ZIKA and CHIKV: Evolution, Epidemiology and Vector Transmission

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Arboviruses with history of urban emergence fromebziituc African cycles: yellow fever, chikungunya, Zika

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

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 Epidemic in the Americas

Recent Chikungunya Activity

Italy chikungunya outbreak prompts CDC travel notice
by NEWS DEBK

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.

- Major 2017-18 outbreaks in India, Pakistan, Sudan, Kenya: tens-of-thousands 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

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

1. None of these mutations has a major effect on infection of *A. aegypti*.
2. All affect initial infection of the *A. albopictus* 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

<table>
<thead>
<tr>
<th>CHIKV Lineage</th>
<th>Year of first appearance</th>
<th>Protein</th>
<th>Amino acid substitution</th>
<th>Approximate infectivity increase or epistatic effect</th>
<th>Epistatic interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>1958</td>
<td>E1</td>
<td>A98T</td>
<td>Completely prevents penetrance for <em>A. albopictus</em> infection</td>
<td>E1-226V</td>
</tr>
<tr>
<td>ECSA</td>
<td>1953</td>
<td>E2</td>
<td>I211T</td>
<td>Enables penetrance for <em>A. albopictus</em> infection</td>
<td>E1-226V</td>
</tr>
</tbody>
</table>

**Founder effect**


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

Rare But Severe Outcomes of Zika Virus Infection

• ZIKV infection first associated in French Polynesia with a ca. 2-10-fold 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**
ZIKV Epidemic in the Americas

* Brazil reported its first case in April 2015.
Zika virus detected in second Indian state

October 28, 2018

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 mosquitoes 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

Christopher M. Roundy,† Sasha R. Azar,† Shannan L. Rossi, Jing H. Huang, Grace Leal, Ruimei Yun, Ildefonso Fernandez-Salas, Christopher J. Vitek, Igor A.D. Paploski, Uriel Kitron, Guilherme S. Ribeiro, Kathryn A. Hanley, Scott C. Weaver, Nikos Vasilakis

Figure 1. Infection, dissemination, and transmission of 3 Zika virus strains by Aedes aegypti mosquitoes from Salvador, Brazil, after artificial feeds with concentrations 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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Doug Watts
A little clean water, please!

Classic or Modern

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