ZIKA and CHIKV: Evolution, Epidemiology and Vector Transmission Scott C. Weaver

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Arboviruses with history of urban emergence fromebziituc African cycles: yellow fever, chikungunya, Zika <u>A. aegypti</u>

A. aegypti A. albopictus (and other Stegomyia subgenus)



Sylvatic cycle

Rural areas

Human cycle

Urban Mosquito Vectors

Aedes (Stegomyia) aegypti



Originated in sub-Saharan Africa, spread throughout the tropics centuries ago from West Africa

Aedes (Stegomyia) albopictus



Originated in Asia, spread to the Americas, Africa and Europe beginning in 1985



Kraemer, M.U., et al., 2015. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus. Elife 4.

Chikungunya Virus

- Attack rates approach 50% in many regions, high apparent:inapparent ratio (**unlike Zika, dengue**)
- Fatal cases (ca. 0.1%) occur mainly in the elderly, perinatal and congenital infections (peripartum transmission), persons with underlying medical conditions
- Arthralgia is highly debilitating and often chronic, resulting in severe economic impacts and massive DALYs



CHIKV Strain Distribution



CHIKV Epidemic in the Americas



Recent Chikungunya Activity

Italy chikungunya outbreak prompts CDC travel notice

E 2 Comments

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Europe, Headlines, US News



io Region and this has prompted the Centers for Disease Control

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As of Sep. 26, 183 confirmed and suspected locally acquired cases of the mosquito borne illness in the coastal areas of Anzio and Latina as well as the city of Rome. Three confirmed cases have also been notified from other areas with a travel history to Anzio.

Local transmission means that mosquitoes in those areas of Italy have been infected with chikungunya and are spreading it to people.

Chikungunya is spread through mosquito bites and can cause symptoms such as fever, headache, nausea, vomiting, rash, and pain in the eyes, joints, and muscles.

Public health officials are responding by spraying for

mosquitoes, issuing guidelines for healthcare providers, and educating the public about chikungunya and how to prevent mosquito bites.

CIDRAP Center for Infectious Disease Research and Policy News & Perspective Infectious Disease Topics Antimicrobial Stewardship Ongoing Progr

FEATURED NEWS TOPICS Zika Yellow Fever MERS-CoV

France reports local chikungunya cluster

Filed Under: Chikungunya Lisa Schnirring | News Editor | CIDRAP News | Aug 21, 2017

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France has reported two locally acquired chikungunya cases in the south, and countries in the Americas reported a small rise in their illness total.

In research developments, researchers from Kenya found that, based on lab studies, *Aedes aegypti* from three of the country's major cities are capable of spreading the disease.

French cluster not linked to imported case In its weekly communicable disease threat report on Aug 18, the European Centre for Disease Prevention and Control (ECDC) said that French officials reported



PAHO / Flickr cc

Chikungunya rash.

Aedes albopictus mosquitoes are established in southern France and in parts of several other European countries, the ECDC said. It added that clusters of locally acquired infections are not unexpected following the introduction of the virus to mosquito populations by a returning traveler.

Chikungunya – Sudan

two confirmed local cases in Var district.

Disease outbreak news 15 October 2018

On 31 May 2018, the State Ministry of Health (SMOH) of the Red Sea State in Sudan reported four suspected cases of chikungunya fever from Swakin locality, in Red Sea State. Among the signs and symptoms were sudden onset of fever, headache, joint pain and swelling, muscle pain and/or inability to walk.

The first suspected case of chikungunya in the neighboring Kassala State was reported on 8 August 2018, in a male travelling from the Red Sea State. Since then cases have been reported in three localities of the State (Kassala, West Kassala and Rural Kassala). On 10 August, among 24 collected blood samples, 22 samples tested positive for chikungunya by PCR and ELISA at the National Public Health Laboratory (NPHL) in Khartoum. On 9 September, an additional 100 samples were collected and pooled in batches of ten: 50% of pools tested positive for mixed chikungunya and dengue viruses, and all pools were positive for chikungunya virus.

From 31 May through 2 October 2018, seven States (Kassala, Red Sea, Al Gadaref, River Nile, Northern State, South Darfur, and Khartoum) have been affected with a total of 13 978 cases of chikungunya, 95% of which are from Kassala State. No hospital admission or death has been officially reported. Approximately 7% of the reported cases were children less than 5 years of age and 60% were females.

- Major 2017-18 outbreaks in India, Pakistan, Sudan, Kenya: tens-ofthousands of cases
- Italy reported 405 cases in the Lazio and Calabria regions, 2017
- France reported 17 cases near Marseilles, 2017

A. albopictus-adaptive CHIKV Evolution

| | First | | | Fitness for A. | Fitness for |
|----------------------|------------|---------|-----------------------------|---------------------|------------------------|
| Lineage | appearance | Protein | Substitution | infection | infection |
| IOL | 2005 | E1 | A226V | 40-fold increase | Slight decrease |
| IOL (SL1) | 2007 | E2 | K252Q | 8-fold increase | No effect |
| IOL (SL2 partial) | 2008 | E2 | K233E | 6-fold increase | No effect |
| IOL (SL3B) | 2008 | E2/E3 | R198Q/S18F (synergistic) | 16-fold increase | No effect |
| IOL (SL4) | 2009 | E2 | L210Q | 5-fold increase | No effect |
| | | | | | |
| Asian | Never | E1 | A226V | No effect | Not done |
| Asian | Never | E2 | K252Q | Little or no effect | Little or no effect |
| Asian | Never | E2 | K233E | Little or no effect | Little or no effect |
| Asian | Never | E2/E3 | R198Q/S18F (synergistic) | Little or no effect | Little or no effect |
| Asian | Never | E2 | L210Q | Slight decrease | Not done |

- 1. None of these mutations has a major effect on infection of *A. aegypti*.
- 2. All affect initial infection of the *A. albopitus* midgut cells
- 3. None is predicted to affect CHIKV lineages now in the Americas (due to **founder effect and resultant epistasis**)

Tsetsarkin KA, et al. Nat Commun. 2014. 5:4084; Chen, R and Weaver, SC, unpublished

Amino acid substitutions that interact epistatically with *A. albopictus*-adaptive mutations

| CHIKV Lineage | Year of first appearance | Protein | Amino acid substitution | Approximate infectivity increase or epistatic effect | Epistatic interaction |
|------------------|--------------------------|---------|-------------------------|--|--------------------------|
| Asian | 1958 | E1 | A98T | Completely | E1-226V |
| | | Foun | der effect | prevents penetrance for <i>A.</i> <i>albopictus</i> infection | |
| ECSA | 1953 | E2 | l211T | Enables penetrance for <i>A.</i> <i>albopictus</i> infection | E1-226V |

Tsetsarkin KA, McGee CE, Volk SM, Vanlandingham DL, Weaver SC, Higgs S. Epistatic roles of E2 glycopr mutations in adaption of chikungunya virus to *Aedes albopictus* and *Ae. aegypti* mosquitoes. PLoS One 4:e6835.

Tsetsarkin KA, Chen R, Leal G, Forrester N, Higgs S, Huang J, Weaver SC. Chikungunya virus emergence constrained in Asia by lineage-specific adaptive landscapes. Proc Natl Acad Sci U S A. 2011. 108:7872-

These epistatic interactions predict that neither strain in the Americas should be transmitted efficiently by *A. albopictus*



Evolution of the CHIKV 3'UTR



Chikungunya Virus 3' Untranslated Region: Adaptation to Mosquitoes and a Population Bottleneck as Major Evolutionary Forces

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Evolution of the Asian Lineage 3'UTR Duplications and Mutations

Ancestral State



Chen R, Wang E, Tsetsarkin KA, Weaver SC. PLoS Pathog. 2013. 9:e1003591.

Rare But Severe Outcomes of Zika Virus Infection

- ZIKV infection first associated in French Polynesia with a ca. 2-10fold increase in Guillain–Barré syndrome
- Microcephaly first detected in northeastern Brazil in 2015 based on a 100-200-fold rise in the incidence coincident with an outbreak of ZIKV infection. A wide range of congenital defects now termed Congenital Zika Syndrome





Baby with Microcephaly



Baby with Typical Head Size



ZIKV Epidemic in the Americas



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Zika virus detected in second Indian state

October 28, 2018



Gujarat has been fumigating public areas in an effort to kill the mosquitos that carry the diseases

India's Zika outbreak is spreading, with officials saying Sunday that the mosquito-borne virus has been detected in the western state of Gujarat after nearly 150 cases were reported this year in neighbouring Rajasthan.

Health authorities in Gujarat said a woman tested positive for Zika and was treated at a state hospital in the capital Ahmedabad, the first confirmed case outside Rajasthan this year.

"Only one case has been found so far. We are taking all precautions," Gujarat Commissioner of Health, Jayanti Ravi, told AFP on Sunday.

The state health department has rallied hundreds of doctors and medical personnel to perform emergency screenings for Zika, including more than 250 pregnant women with fevers.

Gujarat, which borders Rajasthan to the south, has been fumigating public areas in an effort to kill the mosquitos that carry the diseases.

Health authorities in Rajasthan have detected 147 cases of Zika since September, officials say. Almost 440,000 people were under surveillance in Rajasthan's capital Jaipur last month.

Major Hypotheses for the Recent ZIKV Emergence

- 1. ZIKV underwent adaptive evolution to enhance infectivity of urban *mosquito* vectors (like chikungunya virus) or to enhance human viremia (which could also increase the risk of transplacental transmission), or became more virulent for other reasons (enhancement by dengue immunity?).
- 2. The stochastic introduction of ZIKV into naïve populations in the South Pacific allowed for sufficient amplification to facilitate the introduction into Brazil (assisted by increased global travel, expansion of tropical cities and *A. aegypti* populations; i.e. **no major change among ZIKV strains in epidemic transmission potential or virulence**).

African ZIKV strains are typically more infectious for *A. aegypti* and more virulent for mice than Asian or American strains

- 1. How is ZIKV transmitted efficiently by *A. aegypti?*
- 2. Could an African ZIKV strain cause another major outbreak?

Variation in *Aedes aegypti* Mosquito Competence for Zika Virus Transmission

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Figure 1. Infection, dissemination, and transmission of 3 Zika virus strains by *Aedes aegypti* mosquitoes from Salvador, Brazil, after artifical b ood re al s w th a concent ration of 4 log $_{10}$ (A), 5 log $_{10}$ (B), or 6 log $_{10}$ (C) focus-forming units/mL.

Does DENV Immunity Affect ZIKV Infection, or Vice Versa (i.e. Immune Enhancement)?

- No evidence that DENV immunity increases the risk of CZS in ZIKV-infected, pregnant women (Halai et al., 2017)
- Indirect evidence that recent DENV infection provides partial protection against more severe ZIKV infections (Ribeiro et al. 2018)



Main Conclusions

1.CHIKV and probably now ZIKV are now endemic (permanently independent of the enzootic progenitor African enzootic cycles).

2.Although the peak of the CHIKV and ZIKV epidemics in the Americas have passed, transmission continues there and new outbreaks continue to appear in Europe, Africa and Asia.

3.Founder effects resulting from bottlenecks that accompany human introductions, demonstrated for CHIKV and ZIKV, can leave geographically expanded arbovirus populations with low fitness and challenging recovery. These stochastic events, based on epistatic interactions, limit our ability to predict arboviral emergence.

4.Post-emergence adaptive mutations identified in chikungunya (multiple, major adaptive mutations for *A. albopictus* transmission), and Zika viruses (multiple, minor adaptive mutations for *A. aegypti* transmission).



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Questions?



A little clean water, please!



Classic or Modern

- Are you carrying Zika or chikungunya?
- Only dengue. I detest being fashionable!