PIDSP Annual Convention
PIDSP@25: Forging Ahead in Pediatric Infectious Diseases
Feb 21-23, 2018 Crowne Plaza Manila Galeria
Pasig City, Philippines

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

Gubler, D.J. Ann NY Acad Sci 951, 13-24
Nimmannitya Ser al Am J Trap Med Hyg 1969;18: 954-71
Halstead SB et al Am J Trop Med 1969; 18:972-83
Hochedez Pet al Am J Trap Med Hyg 2008; 78:710-3

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


World map
Arctic OCEAN
Arctic OCEAN
Arctic OCEAN
N
GREENLAND (DENMARK)
SVALBARD (NORWAY)
ALASKA (USA)
CANADA
RUSSIA
ICELAND
FAROE ISLANDS
SWEDEN
FINLAND
ESTONIA
LATVIA
LITHUANIA
NORWAY
IRELAND
BELARUS
North Atlantic OCEAN
North Pacific OCEAN
UNITED STATES OF AMERICA
KAZAKHSTAN
MONGOLIA
UZBEKISTAN
TURKMENISTAN
CHINA
NORTH KOREA
SOUTH KOREA
JAPAN
North Pacific OCEAN
AZORES (PORTUGAL)
MADEIRA ISLAND (PORTUGAL)
CANARY ISLANDS (SPAIN)
MOROCCO
ALGERIA
LIBYA
EGYPT
TURKEY
IRAQ
IRAN
AFGHANISTAN
KASHMIR
SAUDI ARABIA
KUWAIT
OMAN
NEPAL
BHUTAN
INDIA
MYANMAR (BURMA)
BANGLADESH
LAOS
THAILAND
CAMBODIA
VIETNAM
PHILIPPINES
GUAM
MEXICO
HAWAIIAN ISLANDS (USA)
THE BAHAMAS
CUBA
BELIZE
GUATEMALA
HONDURAS
NICARAGUA
EL SALVADOR
COSTA RICA
PANAMA
SAN JOSE
JAMAICA
HAITI
PUERTO RICO (USA)
SAINT KITTS AND NEVIS
MONTSERRAT
GUADELOUPE
DOMINICA
MARTINIQUE
BARBADOS
TRINIDAD AND TOBAGO
VENEZUELA
GUYANA
SURINAME
FRENCH GUIANA
COLOMBIA
ECUADOR
GALAPAGOS
PERU
BRAZIL
BOLIVIA
PARAGUAY
CHILE
URUGUAY
ARGENTINA
MAURITANIA
CAPE VERDE
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
SIERRA LEONE
LIBERIA
MALI
BURKINA FASO
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COTE D'IVOIRE
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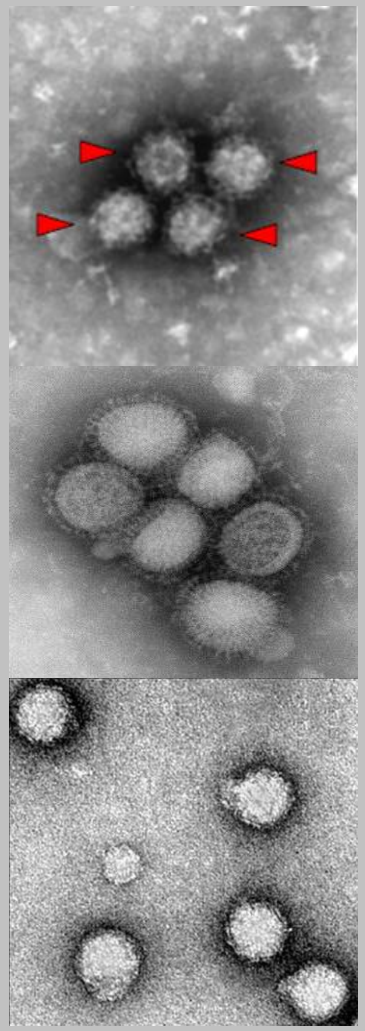
CHAD
SUDAN
ERITREA
YEMEN
DJIBOUTI
ETHIOPIA
SOMALIA
CENTRAL AFRICAN REPUBLIC
CAMEROON
GABON
CONGO
DEMOCRATIC REPUBLIC OF THE CONGO
UGANDA
KENYA
TANZANIA
SEYCHELLES
COMOROS
MADAGASCAR
MAURITIUS
REUNION
ANGOLA
ZAMBIA
MALAWI
MOZAMBIQUE
ZIMBABWE
NAMIBIA
BOTSWANA
SWAZILAND
LESOTHO
SOUTH AFRICA
SRI LANKA
ADAMAN AND NICOBAR ISLANDS (INDIA)
MALAYSIA
INDONESIA
AUSTRALIA
PAPUA NEW GUINEA
SOLOMON ISLANDS
VANUATU
FIJI
NEW CALEDONIA (FRANCE)
TASMANIA (AUSTRALIA)
NEW ZEALAND
South Pacific OCEAN
South Atlantic OCEAN
FALKLAND ISLANDS (UK)
SOUTH GEORGIA (UK)
KERGUELEN ISLAND (FRANCE)
HEARD ISLAND (AUSTRALIA)
Antarctica
France
2014, 2017
Spain
2015
USA
Jun 2016
Senegal
2015
Italy
Sep 2017
Argentina
Mar 2016
India
Jun 2006
SW Indian Ocean
Mar 2006
Kenya
Aug 2016
La Reunion Island (France)
Feb 2006
@Copyright MapsNWorld.com 2011
Map Not To Scale

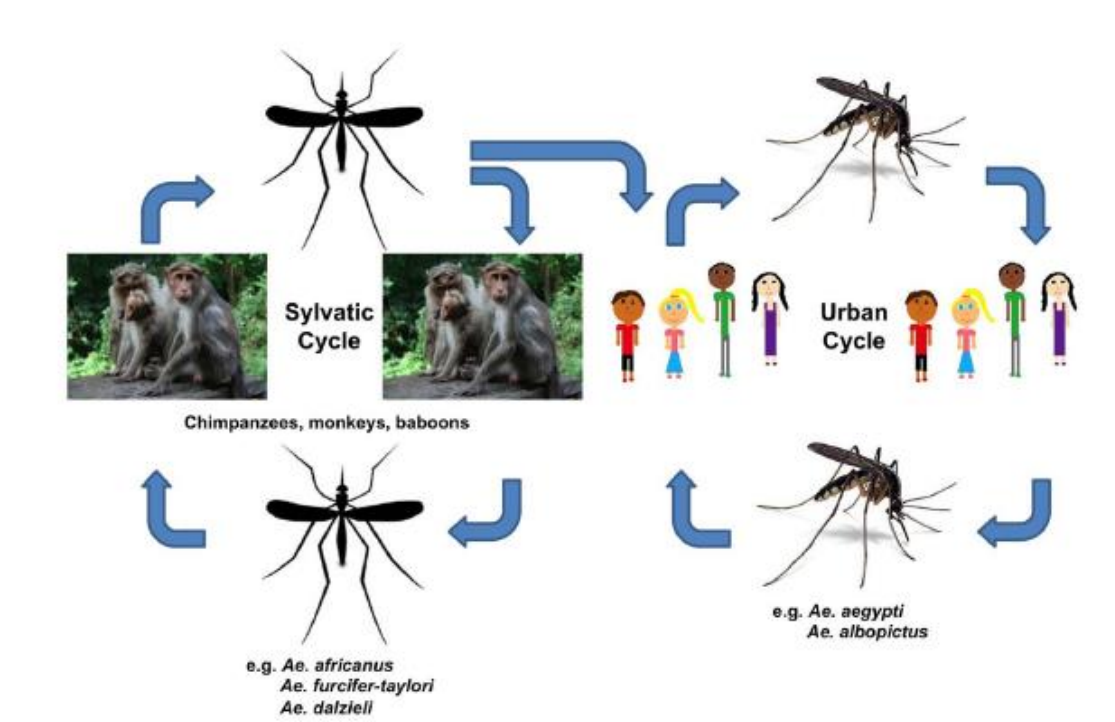
Chikungunya Virus

- 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 (WAf),
  - East/Central/South African (ECSA),
  - Asian genotypes



Background

- Transmitted by the same vector of Dengue virus



Thiboutot MM, et. al, PLoS Neglected Tropical Diseases (2010), Vol 4, Issue 4.

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

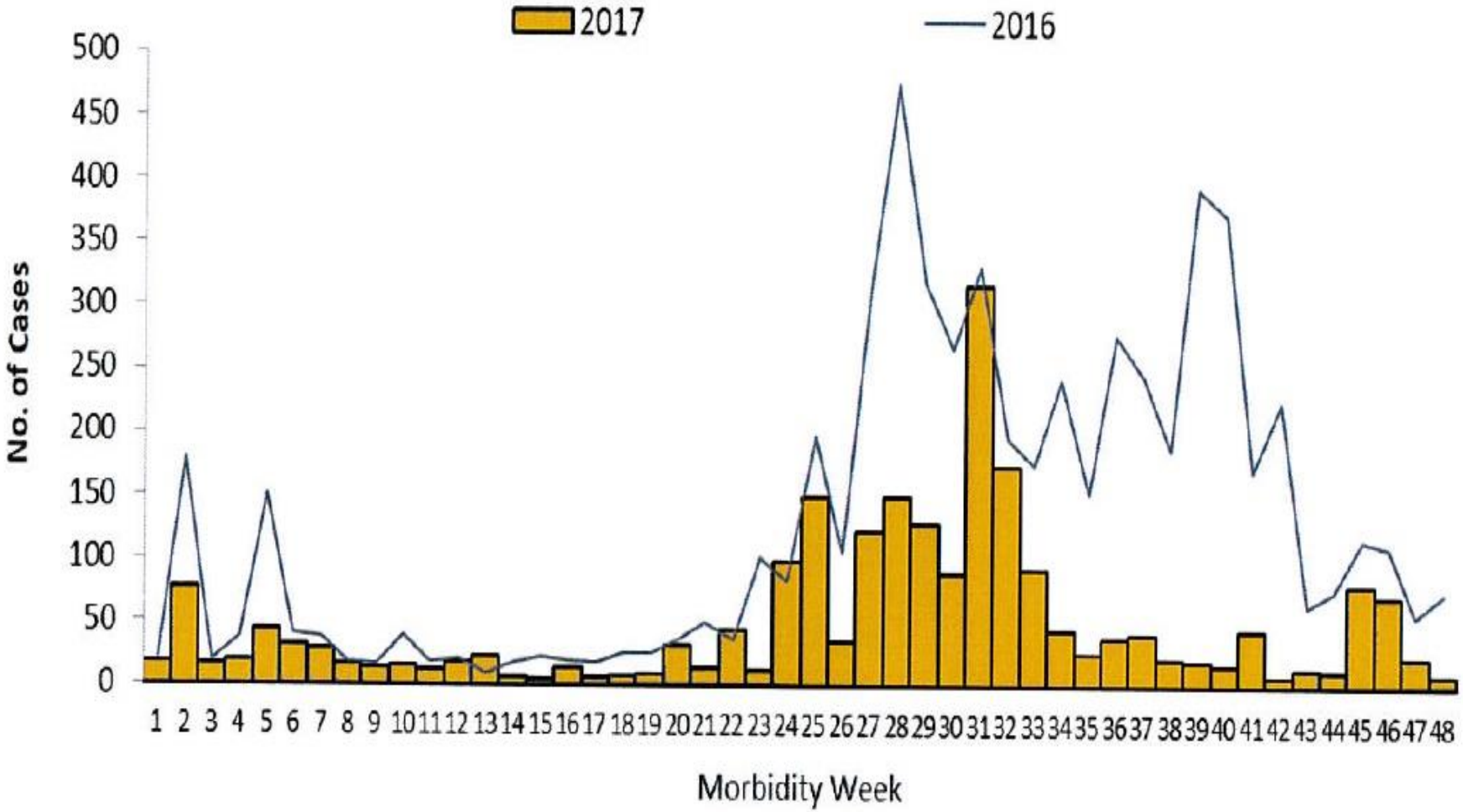
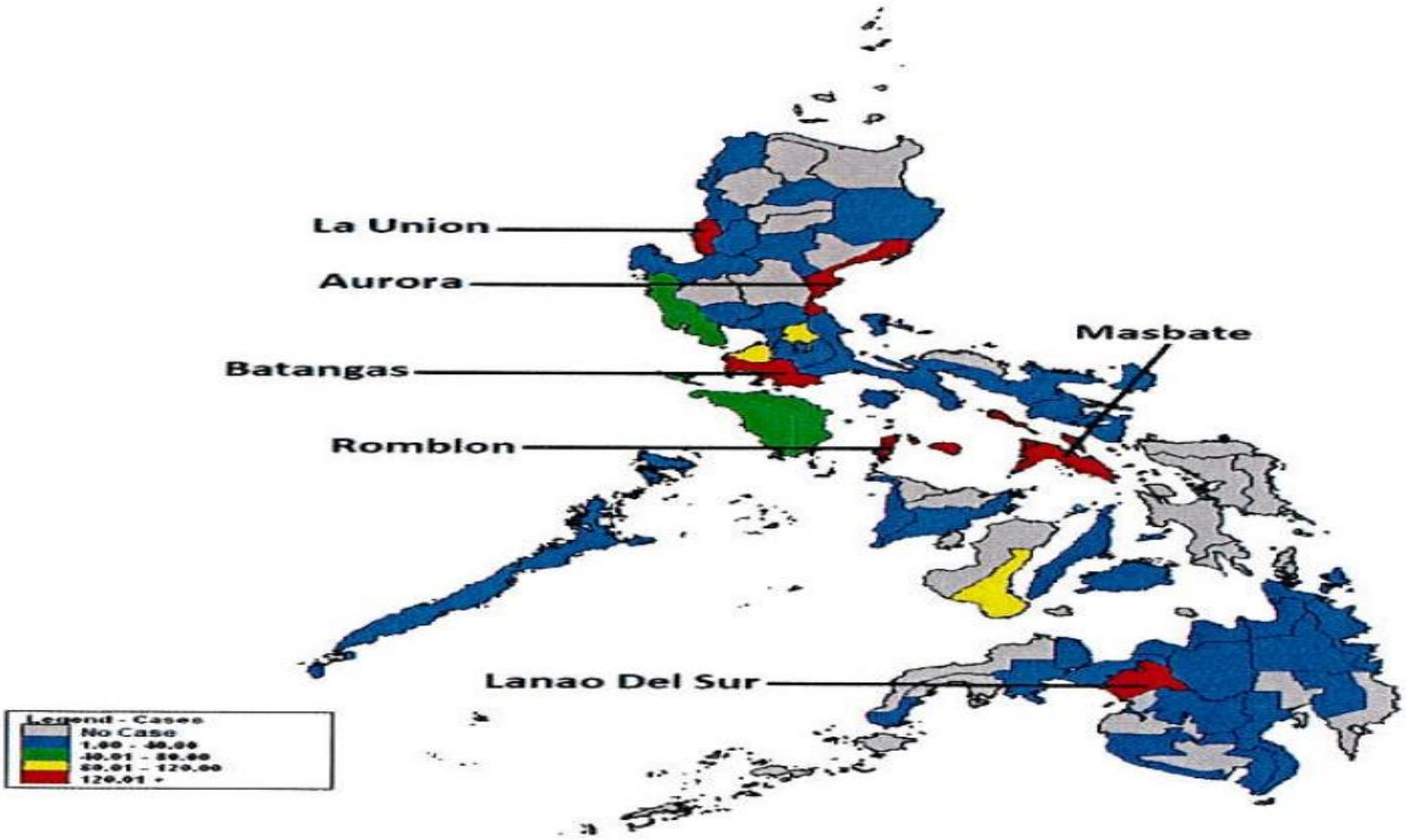


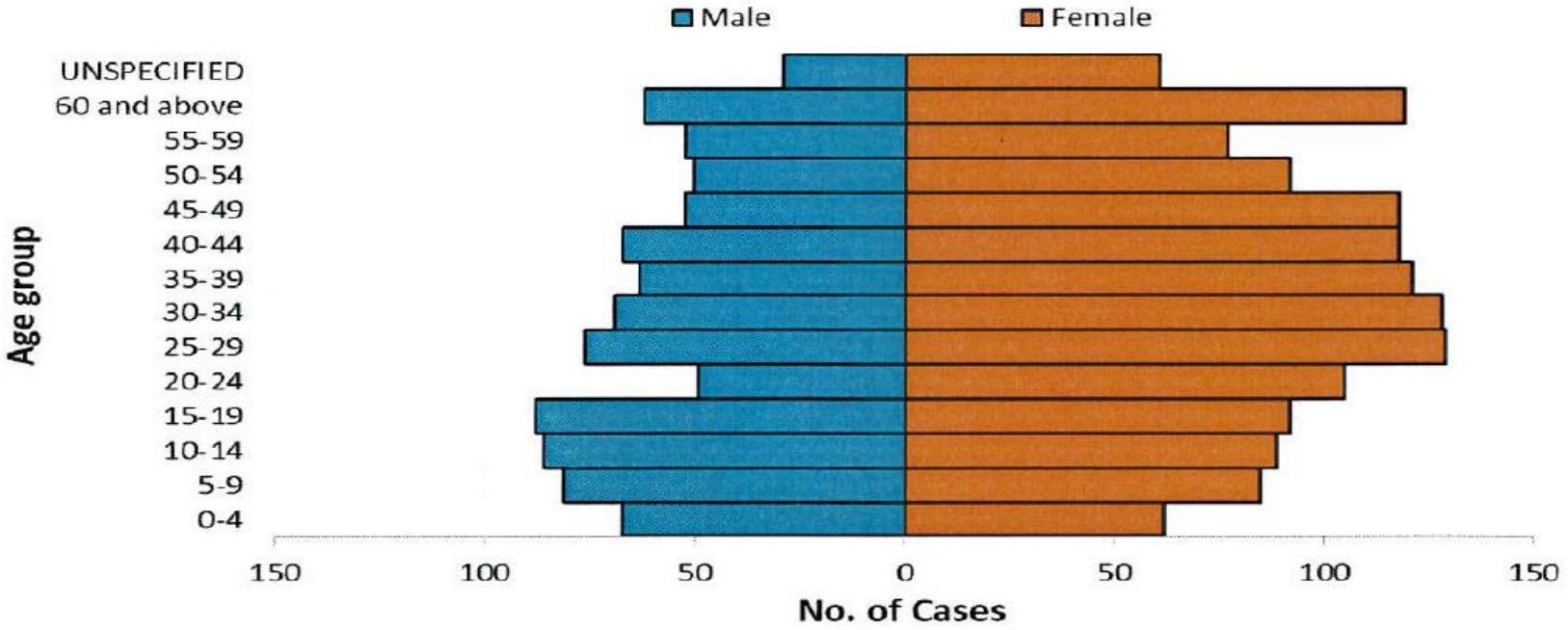
Fig. 3 Reported Chikungunya Cases by Province Philippines, as of January 1 – December 2, 2017* (N=2,287)



Profile of Cases

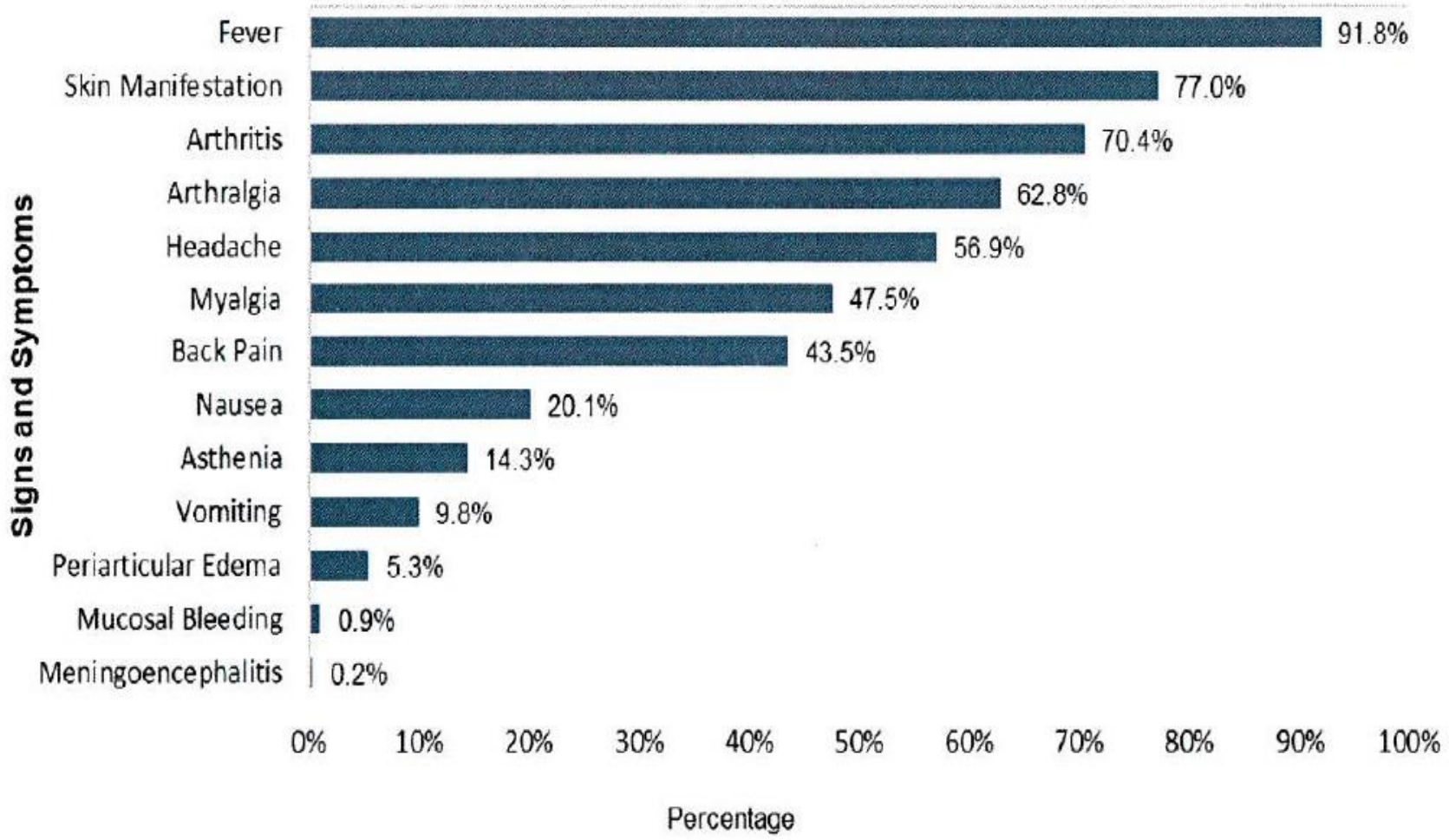
Ages of cases ranged from less than 1 year to 95 years old (median = 32 years). Majority of cases were females (61.0%). Most (9.0%) of the cases belonged to the 25-29 years age group. There were 4 deaths reported (CFR=0.17%).

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**



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

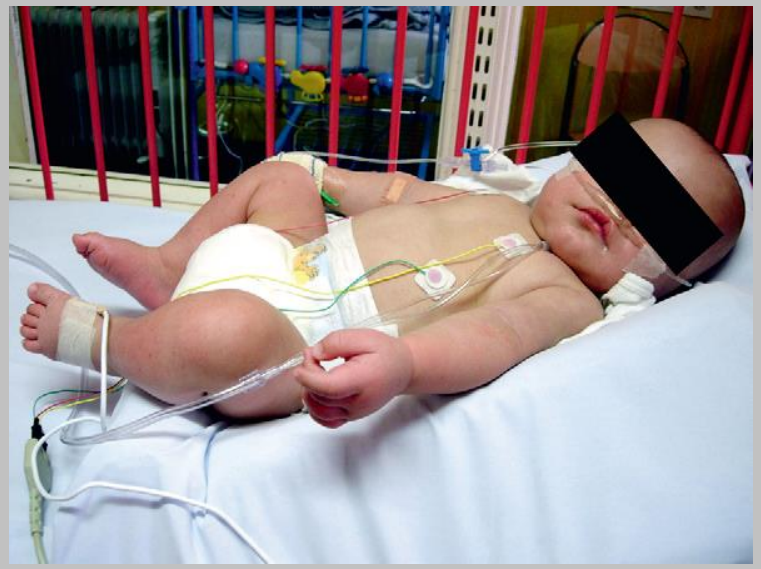
Sebastian et al. Chikungunya Infection in Children, Indian J of Pedia Vol 76, Feb 2009

CHIKUNGUNYA: Clinical Manifestation

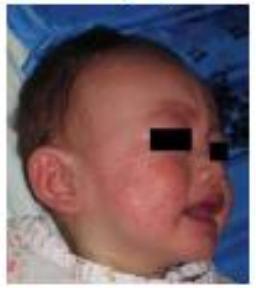
Clinical Manifestations	DENGUE	CHIKUNGUNYA
Fever (T>38.9^{0}C)	++	+++
Myalgias	++	+
Arthralgia	+/-	+++
Headache	++ (retro-orbital)	++
Rash	+	++
Arthritis	-	+++
Tenosynovitis	-	+++
Hypotension	++ (D5-D7)	+/-
Bleeding	++ (D5-D7)	+/-
Shock	+/-	-
Conjuntival injection	+	++

Nimmannitya et al Am J Trap Med Hyg 1969; 18:954-71; Halstead et al Am J Trop Med Hyg 1969; 18:972-83; Feigin and Cherry Textbook of Pediatrics 7th Ed. 2014 Elsevier Saunders Philadelphia; PA ; Staple et al CID Sept. 2009; 49:942-948

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

Sebastian et al. Chikungunya Infection in Children, Indian J of Pedia Vol 76, Feb 2009

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

Sebastian et al. Chikungunya Infection in Children, Indian J of Pedia Vol 76, Feb 2009

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

Sebastian et al. Chikungunya Infection in Children, Indian J of Pedia Vol 76, Feb 2009

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
Sissoko D et al PLoS Negl Trop Dis 2009; 3:e389

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

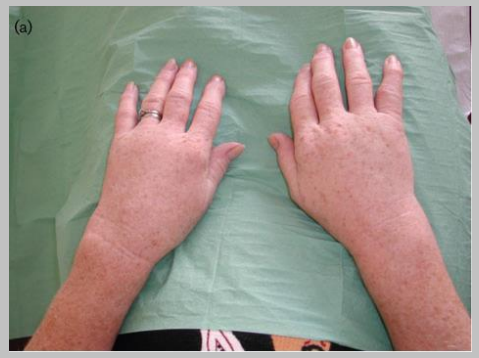
Burt et al The Lancet 2012; 379:662-71
Brighton et al S Afr Med J 1983; 63:313-315
Sissoko D et al PLoS Negl Trop Dis 2009; 3:e389
Mnimunda SP Trans R Soc Trop Med 2010; 104:392-99

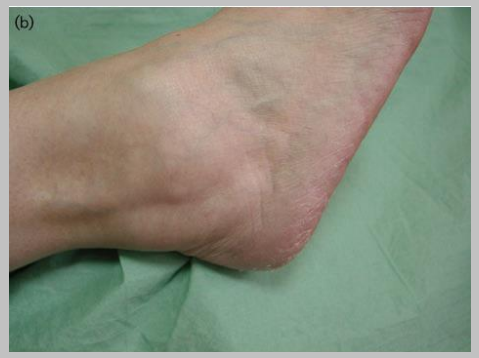
CHIKUNGUNYA: Clinical Manifestation

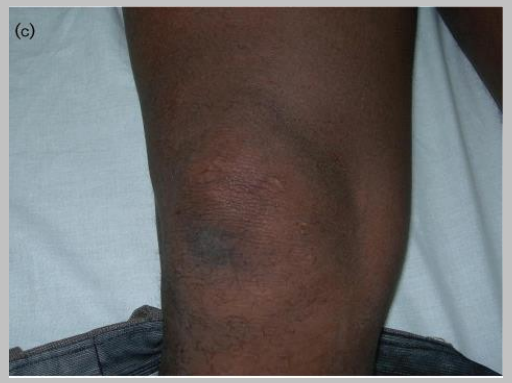
- Chronic Arthralgia Phase
  - Fluctuations in intensity and relapses
    - same joint sites
- Less severe but with reduction in movement and quality of life

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

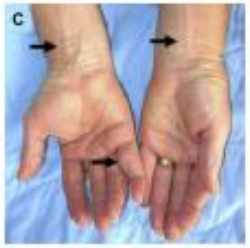
Chronic Manifestations of Chikungunya

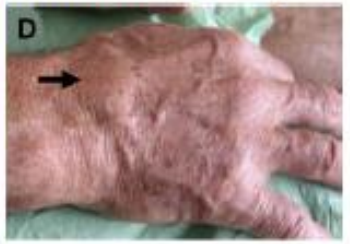






Chronic (months to years)





Inflammatory osteoarthritis

Swollen and stiff joints

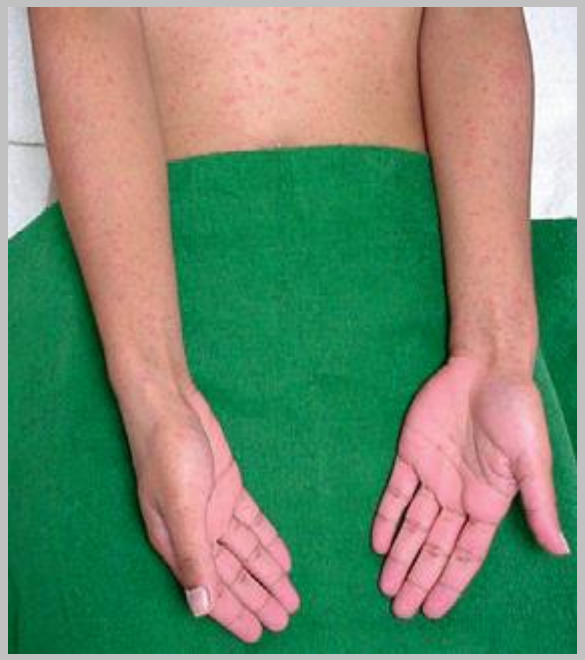
CHIKUNGUNYA: Clinical Manifestation

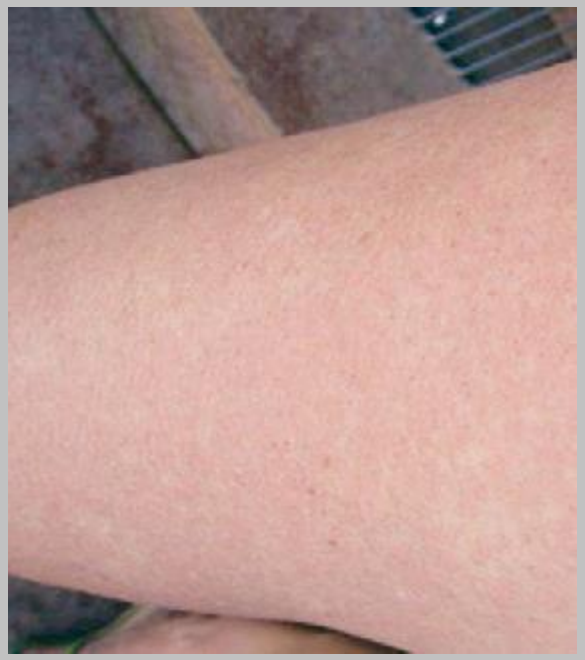
Rash

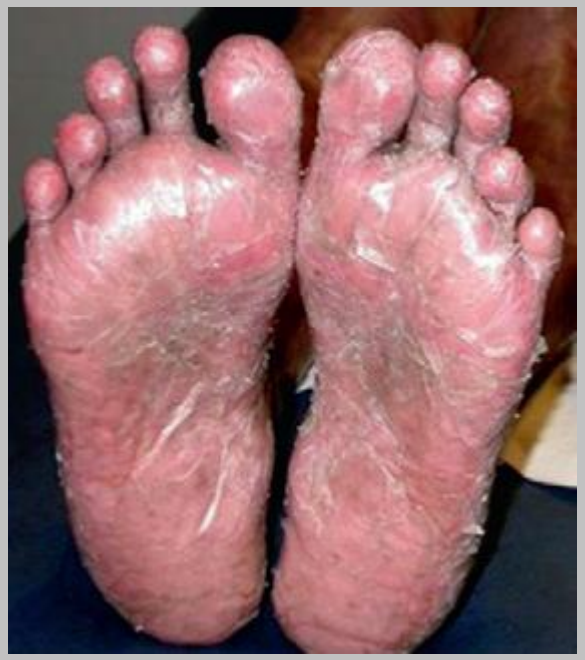
DENGUE	CHIKUNGUNYA
Maculopapular	Maculopapular
Petechiae	Aphthous like ulcers
Urticarial	Vesiculobullous with desquamation
Flushing or erythematous mottling	Vasculitic

Burt et al The Lancet 2012; 379:662-71
Taubitz W et al CID July 2007; 45:el-4
Staple et al CID Sept. 2009; 49:942-948

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

Sebastian et al. Chikungunya Infection in Children, Indian J of Pedia Vol 76, Feb 2009

CHIKUNGUNYA: Clinical Manifestation

Laboratory Findings

	DENGUE	CHIKUNGUNYA
Laboratory Findings		
Leukopenia	+++	++
Neutropenia	+++	+
Lymphopenia	++	+++
Elevated HCT	++	-
Thrombocytopenia	+++	+/-

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.

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

Stacey K. Mardekian and Amity L. Roberts. Diagnostic options and challenges for Dengue and Chikungunya viruses. BioMed Research International Volume 2015, Article ID 834371, 8 pages http://dx.doi.org/10.1155/2015/834371

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

Sebastian et al. Chikungunya Infection in Children, Indian J of Pedia Vol 76, Feb 2009

Genetic Analysis of Chikungunya virus causing re-emergence in the Philippines

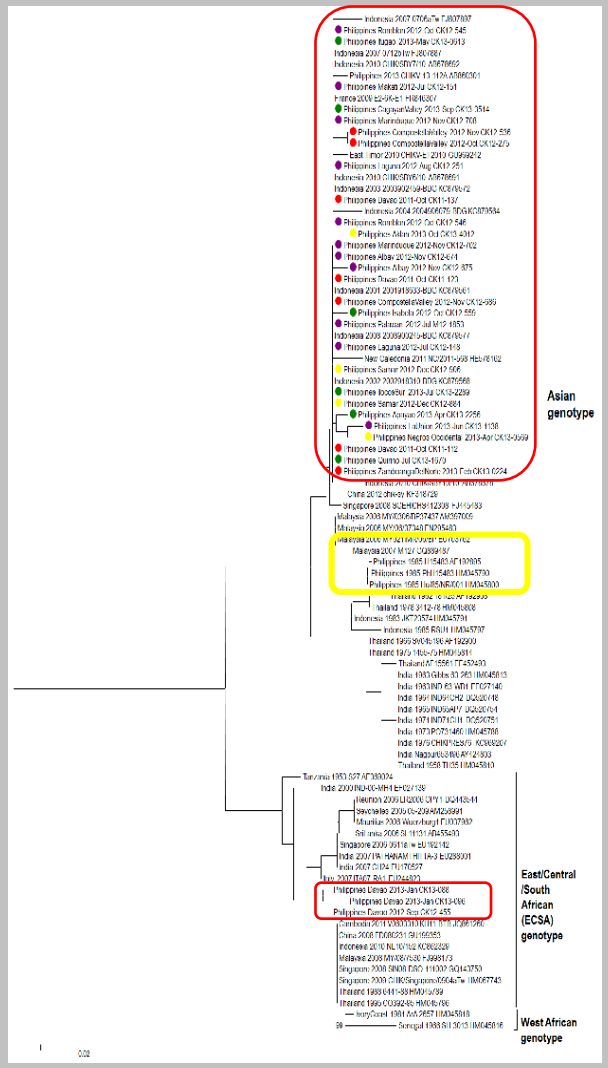
AVA KRISTY SY[1], MARIKO SAITO[2,3], INEZ ANDREA MEDADO[1,3], AMADO O. TANDOC[1], SOCORRO LUPISAN[1], HITOSHI OSHITANI [2]

[1] RESEARCH INSTITUTE FOR TROPICAL MEDICINE (RITM), MUNTINLUPA CITY, PHILIPPINES
[2] DEPARTMENT OF VIROLOGY, TOHOKU UNIVERSITY GRADUATE SCHOOL OF MEDICINE, SENDAI, JAPAN
[3]TOHOKU-RITM COLLABORATIVE RESEARCH CENTER ON EMERGING AND RE-EMERGING INFECTIOUS DISEASES, MUNTINLUPA CITY, PHILIPPINES

- Serum samples from patients with fever, rash, and joint pains was sent to RITM for IgM testing
- Samples collected <5 days after onset of symptoms were tested for CHIKV RNA using 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.



2011-2013 Asian genotype

1985 Asian genotype

2012-2013 ECSA genotype

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

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Neurocognitive Outcome of Children Exposed to Perinatal Mother-to-Child Chikungunya Virus Infection: The CHIMERE Cohort Study on Reunion Island

Patrick Gérardin[1,2,3]*, Sylvain Sampériz[1], Duksha Ramful[1,2,4], Brahim Boumahni[1], Marc Bintner[1], Jean-Luc Alessandri[1], Magali Carbonnier[1], Isabelle Tiran-Rajaoefera[1], Gilles Beullier[5], Irénée Boya[6], Tahir Noormahomed[7], Jocelyn Okoï[8,9], Olivier Rollot[2], Liliane Cotte[1], Marie-Christine Jaffar-Bandjee[1], Alain Michault[1], François Favier[2], Monique Kaminski[3], Alain Fourmaintraux[1], Xavier Fritel[3,10,11]

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**

Table 4. Predictors of global neurodevelopmental delay in multivariable analysis, CHIMERE cohort, Reunion Island, 2008.

Poisson regression model	Total	Children with GND†		Adjusted IRR	(95% CI)	*P* value¶
Chikungunya virus infection						
Yes	32	16	(50.0)	2.79	(1.45–5.34)	0.002
No	119	17	(14.3)	1	-	-
Head circumference*						
−1 S.D≤z-score<+2 S.D	143	28	(19.6)	1	-	-
−2 S.D≤z-score<−1 S.D	4	1	(25.0)	0.82	(0.27–2.41)	0.718
z-score<−2 S.D	4	4	(100)	2.38	(1.41–4.01)	0.001

Developmental quotients (DQ) were measured between 15.8 and 27 months of age.
†Global neurodevelopmental delay (GND) is defined for DQ≤85.
Data are numbers, percentages, adjusted IRR (incidence rate ratio) and robust SE (robust standard error).
¶*P* values are given for adjusted Wald tests.
The model is adjusted for the social deprivation propensity score (see table 2 of ref. [14]) assigning positive or negative points to the rounded-value beta coefficients associated with categories of maternal origin, education, marital status, parity and body mass index; small for gestational age (defined for birth-weight <10th percentile of AUDIPOG growth charts);
*head circumference is corrected for 24 months of postnatal age.
doi:10.1371/journal.pntd.0002996.t004

- **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)**

Neurocognitive Outcome of Children Exposed to Perinatal Mother-to-Child Chikungunya Virus Infection: The CHIMERE Cohort Study on Reunion Island

- 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 encephalapathy can lead to cerebral palsy, microcephaly (dec brain volume), neuronal loss

Gerardin et al. Neurocognitive Outcome of Children Exposed to Perinatal Mother-to-Child Chikungunya Virus Infection: The CHIMERE Cohort Study on Reunion Island. PLOS Neglected Tropical Diseases July 2014 | Volume 8 | Issue 7 | e2996

CHIKUNGUNYA: Treatment

Supportive
- NSAIDS
- Bed rest
- Antipyretics or cold sponging
- Analgesics or mild sedation
- NSAIDS for arthritis after illness
- Physiotherapy
- Hydration

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
Feigin and Cherry Textbook of Pediatrics 7th ed. 2014 Elsevier Saunders Philadelphia, PA

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

CHIKUNGUNYA
Chronic arthritis
Destructive arthropathy reported
Residual neurologic deficits in children

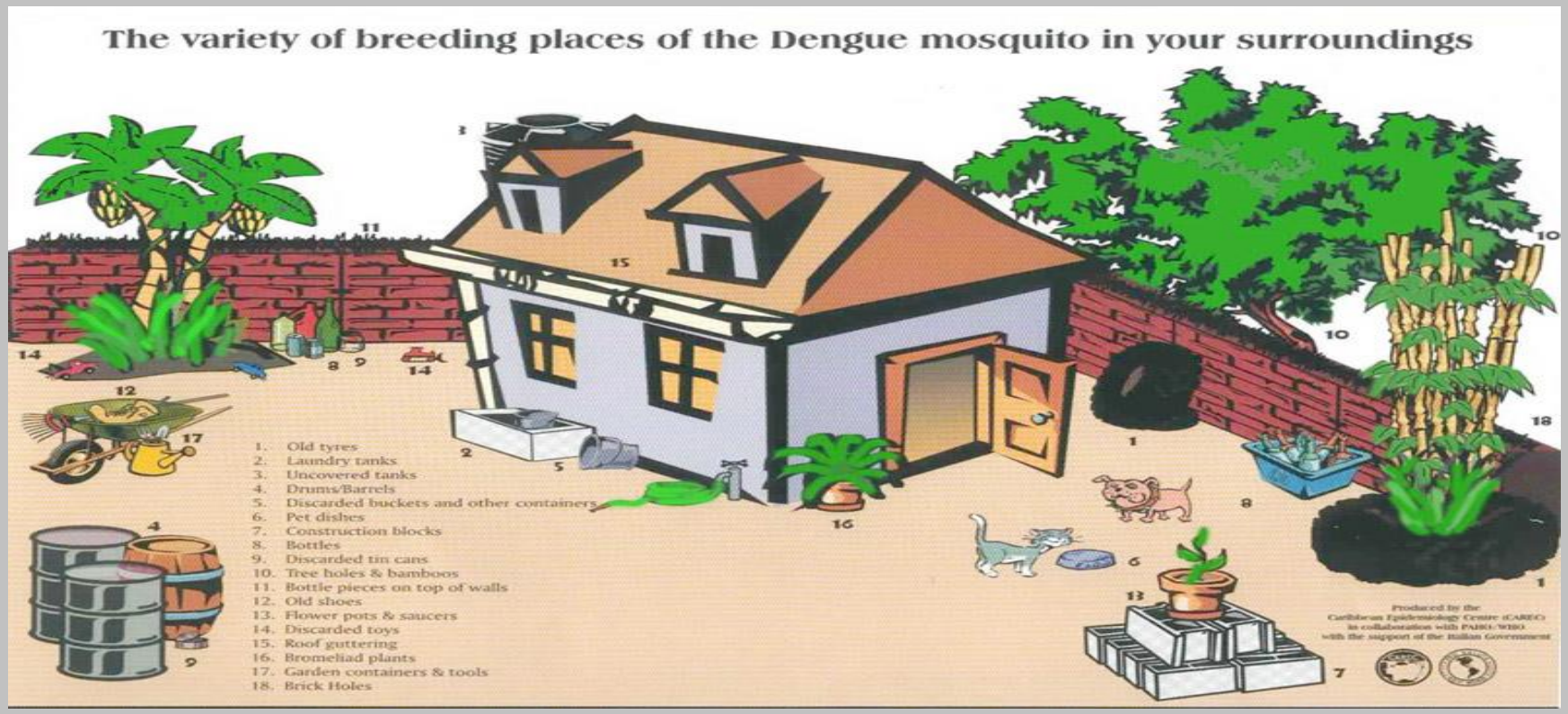
Feigin and Cherry Textbook of Pediatrics 7th ed.
2014 Elsevier Saunders Philadelphia, PA

CHIKUNGUNYA: Prevention

PREVENTION AND CONTROL	VACCINE IN DEVELOPMENT
Integrated Vector Management	Formalin inactivated (Walter Reed) Phase II
Surveillance	Live attenuated vaccine Phase II
Case Management	Chimeric alpha virus approach Phase I
Social Mobilization & Communication about the disease	Virus like particle in Pre-clinical
Outbreak Response	
Research	

Burt et al The Lancet 2012; 379:662-71
Powers et al J Gen Virology 2007; 88:2363-77
Sudeep and Parashar J Biosci Nov 2008; 33(4):443-449

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

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