ASPID Symposium
Updates on Vector-Borne Viruses: Chikungunya

Salvacion R. Gatchalian, M.D. FPPS, FPIDSP, FPSMID
Associate Professor, College of Medicine
University of the Philippines, Manila
CHIKUNGUNYA

• Arthropod-borne virus is a causative agent of emerging infectious diseases
  • Responsible for global public health problem

• Dengue and Chikungunya (CHIKV)
  • Transmitted by same species of mosquito
  • Co-circulate and lead to dual infections and concurrent epidemics
  • Share similar clinical features
CHIKUNGUNYA VIRUS INFECTION

• Re-emerged in Africa and Asia
• Caused large outbreaks
• Public health problem

Burt et al The Lancet 2012; 379:662-71
Hapurrachchi et al J Gen Virology 2010; 91:1067-1076
Chikungunya Virus

• Family Togaviridae, Genus Alphavirus
• Belongs to the Semliki Forest Virus (SFV) antigenic complex group
• Single-stranded plus-sense RNA
• Have geographically associated genotypes:
  • West African (W Af),
  • East/Central/South African (ECSA),
  • Asian genotypes
Background

• Transmitted by the same vector of Dengue virus

Fig. 1 Reported Chikungunya Cases by Morbidity Week, Philippines, as of January 1 – December 2, 2017* (N=2,287)
Fig. 3 Reported Chikungunya Cases by Province Philippines, as of January 1 – December 2, 2017* (N=2,287)
Profile of Cases

Ages of cases ranged from less than 1 year to 95 years old (median = 32 years). Majority of cases were females (61.0%). Most (9.0%) of the cases belonged to the 25-29 years age group. There were 4 deaths reported (CFR=0.17%).

Fig. 4 Reported Chikungunya Cases by Age Group and Sex
Philippines, as of January 1 – December 2, 2017* (N=2,287)

Most common signs and symptoms that have been experienced by the reported chikungunya cases were fever (91.8%), skin manifestation (77.0%) and arthritis (70.4%).
Fig. 5 Signs and Symptoms Experienced by Reported Chikungunya Cases, Philippines, as of January 1 – December 2, 2017**

- Fever: 91.8%
- Skin Manifestation: 77.0%
- Arthritis: 70.4%
- Arthralgia: 62.8%
- Headache: 56.9%
- Myalgia: 47.5%
- Back Pain: 43.5%
- Nausea: 20.1%
- Asthenia: 14.3%
- Vomiting: 9.8%
- Periarticular Edema: 5.3%
- Mucosal Bleeding: 0.9%
- Meningoencephalitis: 0.2%
Clinical Features

• Asymptomatic illness to severe debilitating disease
• Children and elderly are most at risk for severe disease
• Incubation period: 2-4 days (range 2-12 days); no prodrome
• Prototypical features: fever, rash and arthralgia

## CHIKUNGUNYA: Clinical Manifestation

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (T&gt;38.9°C)</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgias</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Headache</td>
<td>++ (retro-orbital)</td>
<td>++</td>
</tr>
<tr>
<td>Rash</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Arthritis</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Hypotension</td>
<td>++ (D5-D7)</td>
<td>+/-</td>
</tr>
<tr>
<td>Bleeding</td>
<td>++ (D5-D7)</td>
<td>+/-</td>
</tr>
<tr>
<td>Shock</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Acute Manifestations

Acute (2-10 days)

Edematous rash

Myalgia
Chikungunya: Clinical Manifestation

• Fever
  • Abrupt in onset
  • High grade
  • Majority have a single spike of fever followed by either rapid or slow return to baseline
  • Less than 1/3 have secondary spikes seen in dengue

• Rash
  • End of febrile phase (day 3-5), diffuse irritating maculopapular rash commonly on arms, back, shoulders
  • Rash lasts 48 hrs
  • Can have pigmentary changes: asymptomatic brown-black pigmentation in centrofacial area
  • No enanthem
Chikungunya: Clinical Manifestation

• Arthritis
  • Join pain can be severe, preventing sleep
  • Polyarticular, frequently in lower limbs and small joints
  • Arthritis and arthralgia uncommon in children but can be severe
  • Residual arthralgia is less frequent in children vs adults

• Hemorrhagic manifestations
  • Not as common as in dengue
  • If bleeding manifestations occur, less severe than dengue
Chikungunya: Clinical Manifestation

- Neurologic
  - Not common
  - BFC
  - Altered level of consciousness, blindness due to retrobulbar neuritis and accuse flaccid paralysis
  - No specific neurologic finding or CSF abnormalities

CHIKUNGUNYA: Clinical Manifestation

• Polyarthralgia most often seen with CHIKV
  • Most disabling
  • Arthralgia is symmetrical
  • > 1 joint affected: fingers, wrists, elbows, ankles, toes and knees
  • Some fully recover
  • Some with persistent arthralgia for months to years

• Retrospective cohort study by Sissoko and colleagues
  • 57% with persistence or recurrence of arthralgia 15 months after initial infection
  • Joint symptoms persists for years

Burt et al The Lancet 2012; 379:662-71
CHIKUNGUNYA: Clinical Manifestation

- Study of serologically proven CHIKV
  - 12% with residual joint symptoms (stiffness, swelling and pain) 3 years after
- Likelihood of persistent arthralgia dependent on age
- Other factors
  - Underlying disorders
  - Severity of pain at disease onset
  - Children at risk for severe manifestations

Burt et al The Lancet 2012; 379:662-71
CHIKUNGUNYA: Clinical Manifestation

• Chronic Arthralgia Phase
  • Fluctuations in intensity and relapses
    • same joint sites

• Less severe but with reduction in movement and quality of life

Burt et al. The Lancet 2012; 379:662-71
Staple et al CID Sept. 2009; 49:942-948
Feigin and Cherry Textbook of Pediatrics 7th ed.
2014 Elsevier Saunders Philadelphia, PA
Chronic Manifestations of Chikungunya

Chronic (months to years)

Inflammatory osteoarthritis

Swollen and stiff joints
## CHIKUNGUNYA: Clinical Manifestation

### Rash

<table>
<thead>
<tr>
<th>DENGUE</th>
<th>CHIKUNGUNYA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular</td>
<td>Maculopapular</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Aphthous like ulcers</td>
</tr>
<tr>
<td>Urticarial</td>
<td>Vesiculobullous with desquamation</td>
</tr>
<tr>
<td>Flushing or erythematous mottling</td>
<td>Vasculitic</td>
</tr>
</tbody>
</table>

References:
- Taubitz W et al, CID July 2007; 45:el-4
Rashes seen in Chikungunya
Chikungunya

- CHIKV: fever occurs earlier and is of shorter duration; arthritis, arthralgia, myalgia, maculopapular rash more common
- constitutional symptoms in both diseases
- DENV: serious hemorrhagic manifestations, hepatomegaly, shock more frequent; post-illness bradycardia

# CHIKUNGUNYA: Clinical Manifestation

## Laboratory Findings

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>DENGUE</th>
<th>CHIKUNGUNYA</th>
</tr>
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<tbody>
<tr>
<td>Leukopenia</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Neutropenia</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Lymphopenia</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Elevated HCT</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>+/-</td>
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</tbody>
</table>
CHIKUNGUNYA: Diagnosis

• Based on clinical, epidemiological and laboratory criteria
• Laboratory parameters variable often do not aid in diagnosis
• Confirmed by:
  • Detection of virus
  • Viral RNA
  • CHIKV-specific antibodies
• Type of test dictated by timing and volume of samples
• Historically, diagnosed based on serology
• Molecular techniques
  • RT PCR

Staple et al CID Sept. 2009; 49:942-948
Powers et al J Gen Virology 2007; 88:2363-77
Burt et al The Lancet 2012; 379:662-71
Table 2: Diagnostic tests for CHIKV infection.

<table>
<thead>
<tr>
<th>Premise</th>
<th>Diagnostic method</th>
<th>Sample types</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of virus</td>
<td>Virus isolation (in vivo or in vitro)</td>
<td>Serum, plasma, whole blood, and fresh or FFPE tissues</td>
<td>Variable</td>
<td>100</td>
<td>Highly specific</td>
<td>Technical, laborious</td>
<td>[1]</td>
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<tr>
<td></td>
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<td></td>
<td>Requires biosafety level 3 containment</td>
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<td></td>
<td></td>
<td>May take 1-2 weeks</td>
<td></td>
</tr>
<tr>
<td>Detection of viral antigen</td>
<td>ELISA or immunochromatographic assay (ICA)</td>
<td>Serum and CSF</td>
<td>85 (serum)</td>
<td>89 (serum)</td>
<td>Early diagnosis</td>
<td>Commercial assays not widely available</td>
<td>[16, 17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80 (CSF)</td>
<td>87 (CSF)</td>
<td></td>
<td>Requires biosafety level 3 containment</td>
<td></td>
</tr>
<tr>
<td>Detection of viral nucleic acid</td>
<td>RT-PCR</td>
<td>Serum and dried blood spots</td>
<td>100</td>
<td>Up to 100</td>
<td>Highly sensitive and specific</td>
<td>Expensive reagents and specialized equipment</td>
<td>[13, 16, 18–20]</td>
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<td>Rapid turnaround time</td>
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<td></td>
<td></td>
<td>Multiplex available</td>
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<tr>
<td></td>
<td>Real-time RT-PCR</td>
<td>Serum and dried blood spots</td>
<td>100</td>
<td>Up to 100</td>
<td>Multiplex available</td>
<td>Expensive reagents and specialized equipment</td>
<td>[13, 16, 18–20]</td>
</tr>
<tr>
<td></td>
<td>Isothermal amplification methods (RT-LAMP)</td>
<td></td>
<td>100</td>
<td>95.25</td>
<td>Does not require specialized equipment (i.e., thermocyclers)</td>
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<tr>
<td>Detection of host antibody response</td>
<td>ELISA</td>
<td>Serum CSF</td>
<td>IgM: 17 (serum), 48 (CSF) IgG: 45 (serum), 63 (CSF) IgG: 53 (serum)</td>
<td>IgM: 95 (serum)</td>
<td>Widely available</td>
<td>Possible cross-reactivity with other alphaviruses</td>
<td>[4, 16, 17, 20–22]</td>
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<td></td>
<td>Relatively cheaper and easier to perform</td>
<td>Elevated IgM does not distinguish recent past infection from acute infection</td>
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<td></td>
<td>Rapid bedside tests are available</td>
<td>Lack the ability to quantify antibodies, are subjective, and require special equipment and training</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Sensitive and specific</td>
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<td>[4, 16, 17, 20–22]</td>
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<td></td>
<td></td>
<td></td>
<td>Commercially available</td>
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<tr>
<td></td>
<td>IFA</td>
<td>Serum</td>
<td>85–97</td>
<td>90–98</td>
<td>Very specific for alphaviruses; gold standard for confirmation of serologic test results</td>
<td>Requires the use of live virus (requires Biosafety level 3 containment)</td>
<td>[4, 16, 17, 20–22]</td>
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<td></td>
<td>PRNT</td>
<td>Serum</td>
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</table>
Chikungunya: Laboratory Tests

- CHIKV: leukopenia with relative lymphocytosis by day 3-6; insignificant rise in Hct by day 2-4; thrombocytopenia is mild and bleeding does not occur
- Can use virus isolation, viral RNA detection, serology, PCR
- Most sensitive: IgM capture ELISA
Serum samples from patients with fever, rash, and joint pains were sent to RITM for IgM testing.

Samples collected <5 days after onset of symptoms were tested for CHIKV RNA using one-step RT-PCR targeting E1 gene using primers and protocol by Hasebe, *et al* (2002) and Arias-Goeta, *et al* (2013) and directly sequenced.

Phylogenetic analysis was performed using neighbour joining method using Kimura-2 parameter model (K2+G) on partial E1 gene (733 bp) by MEGA 6.05.
Results

- From 2011-2013, 5,729 have been received for testing. 2,891 samples (50%) have detectable CHIKV anti-IgM.
- 31 samples were sequenced for partial E1 gene.
- Most belongs to the Asian genotype and were clustered into the same branch and were very closely related regardless of geographic location and date of collection.
- 3 samples from Davao (collected in 2012 and 2013) belongs to ECSA and have the A226V mutation.

Sy et al. Genetic Analysis of Chikungunya virus causing re-emergence in the Philippines. Research Institute for Tropical Medicine (RITM), Muntinlupa City, Philippines; Department of Virology, Tohoku University Graduate School of Medicine, Sendai, Japan; Tohoku-RITM Collaborative Research Center on Emerging and Re-emerging Infectious Diseases, Muntinlupa City, Philippines
Neurocognitive Outcome of Children Exposed to Perinatal Mother-to-Child Chikungunya Virus Infection: The CHIMERE Cohort Study on Reunion Island

Patrick Gérardin1,2,3,9*, Sylvain Sampériz1,3, Duksha Ramful1,2,4,5, Brahim Boumahni1, Marc Bintner1, Jean-Luc Alessandri1, Magali Carbonnier1, Isabelle Tiran-Rajaoefera3, Gilles Beullier5, Irénée Boya6, Tahir Noormahomed7, Jocelyn Okoi8,9, Olivier Rollot2, Liliane Cotte1, Marie-Christine Jaffar-Bandjee1, Alain Michault1, François Favier2, Monique Kaminski3, Alain Fourmaintraux1, Xavier Fritel3,10,11

1 CHU de La Réunion Saint-Denis/Saint-Pierre, La Réunion, France, 2 INSERM CIC-EC (CIE2), Saint-Pierre, La Réunion, France, 3 INSERM UMRS 953, “Epidemiological Research Unit on Perinatal Health and Women and Children Health”, UPMC Université Paris 6, Paris, France, 4 GRI, Research Group on Immunopathology and Infection, EA4517, Université de La Réunion, INSERM UMRS 945 “Immunity and Infection” Saint-Denis, La Réunion, France, 5 Centre Hospitalier Gabriel Martin, Saint-Paul, La Réunion, France, 6 Centre Hospitalier de l’Est Réunion, Saint-Benoît, La Réunion, France, 7 Clinique Sainte-Clotilde, Sainte-Clotilde, La Réunion, France, 8 Clinique Durieux, Le Tampon, La Réunion, France, 9 Centre d’Action Médico-Sociale Précoce (CAMSP), Saint-Louis, La Réunion, France, 10 Poitiers University Hospital, Poitiers, France, 11 INSERM CIC-P 0802, Poitiers, France

- EXPOSED-INFECTED (EI):
  - Infants of mothers infected during pregnancy with:
    - (+) RT-PCR and/or
    - (+) CHIKV IgM via ELISA
  - before the 10th day of life (or 15th day of life if CSF was used)
- EXPOSED-UNINFECTED (EU)
  - Mothers who were RT-PCR negative but seroconverted on follow-up
CHIKV has a 3-fold increased risk of GND after adjusting maternal social situation and neonatal characteristics, such as SGA and HC.

- Neurodev dysfunction identified in 23/33 (73.9%) of infected children
  - Areas most affected: coordination, language (n=19), sociability (n=12) and movement/posture (n=9)
• CHIKV is an independent predictor of Global neurodevelopment delay (3x risk after adjusting for maternal social situation, neonatal characteristics like SGA and HC)

• Protracted high fever in mother might trigger cognitive dysfunction in offspring
  • High fever throughout pregnancy, associated with other maternal infections, linked to various neurologic outcomes such as neural tube defects, seizures or CP, autism or epilepsy etc.

• CHIKV encephalopathy can lead to cerebral palsy, microcephaly (dec brain volume), neuronal loss
# CHIKUNGUNYA: Treatment

<table>
<thead>
<tr>
<th>Supportive</th>
</tr>
</thead>
<tbody>
<tr>
<td>- NSAIDS</td>
</tr>
<tr>
<td>- Bed rest</td>
</tr>
<tr>
<td>- Antipyretics or cold sponging</td>
</tr>
<tr>
<td>- Analgesics or mild sedation</td>
</tr>
<tr>
<td>- NSAIDS for arthritis after illness</td>
</tr>
<tr>
<td>- Physiotherapy</td>
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<tr>
<td>- Hydration</td>
</tr>
</tbody>
</table>
CHIKUNGUNYA: Treatment

• Ribavirin
  • Anti-viral activity vs. RNA viruses
  • Moderate beneficial effect (Ravichandran and Manian) in alleviating arthralgia and swelling
  • Still needs more evidence

Burt et al The Lancet 2012; 379:662-71
CHIKUNGUNYA: Treatment

• Chloroquine
  • Inhibits CHIKV infection in cell culture thru effects on endosomal modification
  • Anti-inflammatory activity
  • Used in chronic inflammatory diseases
  • No effect in a double-blinded trial

Burt et al The Lancet 2012; 379:662-71
CHIKUNGUNYA: Treatment

- Monoclonal Antibody
  - Passive transfer of CHIKV immune serum protects vs. CHIKV-induced lethality in mouse models
  - May have value
  - 2 Human Monoclonal Antibodies neutralizing CHIKV in vitro were tested
    - 5F10
    - 8B10
  - Tested efficacy in vivo as prophylactic and therapeutic treatments
    - Significant delay in CHIKV driven lethality

Fric J et al JID Jan 2013; 207:319-22
Burt et al The Lancet 2012; 379:662-71
### CHIKUNGUNYA: Prognosis

<table>
<thead>
<tr>
<th>CHIKUNGUNYA</th>
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</thead>
<tbody>
<tr>
<td>Chronic arthritis</td>
</tr>
<tr>
<td>Destructive arthropathy reported</td>
</tr>
<tr>
<td>Residual neurologic deficits in children</td>
</tr>
</tbody>
</table>
## CHIKUNGUNYA: Prevention

<table>
<thead>
<tr>
<th><strong>PREVENTION AND CONTROL</strong></th>
<th><strong>VACCINE IN DEVELOPMENT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated Vector Management</td>
<td>Formalin inactivated (Walter Reed) Phase II</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Live attenuated vaccine Phase II</td>
</tr>
<tr>
<td>Case Management</td>
<td>Chimeric alpha virus approach Phase I</td>
</tr>
<tr>
<td>Social Mobilization &amp; Communication about the disease</td>
<td>Virus like particle in Pre-clinical</td>
</tr>
<tr>
<td>Outbreak Response</td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td></td>
</tr>
</tbody>
</table>

Burt et al The Lancet 2012; 379:662-71  
Powers et al J Gen Virol 2007; 88:2363-77  
The variety of breeding places of the vector mosquito in your surroundings

Without containers there is no mosquito; without mosquitoes there is no DENGUE or CHIKUNGUNYA.
Get rid of breeding places in your surroundings
Chikungunya Control

Everyone’s concern.
The success depends on the involvement of all levels of society - from household, family, community, NGOs, social organizations, local & national authorities.
CHIKUNGUNYA

• Important clinical findings include:
  • Abrupt onset of fever and shorter duration of illness
  • Maculopapular rash
  • Polyarthralgia with arthritis/tenosynovitis
  • Conjunctival injection
  • Chronic phase
  • Lymphopenia
CHIKUNGUNYA

• CHIKV did not have much attention
  • Low to rare mortality
  • Infrequent occurrence
  • Absence in developed countries
• 2005 – 2007 outbreak
  • Awareness in scientific community and the public
• Prolonged arthralgic syndrome for weeks or months or years
  • Serious economic and social impact on individual and community
• Need to be alert and astute
  • Dengue and CHIKV present
  • CHIKV diagnosed based on fever, arthralgia and/or rash lead to over-diagnosis
  • If no rash during fever or low WBC count consider dengue as differential
ACKNOWLEDGEMENTS

• Would like to thank the ff:
  • Dr. Rose Capedning
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    • Rowena Capistrano, R.N.
    • Albert Anduyon
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  • Abe Sepulveda