, Karolinska Institutet. Forskarna vaccinerade sig för att de behöver skyddet mot sjukdomen i sitt fortsatta arbete med viruset. Vanligtvis är det här ett vaccin som svenskar tar

när de ska resa till länder som har ett utbrott av chikungunya, en sjukdom som sprids med myggor i tropiska och subtropiska länder i Central- och Sydamerika, Afrika och Asien. Chikungunya betyder "att bli böjd" på makonde, ett språk som talas i Tanzania, det land där det allra första utbrottet kom. Sjukdomen är sällan dödlig, men går inte att bota, och kan orsaka ledsmärtor så svåra att de drabbade inte klarar av att rata på ryggen. I låginkomstländer har chikungunya drabbat samhällen hårt. En man eller kvinna svårt sjuk i chikungunya kan inte arbeta och försörja sin familj.

forskningsprojekt som handlade om att försöka förstå chikungunya-virusets funktioner och strukturer. Vi använde våra kunskaper i virusgenetik och valde ut delar av virusets genom som vi misstänkte kunde ha betydelse. Sedan tog vi bort just de delarna och studerade

Toppklass!

○ **Vetenskapsrådet har gett forskningen vid Karolinska Institutet högsta betyg i en utvärdering av svenska lärosätens medicinska grundforskning och dess påverkan på samhället. Läs mer på nyheter.ki.se**

VACCINET MOT VIRUSET togs fram efter en upptäckt av **Peter Liljeström**, professor emeritus i smittskydd vid Institutionen för mikrobiologi, tumör och cellbiologi, Karolinska Institutet. Upptäckten gjordes under ett grund-

de fick fr En virus replik Perfekt vaccin



Gerald McInerney vaccineras mot viruset i hans forska om.



Ett vaccin måste ha förmågan att stimulera immunförsvaret utan att självt ge en sjukdom. Det var också mycket viktigt att konstatera att det muterade viruset förblev stabilt och inte kunde omvandlas tillbaka till ett aktivt virus, säger Peter Liljeström.

"Det känns jättebra att vår upptäckt blev ett vaccin!"

har fått stöd av den internationella organisationen CEPI som har som villkor att länder i låg- och medelkomstländer ska få tillgång till ett lägre pris vid ett utbrott i turerna. Det är en av orsakerna till att det känns jättebra att vår upptäckt blev ett vaccin! Jag har ju forskat i immun och infektionssjukdomar människors liv bättre, och jag att jag nådde mitt mål

med att vara KI professor, säger Peter Liljeström, som numera är pensionerad, men fortfarande aktiv som forskare.

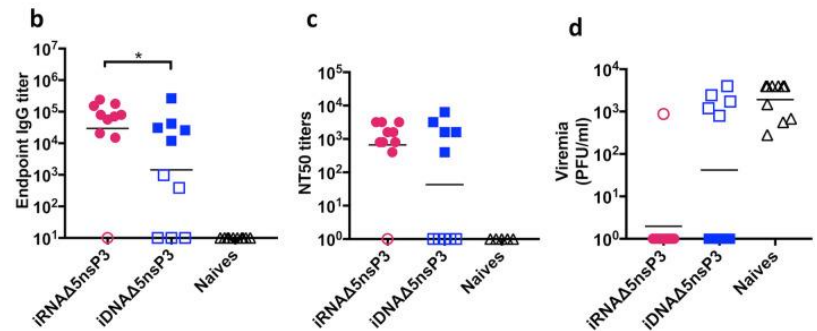
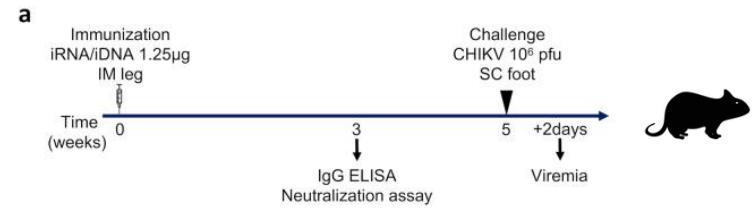
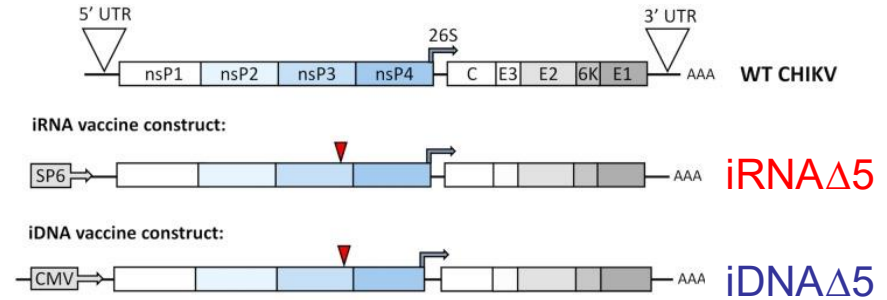
SPORADISKA UTBROTt av chikungunya har förekommit även i USA och i södra Europa. Den globala uppvärmingen medför att myggor sprider sig norrut. Det är en av orsakerna till att det är viktigt att fortsätta studera viruset. Vi vet nu att det muterade virus som används i vaccinet fungerar, men vi vet inte varför. Om vi förstår mekanismen kanske vi också kan använda kunskapen för att skapa vaccin mot andra virus, säger Gerald McInerney.

CHIK Δ 5 can also be delivered as mRNA or DNA vaccine constructs

Intramuscular injection of 1.25 μ g iRNA or iDNA alone was sufficient to generate protective immune responses in C57BL/6J mice

(b) Anti-CHIKV IgG endpoint titers and (c) 50% neutralization titers (NT50) were determined three weeks after a single immunization with the candidate vaccines.

(d) Viremia was determined by plaque assay using serum samples collected at day two post challenge. Filled symbols indicate mice that were protected against challenge, whereas open symbols indicate mice that were not protected against infection with CHIKV. The line indicates the geometric mean of each group (n = 10 animals per group).



Acknowledgements

CHIKV- Δ 5

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Alphavirus Research Group

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Dept Microbiology, Tumor and Cell Biology



Mykhailo Guzyk, Shirley Braspenning, Marie Peters, Hanna Bley,
Laura Perez Vidakovics, Gerry McInerney

Previous – Kai Eng, Bastian Thaa, Lifeng Liu

PhD student position open – check out ki.se/jobs

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