A One Health Case Study of Chikungunya: An Emerging Disease

Renee Prater, DVM, MS, PhD; Teresa R. Johnson, MS, PhD;
Alexis M. Stoner, MPH; Matthew D. Cannon, DO;
Nammalwar Sriranganathan BVSc, MVSc, PhD, ACVM.

Learning Objectives

1. Define the pathogenesis of Chikungunya virus (CHIK-V) and describe the factors which contribute to the processes of virus infection, spread, and disease causation.
2. Identify the role of domesticated and wild animals in the spread of CHIK-V.
3. Recall the epidemiology of CHIK-V including the distribution and determinants of disease.
4. Identify preventive measures and vector control procedures that can be applied to reduce the transmission of CHIK-V and how they may differ across populations.
5. Based on clinical signs and relevant diagnostic tests, differentiate between Chikungunya fever and other differential diagnoses including: Dengue, typhoid, Lyme disease, rheumatoid arthritis, West Nile and lupus.
6. Recall the proper treatment protocols for a patient diagnosed with CHIK-V.

Emerging Diseases

Defined: “infectious diseases whose incidence in humans has increased in the past two decades or threatens to increase in the near future.” - Centers for Disease Control

Common Associated Characteristics

- Often do not respect national boundaries
- Typically are infections spreading to new regions or populations
- May result from changes or evolution of existing organisms
- Previously unrecognized infection undergoing ecologic transformation
- Old infections re-emerging due to antibiotic resistance
- Breakdown in public health measures

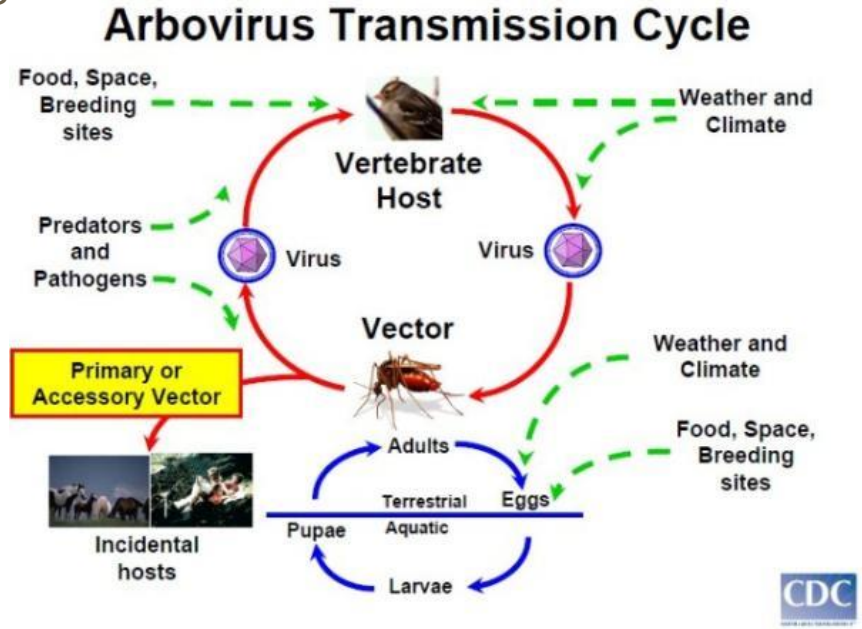
Examples

- Severe Acute Respiratory Illness (SARS)
- Lyme disease
- Ebola in West Africa
- Bubonic plague

Emerging Diseases

Environmental changes have greatly impacted the distribution of vectors and transmission of diseases resulting in the spread of infectious diseases

- **Urbanization**
- **Global Warning**
- **Deforestation**
- **Increased human global travel**



One Health

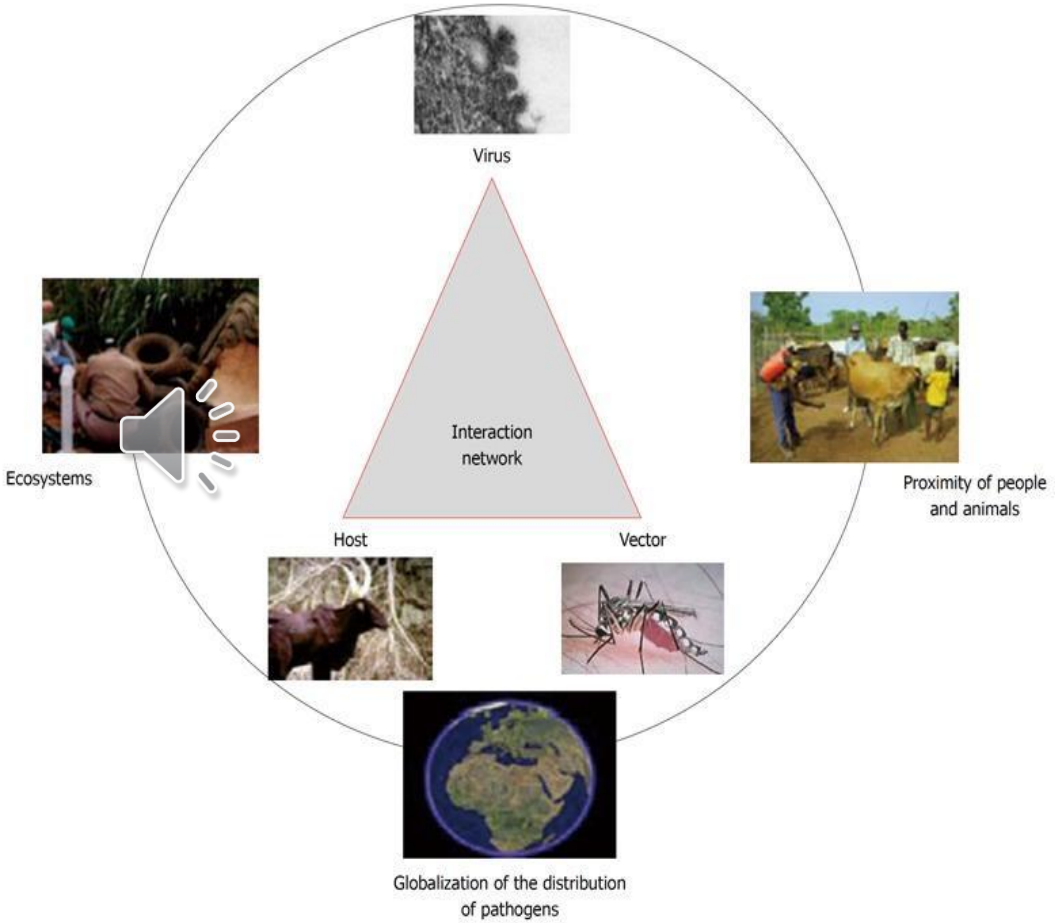
"**The collaborative effort of multiple disciplines - working locally, nationally, and globally - to attain optimal health for people, animals and the environment**"
The American Veterinary Medical Association. One Health Initiative Task Force.

Important <u>intersection</u> between animal, human, and ecosystem which:

- impacts the health of each component
- is affected by economics, culture, and the global context
- may be directly influenced by appropriate detection, response and prevention

One Health

As our interactions with the environment and the ecosystems around us change, human and animal health, the ecosystem, and the environment may be dramatically affected.



Review Questions

How is Chikungunya a disease that is illustrative of the One Health philosophy?

Can you think of another example of an emerging disease either within the US or a different country?

Based on the One Health relationship, what factors contributed to the development and spread of disease in the example you described above?

Chikungunya virus (CHIK-V)

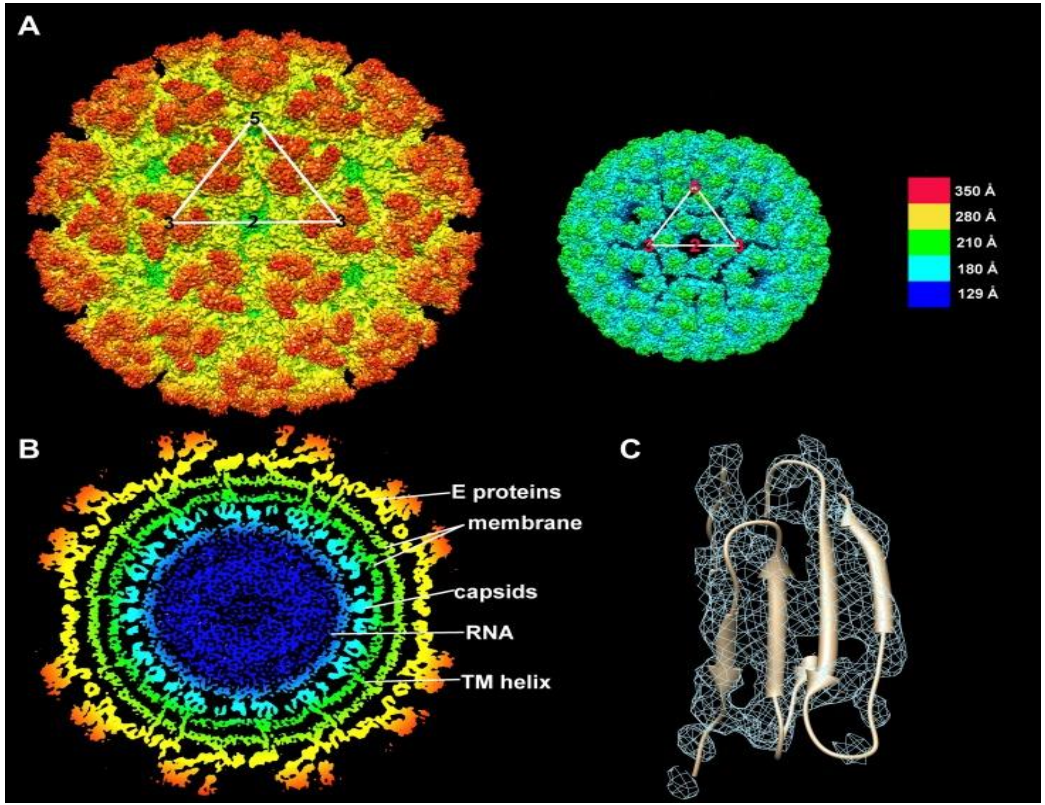
Single-stranded positive sense RNA virus

Family *Togaviridae*

Genus *Alphavirus*

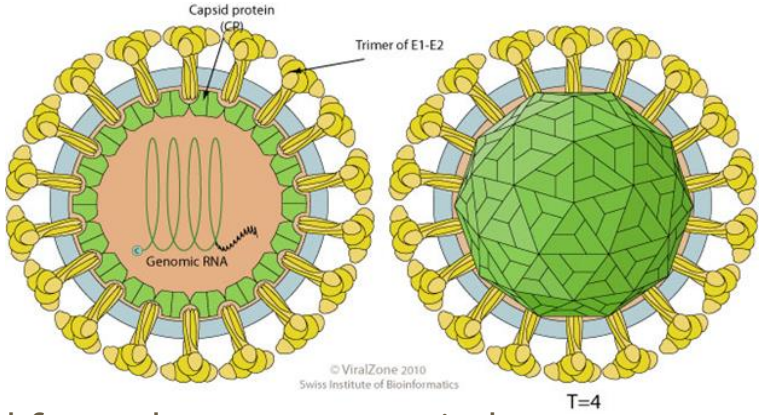
Similar to viruses that cause:

- **West Nile**
- **Yellow fever**
- **Eastern, Western, or Japanese equine encephalitis**



An interactive graphic of Chikungunya virus, its epidemiology, and its diagnosis and treatment:
http://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMra1406035&aid=NEJMra1406035_attach_1&area=

CHIK-V surface proteins



The viral genome encodes surface proteins E1 and E2.

These proteins are inserted into the viral envelope and form the outer protein layer surrounding the virus.

E1 is a **fusion protein** (fuses to receptor -prohibitin- on the host cell membrane)

E2 is an **attachment protein** (E1 and E2 form a complex to enhance viral endocytosis through clathrin-coated pits).

Mutations in these proteins alter viral replication.

These proteins may also serve as targets for humoral immune response and drug development.

CHIK-V
Entry into host cells

Virus attaches to host cell using E1, E2

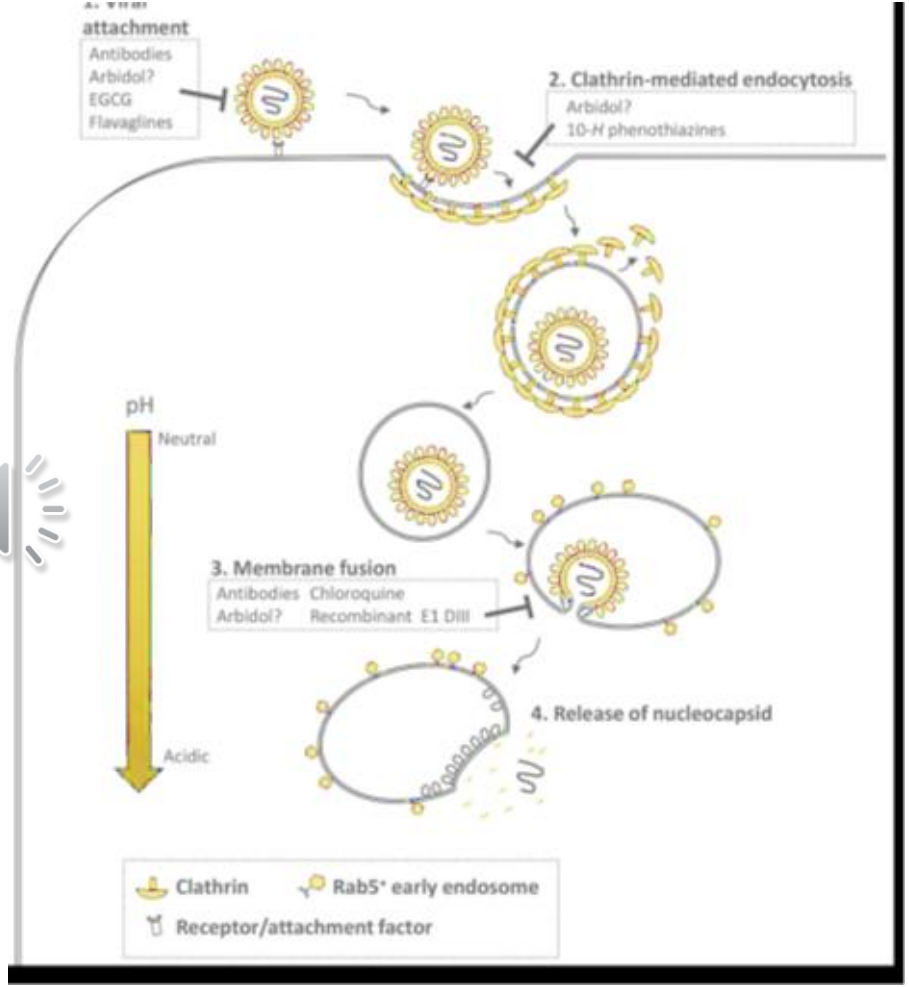
Target cell is usually dermal fibroblast, then skeletal muscle, tendons, joints.

Virus is internalized via clathrin-mediated endocytosis

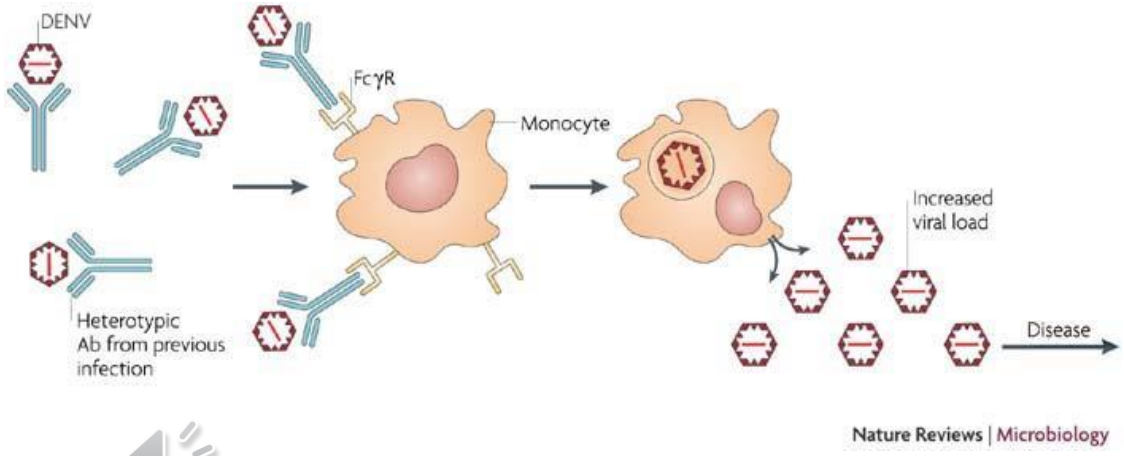
Virus is delivered to Rab5+ endosome

E1 and E2 undergo conformational change leading to membrane fusion

Nucleocapsid is released into cytosol



CHIK-V interaction with antibodies



E1 and E2 proteins are targets for antibody production.

However, this process can actually enhance infection by antibody-dependent enhancement or ADE:

1. Antibodies are formed vs. E1 and E2
2. Antibodies bind E1 and E2
3. Fc portion of the antibody bound to E1 and E1 binds to FcR on macrophages, which facilities infection of these cells.
4. This allows widespread dissemination of virus to multiple target organs.

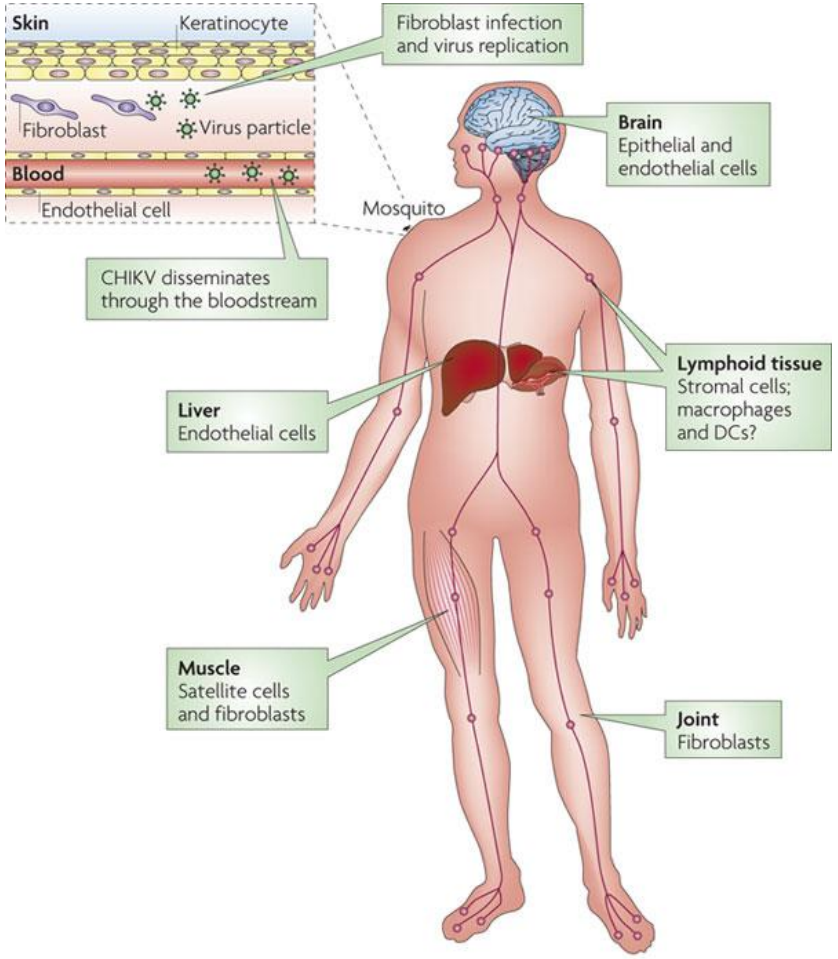
Systemic CHIK-V targets

Initial host cell target: dermal fibroblasts at the site of *Aedes* mosquito bite.

CHIK-V replicates in the fibroblasts.

ADE facilitates systemic distribution of the viral particles via macrophages to:

- Liver
- Muscle
- Joints
- Lymphoid tissue (lymph nodes/spleen)



Nature Reviews | Microbiology

Transmission of CHIK-V: Role of the mosquito

CHIK-V is transmitted through the bite of infected mosquitoes.

Female mosquito is the only one who bites animals and people.

When she bites, she injects a small amount of saliva into the wound to delay blood clotting.

Since CHIK-V replicates in salivary glands, this saliva deposit transmits the virus to the skin of her victim.

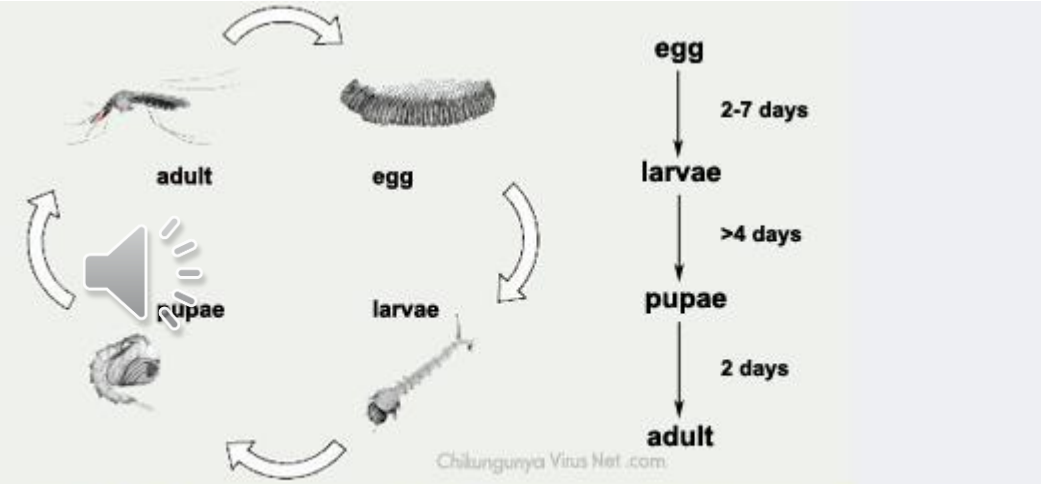
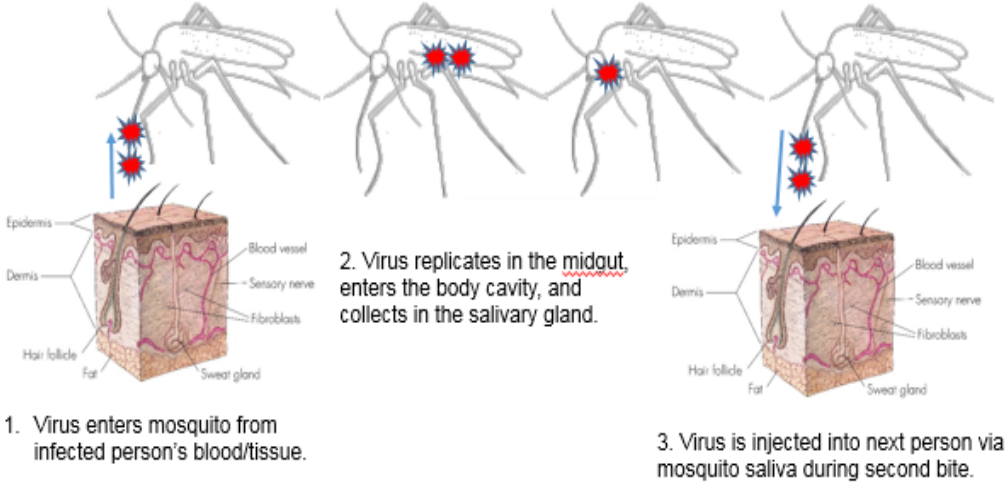


Figure 1: Life cycle of Aedes aegypti: there is an aquatic phase (larvae, pupae) and a terrestrial phase (eggs, adults)

Transmission of CHIK-V: Critical Factors

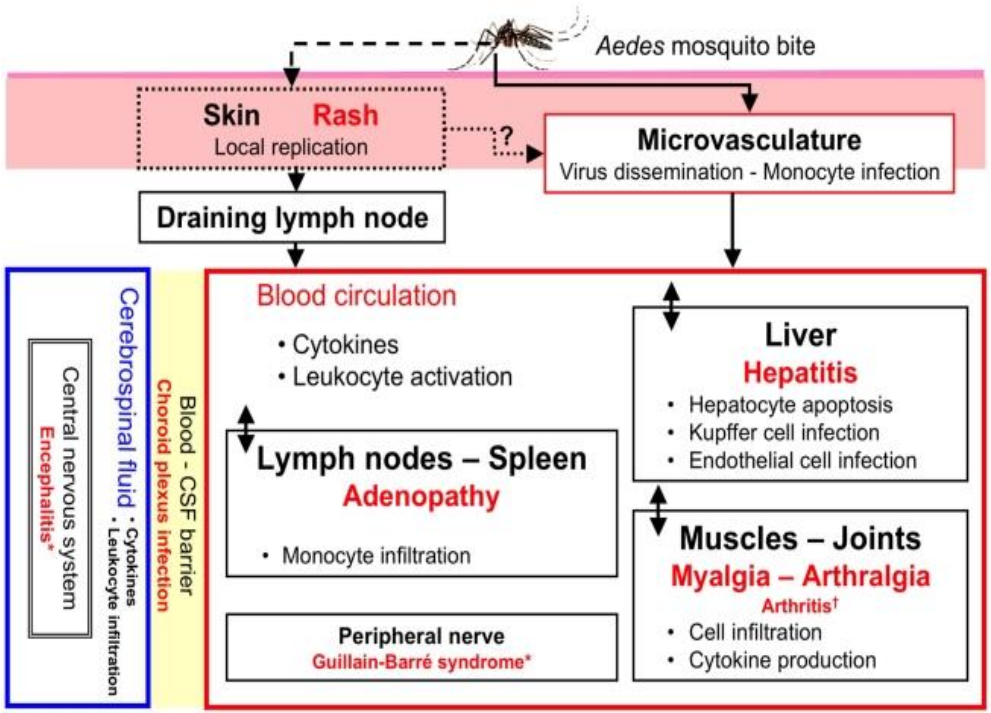
Critical Factor #1: In the mosquito, the virus in the ingested blood must be able to infect cells of the midgut of the mosquito, then disseminate to replicate in the salivary glands.

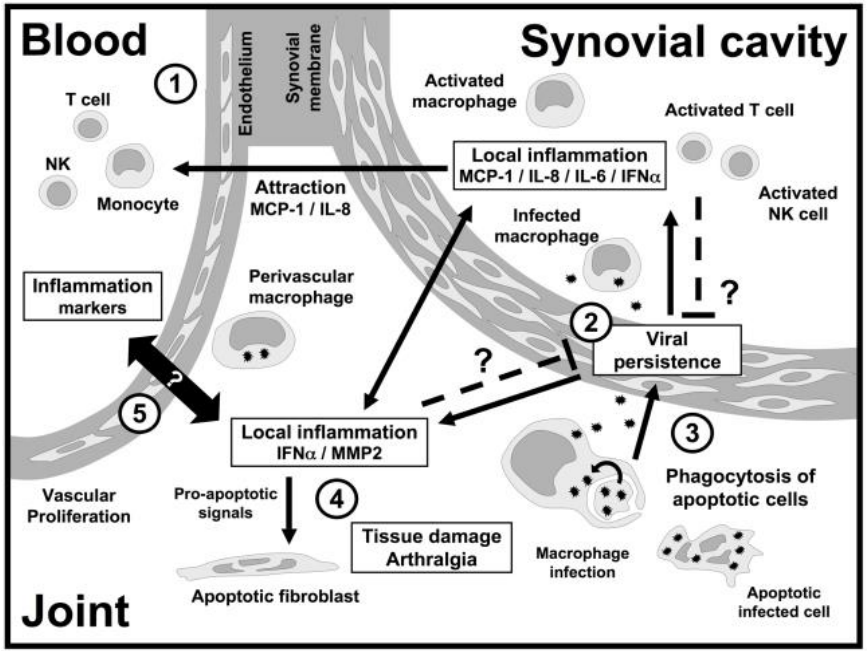


Critical Factor #2: In the bitten and infected host, the virus must replicate in the local dermal fibroblasts and migrating macrophages for transport to the vascular endothelium in order to replicate and establish viremia at a concentration sufficiently high that the virus may be transmitted back to a mosquito during feeding.

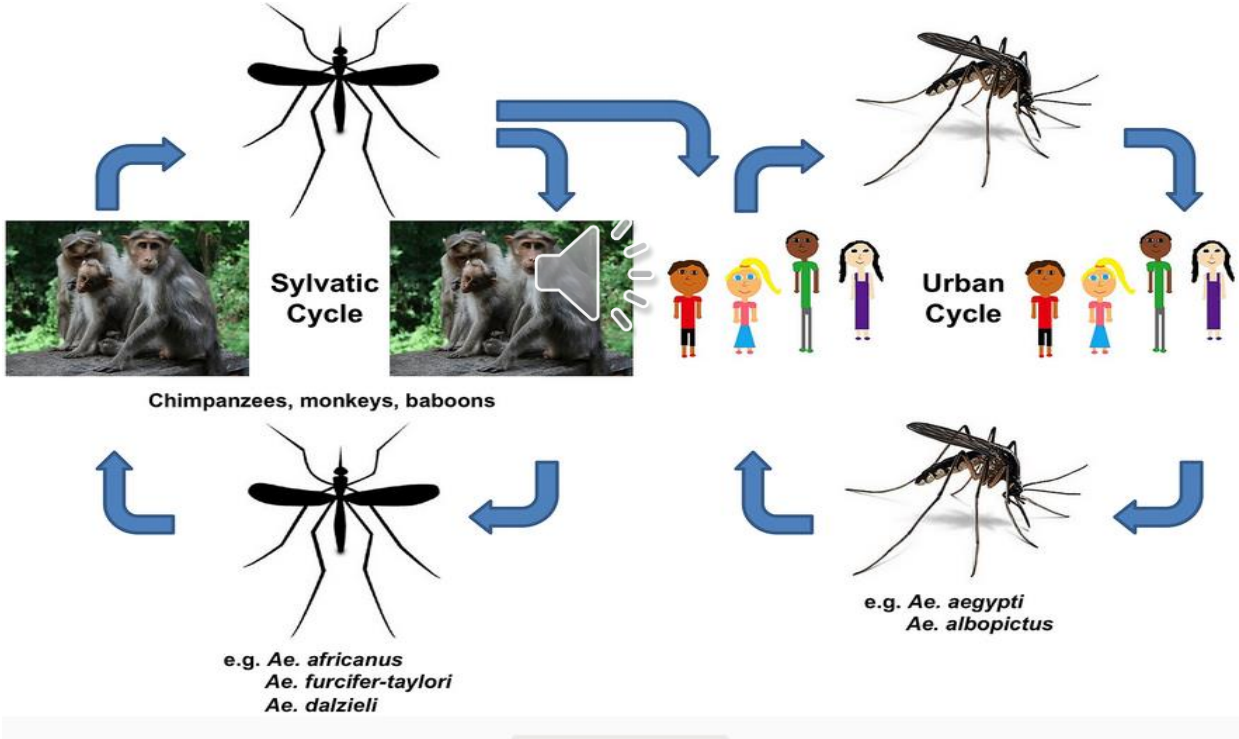
Transmission of CHIK-V

As virus replicates in the infected host, it is disseminated to tissues as the infected macrophages migrate throughout the body, potentially establishing persistent infection. Infected macrophages may also traffic to the joint spaces where the virus-specific immune response and/or an autoimmune response creates an inflammatory environment, leading to the arthralgia seen in acute and recurrent disease as shown in the diagrams below.





CHIK-V Transmission Cycles: Sylvatic vs. Urban



Evolution of the Virus

1950s

- Re-emergence of CHIK-V in the human Population
- Sub-Saharan Africa

Virus Spread

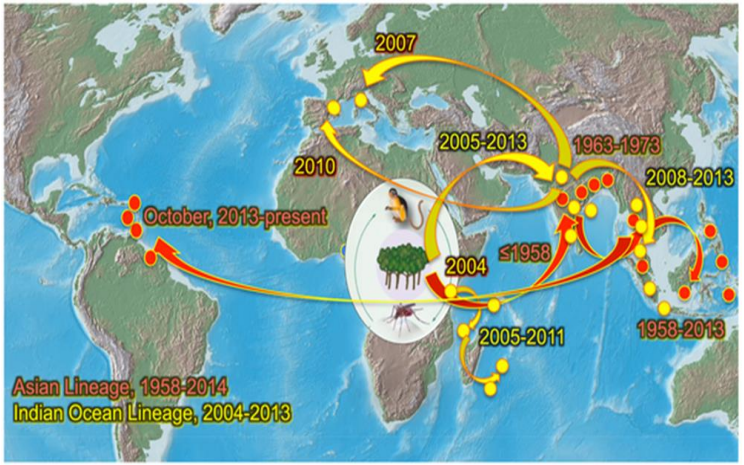
- First to Central/East Asia
- Then to Southeast Asian countries around Indian Ocean

Genetic Drift

- Gave gave rise to 3 distinct but related lineages - the West African, the East/Central/South African (or ECSA), and the Asian genotypes

2004

- Single point mutation (A226V) appeared in the ECSA lineage during an outbreak in coastal Kenya which increased virion stability
- Altered CHIK-V transmission



Carriers of Chikungunya

Africa, India, and Southeast Asia	Western Hemisphere
• Sylvatic transmission between infected non-human primates and *Aedes spp. mosquitos* • China – Bats • Asymptomatic infection of rodents	• Animal reservoirs have yet to be determined • Mosquito-human-mosquito is primary mode of infection

Carriers of Chikungunya - Emerging Concerns

Concern within the medical community has been the possibility for livestock and domesticated animals to be infected and serve as reservoirs for CHIK-V, increasing transmission to human populations living in close contact with these animals.

However, research supports the hypothesis that, while domesticated and wild animals may be exposed to CHIK-V, most cannot support virus replication at all or at a level that produces viral titers in the blood high enough for mosquitoes to be infected during feeding.

Table 1 Number of specimens tested by qRT-PCR and by ELISA, and number of seropositive animals

		qRT-PCR	ELISA	
Species	**Sampling location**	**Number tested***	**Number tested**	**Number positive (%)**
Domestic carnivores				
Cat - *Felis catus*	Reunion	38	37	0
Dog - *Canis lupus*	Reunion	69	68	0
Farm mammals and poultry (Reunion Island)				
Horse - *Equus ferus*	Reunion	76	97	0
Cattle - *Bos primigenius*	Reunion	115	116	0
Goat - *Capra aegagrus*	Reunion	95	115	0
Sheep - *Ovis aries*	Reunion	25	49	0
Pig - *Sus scrofa*	Reunion	48	108	0
Poultry - *Gallus gallus*	Reunion	37	113	0
Wild mammals				
Shrew - *Suncus murinus*	Reunion	105	45	0
Ship rat - *Rattus rattus*	Reunion	74	75	3 (4.0%)
Norway rat - *Rattus norvegicus*	Reunion	6	17	0
House mouse - *Mus musculus*	Reunion	33	20	0
Reptiles				
Panther chameleon - *Chamaeleo pardalis*	Reunion	17	not tested	not tested
Non-human primates				
Brown lemur - *Eulemur fulvus*	Mayotte	53	52	2 (3.8%)
Crab-eating macaques - *Macaca fascicularis*	Mauritius	not tested	134	1 (0.7%)
Crab-eating macaques - *Macaca fascicularis*	Reunion	not tested	1	1 (100.0%)
Hamadryas Baboon - *Papio hamadryas*	Reunion	not tested	2	0
Southern Pig-tailed Macaque - *Macaca nemestrina*	Reunion	not tested	1	0
Campbell's Monkey - *Cercopithecus campbelli*	Reunion	not tested	1	0
Total		**791**	**1051**	**7**

*All samples were negative by qRT-PCR.

Transmission pathways of CHIK-V

Most CHIK-V genotypes (African, ECSA and Asian) are transmitted between humans, non-human primates, and bats by a single arthropod vector, the *Aedes aegypti* mosquito.

However, the newly emerged Indian Ocean Lineage (IOL) strain of CHIK-V (that contains a mutation in E1) is transmitted between animals and people via two arthropod vectors, the *Aedes aegypti* and *Aedes albopictus* mosquitoes.

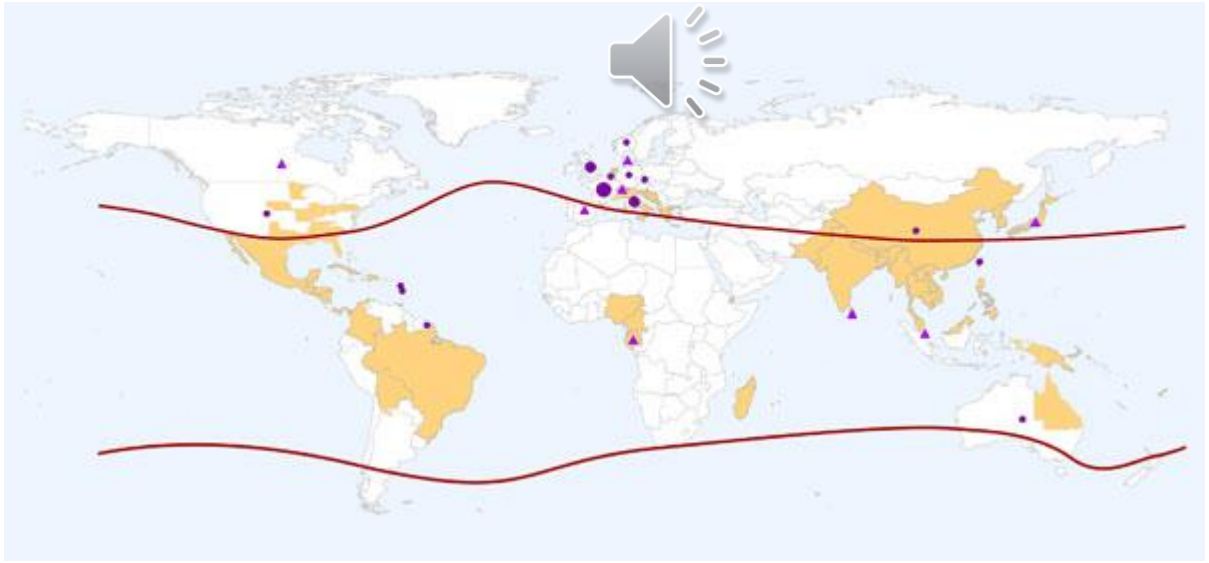
The ability to infect this additional vector will accelerate global spread the CHIK-V. WHY?

Insect vectors affect transmission of CHIK-V

	Ae aegypti mosquito	*Ae albopictus* mosquito
Geographic distribution	Tropical areas of the world	Widespread, on all continents
Feeding behaviors	Primarily at dawn and dusk	All day, dawn to dusk, aggressive
Habitat	Near humans, stagnant water	Near humans and in wooded areas
Temperature tolerance	Tropical, larvae die in winter	Global, larvae survive temperate winters
CHIK-V genotype transmitted	African, ECSA, Asian, IOL	IOL

Geographic distribution of *Aedes* spp worldwide

Aedes aegypti mosquitoes live between the two red lines in the tropics.
Aedes albopictus mosquitoes live on all continents in the gold-filled domains.
(imported cases of CHIK-V are represented by purple dots and triangles).
This demonstrates a broadening geographic area for CHIK-V infections.



Review questions

Why are vector borne diseases a major concern in the US and globally?

What caracteristics of vector-borne disease make then difficult to control and prevent rapid transmission?

What changes in human behavior may contribute to the spread of CHIK-V?

What changes in human behavior may contribute to the spread of mosquito vectors for CHIK-V?

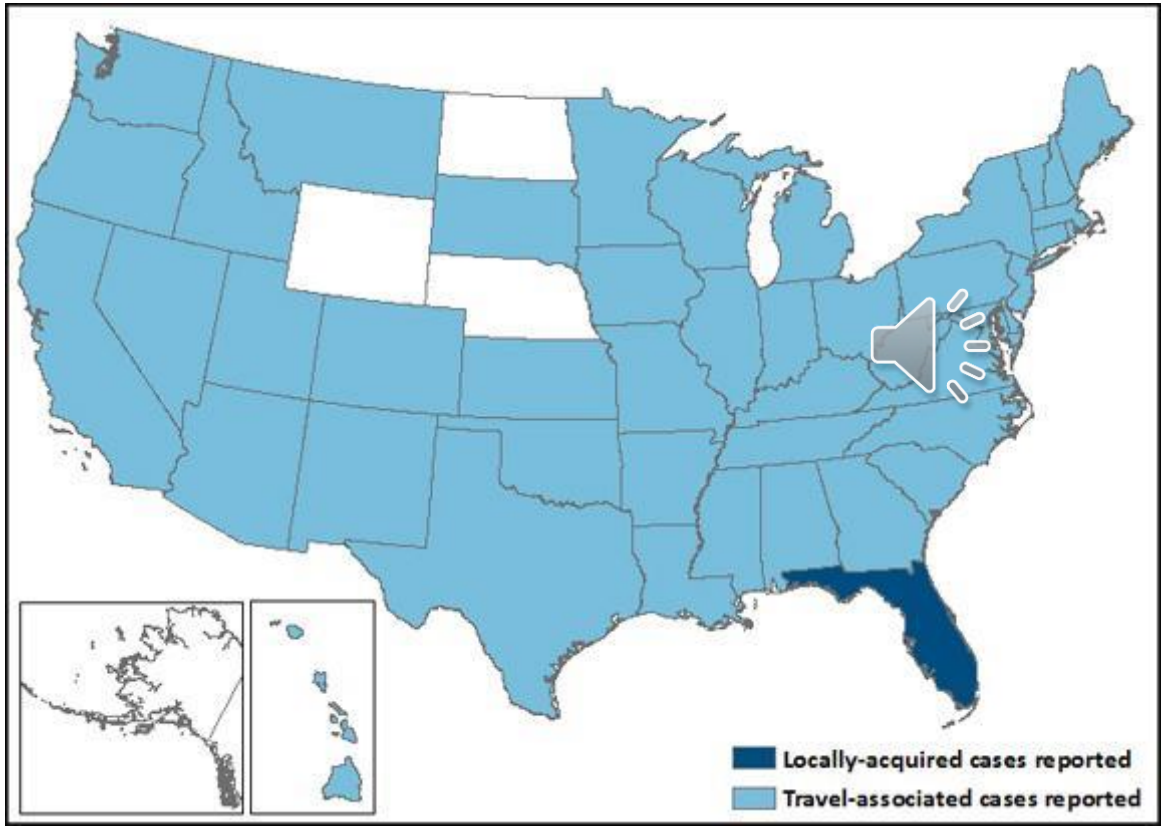
Would it be predicted that a single point mutation in a viral genome would have a dramatic impact on viral host tropism or disease pathogenesis? Why or why not?

How does the CHIK-V E1 mutation and generation of the IOL strain compare with the emergence and pathogenesis of newly emergent influenza viruses?

Global Epidemiology of CHIK-V

Current or previous local transmission of chikungunya virus as of 2010

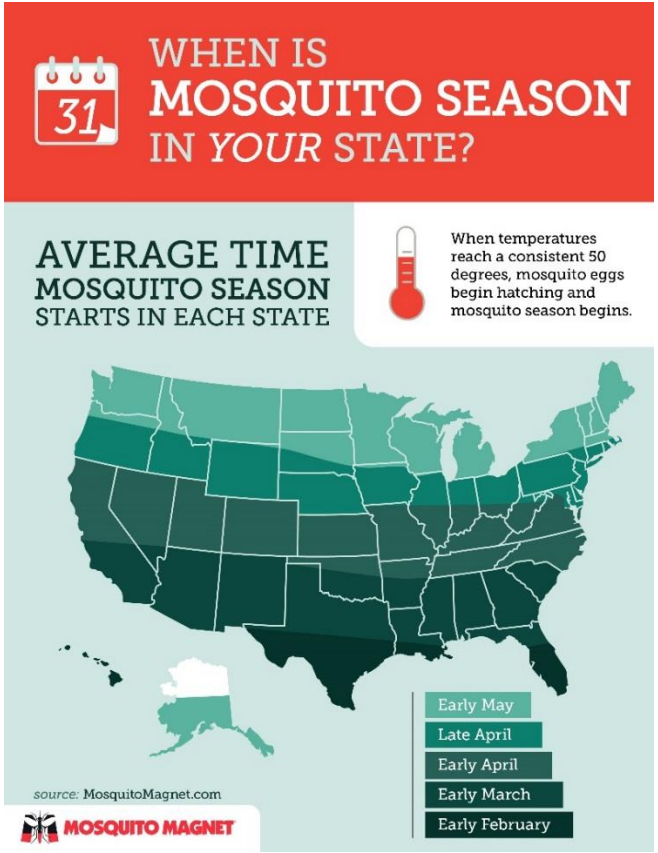
2014 Distribution of CHIK-V in the United States



CHIK-V was historically a disease of the far East and sub-Saharan Africa.

The disease has recently spread to Central America and is now moving northward into North America (the US and Canada).

Using CHIK-V Epidemiology in vector/disease control



We can use our knowledge of the distribution of the insect vectors, and their active breeding seasons, to plan judicious use of insecticides in high-risk areas.

Since there is presently neither a cure nor vaccine to prevent CHIK-V infection, the basis of control of CHIK-V spread is environmental and vector control.

Critical factor #3:

This map demonstrates the peak *Aedes spp.* mosquito seasons in the US. Knowledge of peak active seasons of the insect vectors is the basis of control of the spread of disease.

Review Questions

If Chikungunya has mainly been introduced to the US through global travel, why are we concerned about increasing preventive efforts within this country?

What are potential reasons for the spread of CHIK-V across the globe?

What are potential reasons for the spread of Chikungunya to the US?

What are the implications for the increasing rates of CHIK-V in the US?

Diagnosis of CHIK-V

The word Chikungunya means “to walk bent over” in Swahili, the official language of Tanzania.

This term describes the classic symptoms:

- Fever
- Back pain
- Polyarthralgia
- Headache
- Nausea, vomiting, diarrhea
- +/- facial edema
- +/- pruritic rash with desquamation of palms and soles of the feet

Differential Diagnosis of CHIK-V

Based on symptoms, geographic location, travel history, exposure to insects or sick people/animals, and pre-travel prophylaxis, several other diseases must be considered before a definitive diagnosis of CHIK-V is made:

Acute Dengue fever	Measles
Leptospirosis	Parvovirus
Malaria	Enterovirus
Typhoid	Adenovirus
Rickettsia (Rocky Mountain Spotted Fever)	Other alphavirus infections such as West Nile virus and yellow fever virus
Group A streptococcus	Post-infectious arthritis
Rubella	Rheumatologic conditions

Differentiating CHIK-V from Dengue Fever

This table demonstrates the need for careful comparison of clinical features to diagnose these 2 similar diseases, given the overlapping geographic distribution.

(*note: Raynaud's phenomenon is a condition whereby small arteries in the skin spasm, which limits blood circulation and causes numbness/discoloration).

CLINICAL FEATURES	CHIK-V	Dengue Virus
Fever, asthenia	Common	Common
Myalgia	Possible	Very common
Polyarthritis	Very common	None
Tenosynovitis	Yes	None
Leukopenia	None	Yes
Thrombocytopenia	None	Yes
Rash	Days 1-4	Days 3-7
Retro-orbital pain	Rare	Common
Hypotension	Possible	Common
Second stage	Tenosynovitis, Raynaud's	Fatigue

Timing is everything when diagnosing tropical disease:

The time span from exposure to onset of clinical symptoms is another very helpful way to differentiate between several diseases that present similarly.

DISEASE	MEAN INCUBATION PERIOD days (range of days)
Chikungunya	2-4 (1-14)
Dengue	4-8 (3-14)
Malaria	6-30
Leptospirosis	5-14
Typhoid	7-18
Hepatitis A	28 (15-50)

Diagnosis Confirmation

In developed countries, additional diagnostics would be performed to diagnose CHIK-V:

- Blood smear to identify malaria
- Blood/urine/fecal culture for *Salmonella typhi*
- Serologic tests (IgG or IgM) specific for CHIK-V
- PCR for CHIK-V nucleic acid material.

Critical factor #4:

Socioeconomic factors play a critical role in diagnosing CHIK-V, but not in its treatment.

Determinants of Health - Controlling CHIK-V

Cultural practices, living conditions, and socioeconomic factors play a vital role in the susceptibility of developing CHIK-V, and in the diagnostic process.

However, once diagnosed, management of CHIK-V is similar everywhere.

The management centers on controlling **vectors** and other **environmental factors**

- **Source reduction** (remove stagnant water to reduce mosquito breeding)
- **Biocontrol** (import natural predators, e.g., dragonflies, mosquitofish, lizards, etc.)
- **Introduce sterilized males** (to reduce mosquito breeding)
- **Trapping or insecticides** to kill larvae and adults (including thuringiensis toxin)
- **Exclusion** (mosquito nets and window screens)

United States Clinical Case Scenario

Review Questions

When thinking about these two cases, why is it important to understand global differences between the burden of disease and how the disease presents in different cultural settings?

What were the key symptoms described by the patient that are associated with CHIK-V?

What questions did Dr. Smith ask to rule out differential diagnoses?

What were the key questions that were influential in diagnosing the patient and what were the key lab results that confirmed the diagnosis?

What was the treatment plan for the patient and how can the patient prevent future occurrences of CHIK-V?

What follow-up is needed and what are the long-term effects of CHIK-V?

El Salvador Clinical Scenario

El Salvador Clinical Scenario

Translation of initial student encounter:

Student Doctor (SD): Hello, nice to meet you. I'm Student Doctor Perdomo. What is your name?

Patient (Pt): My name is Maria Espinosa. How are you doctor?

SD: Good, and you? Nice to meet you. What brings you in today?

Pt: I have pain in my muscles and also in

Review Questions

How were the patient presentations similar between the 2 cases?

What considerations led to the prompt diagnosis of the patient in El Salvador?

What other conditions were the medical providers discussing with the patient as a differential to her diagnosis? What were the warning signs to be aware of that she should recognize and know to return to be further assessed?

Is the treatment of Chikungunya and the methods of prevention any different from the patient seen in the U.S. and the patient seen in El Salvador?

What are some of the major barriers to prevention that are occurring in regards to reducing the transmission of CHIK-V?

What preventive measures can be taken to prevent the transmission of CHIK-V, and do these measures differ in the US vs. El Salvador?

Summary

Chikungunya is prevalent across the globe and recently became an emerging disease within the United States.

One Health illustrates many of the important influences on the spread of the disease.

Environmental factors and other health determinants also play a major in disease transmission

Environmental control and other preventive measures should be encouraged to stop the spread of Chikungunya

References

1. http://wwwnc.cdc.gov/eid/page/background-goals
2. https://www.avma.org/KB/Resources/Reports/Documents/onehealth_final.pdf
3. http://classics.mit.edu/Hippocrates/airwatpl.html
4. McBride CS, et. al. *Nature*. 2014; 515:222-227. doi:10.1038/nature13964
5. http://www.phac-aspc.gc.ca/owoh-umus/index-eng.php
6. Devaux CA. *World Journal of Virology*. 2012; 1(1):11-22. doi: 10.5501/wjv.v1.i1.11
7. http://viralzone.expasy.org/all_by_species/3.html
8. Sun S, et. al. *eLife* 2013; 2:e00435. doi: 10.7554/eLife.00435
9. Wintachai P, et. al. *Journal of Medical Virology*. 2012; 84:1757-1779. doi:10.1002/jmv.23403
10. Van Duijl-Richter MKS, et. al. *Viruses*. 2015; 7(7):3647-3674. doi:10.3390/v7072792
11. Whitehead SS, et. al. *Nature Reviews Microbiology*. 2007; 5:518-528. doi: 10.1038/nrmicro1690
12. Schwartz O and Albert ML. *Nature Reviews Microbiology*. 2010; 8:491-500. doi:10.1038/nrmicro2368
13. http://www.chikungunyavirusnet.com/life-cycle-of-aedes-aegypti.html
14. Dupuis-Maguiraga L, et. al. *PLoS Neglected Tropical Diseases*. 2012; 6(3):e1446. doi:10.1371/journal/pntd/0001446
15. Coffey LL, et al. *Viruses* 2014 6(11):4628-4663. doi: 10.3390/v6114628
16. Thiboutot MM, et. al. *PLoS Neglected Tropical Diseases*. 2010; 4(4):e623. doi: 10.1371/journal.pntd.0000623
17. Stapleford KA, et. al. *Cell Host and Microbe*. 2014; 15(6):706-716. doi: 10.1016/j.chom.2014.05.008
18. Weaver SC. *PLoS Neglected Tropical Diseases* 2014; 8(6): e2921. doi:10.1371/journal.pntd.0002921
20. Filipe AR and Pinto MR. *American Journal of Tropical Medicine and Hygiene.* 1969; 18(3):423-426
21. Vourc'h G, et. al. *Veterinary Research* 2014; 45:52. doi: 10.1186/1297-9716-45-52
22. Soumahoro MK, et. al. *EID Journal*. 2010; 16:1. doi: 10.3201/eid1601.080776. http://wwwnc.cdc.gov/eid/article/16/1/08-0776-techapp1

References - continued

23. http://www.cdc.gov/chikungunya/pdfs/chikungunyaworldmap_03-10-2015.pdf
24. http://www.cdc.gov/chikungunya/pdfs/2014map-final.pdf
25. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/15vol41/dr-rm41-01/cmment-eng.php
26. http:.//www.mosquitomagnet.com/blog/mosquito-season
28. Laoprasopwattana KM, et. al. *Pediatric Infectious Disease Journal*. 2012; 31(5)459-463. doi: 10.1097/INF.0b013e31824bb06d
29. Hyle EP and Alame D. *New England Journal of Medicine.* 2015; 372:1657-1664. doi: 10.1056/NEJMcpc1415172
30. Feder J, et. al. American Family Physician 2013;88:524.
32. Lakshmi V, et. al.. *Clinical Infectious Diseases*. 2008; 46(9):1436-1442. doi: 10.1086/529444
33. Grivard P, et. al. *Pathologie Biologie (Paris)*. 2007; 55(10):490-494
34. National Institute of Communicable Disease, New Delhi. *Chikungunya fever. CD Alert*. 2006. 10:6–8
35. Magurano F, et. al. *Vector-Borne and Zoonotic Diseases.* 2015; 15(4):258-260. doi: 10.1089/vbz.2014.1724
36. Ravinder K and Gupta K. *JK Science*. 2007; 9:109–110
37. Miller M and Cassidy JT. In Nelson Textbook of Pediatrics, 19th edition (2010) by Richard E., Md Behrman (editor), Robert M., Md Kliegman (editor), Hal B., Md Jenson (editor) by WB Saunders, 18th edition. WB. Saunders; Philadelphia: 2007. Postinfectious Arthritis and Related Conditions; cap: 147; pp. 519–522
38. Yu DT. Reactive Arthritis; http://www.uptodate.com/contents/reactive-arthritis-formerly-reiter-syndrome
39. Bruck N, et. al. *Pediatric Rheumatology*. 2010; 8:4. doi: 10.1186/1546-0096-8-4
40. Meyerhoff JO, et. al. Lyme Disease. Medscape. http://emedicine.medscape.com/article/330178-overview.
42. Fradin MS. *Annals of Internal Medicine* 1998;128:11. 931–940. doi:10.1059/0003-4819-128-11-199806010-00013.
43. Canyon DV and Hii JL. *Medical and Veterinary Entomology* 1997;11(4):319–323. doi:10.1111/j.1365-2915.1997.tb00416.x
44. http://diseasemaps.usgs.gov/mapviewer/