Chikungunya: looking at the immediate impact and expecting the long term consequences

Pilar Ramon-Pardo
PAHO/WHO - Communicable Diseases and Health Analysis
3 March 2015
Preparedness and Response for Chikungunya Virus
Introduction in the Americas

Preparedness and Response Plan for Chikungunya Virus
Introduction in the Caribbean sub-region

CHIKV in the Americas
A woman arrives at a health center unable to stand straight and having difficulty walking because of back and joint pain caused by the chikungunya virus. Symptoms of the disease usually appear from three to seven days after a mosquito bite.
Severe & atypical forms

- Description
- Vertical Transmission
- Lethality

Chronic manifestations

- Overview
- In the Americas
1. Severe and atypical forms
1.1 Description

Torres et al.
Risk Factors

• **Severe forms**
  - Underlying conditions:
    - Cardiovascular disease (including HTA)
    - Respiratory diseases (Chronic bronquitis, asthma)
    - Neurological disorders
  - Use of non-steroid antiinflammatoires
  - > 60 years old
  - New-borns / pregnancy
  - Immunocompromised (diabetes mellitus)

• **Death**
  - > 85 years old
  - Alcohol abuse

---
Case definitions

• Atypical case

Confirmed CHIKV case + other symptoms than fever and arthralgia

• Severe atypical case

Atypical case + 1 organ failure

Prospective recruitment of all the atypical cases

- 610 atypical cases (average: 70 yo, M/F ratio: 0.8)
- 222 severe cases (36%) → 14% ICU
- 65 deaths (29%) → Mortality of the atypical cases 10.7%
- Risk of death: 30 times higher in >65 yo vs <45 yo
Atypical manifestations

• Digestive (39%)
  o Nausea, vomit, diarrhea, abdominal pain

• Ophthalmology
  o Optic neuritis, retinitis, episcleritis

• Dermatology
  o Hyperpigmentation
  o Mucous ulcers (oral cavity, genital)
  o Bullous dermatitis

# Severe neurologic manifestations

| Encephalitis/ Encephalomyelitis Meningoencephalopathy, myelitis | • 1st case: Bangkok 1964  
• 1.3 - 3/1000 cases (Reunion, India)  
• RNA viral / IgM anti-CHIK in CSF  
• Viral tropism? |
| --- | --- |
| Neuropatic manifestations | • Early with encephalytis (CSF positive)  
• Late: 1 - 3 weeks after starting of the disease, Guillen-Barré like (CSF negative) |
| Guillain Barré syndrome | • Immunoglobuline in CSF  
• Sequelae and severe forms are possible |
| Cerebelose syndrom | • Non specific |
| Seizures Confusion | • Increased mortality |

---

*Tournebize et al. Rev Neurol 2009;165:48-51*  
*Wielaneck et al. Neurology 2007*
Non-specific viral encephalitis but with characteristic signs

- **Clinical manifestations**
  - 30% rash
  - Associated myelo-neuropathy

- **Radiology**
  - White substance damage
  - Fronto-parietal and periventricular lesions
  - Sub-cortical demyelination (≠ HSV)

Severe Non-neurologic Manifestations

- **Renal** (previous renal disease)
- **Hepatic** (fulminant hepatitis, toxic)
- **Hydro-electrolyte** (Syndrome of Inappropriate Antidiuretic Hormone Secretion, supra-renal failure)
- **Cardiac**
  - Viral myocarditis (35 cases)
  - Cardiac failure
- **Respiratory**
  - Pneumonia (S. pneumoniae)
  - Pulmonary edema
  - Respiratory distress
- **Haemorrhagic** (very infrequent)

Case Report

Chikungunya fever: Atypical and lethal cases in the Western hemisphere
A Venezuelan experience

Jaime R. Torres a,*, Leopoldo Códoa G. a, Julio S. Castro a, Libsen Rodríguez b, Víctor Saravia a, Joanne Arvelaez c, Antonio Ríos-Fabra d, María A. Longhi d, Melania Marcano c

a Infectology Section, Tropical Medicine Institute, Universidad Central de Venezuela, Caracas, Bolivarian Republic of Venezuela
b Infectious Diseases Service, Centro Médico Docente La Trinidad, Caracas, Bolivarian Republic of Venezuela
c Clínica RESCARN de Chuao, Caracas, Bolivarian Republic of Venezuela
d Policlinica Metropolitana, Caracas, Bolivarian Republic of Venezuela

IDCases 2 (2015) 6–10
Severe and atypical cases

**Similar**
- Renal failure
- Hepatic failure
- Respiratory failure
- Elder age with underlying conditions

**But different**
- Nasal necrosis
- Extensive cutaneous lesions
1.2 Mother to Child Transmission
Maternal signs and symptoms (n = 658)

- Arthralgia: 615
- Fever: 408
- Headache: 354
- Edema: 355
- Diarrhea: 78
- Aphthae: 63
- Epistaxis or...: 59
## Pregnancy outcome according to CHIK infection during pregnancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infected n=658</th>
<th>Not infected n=655</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission during pregnancy</td>
<td>266</td>
<td>191</td>
<td>1,32 (1,18-1,95)</td>
</tr>
<tr>
<td>Still birth after 22 weeks</td>
<td>5</td>
<td>8</td>
<td>0,61 (0,18 – 2,07)</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>19</td>
<td>15</td>
<td>1,54 (0,68 – 3,49)</td>
</tr>
<tr>
<td>Admission to neonatal care</td>
<td>53</td>
<td>54</td>
<td>1,03 (0,67 -1,58)</td>
</tr>
</tbody>
</table>
MTCT

- 1st trimester risk ≈ 0
- 2nd and 3rd trimester risk = 0
- Peripartum risk ≈ 50%

CHIK in neonates

- All symptomatic neonates were born to viremic mothers (n=19)
- 36/38 mothers had obvious ongoing symptoms of CHIK
- Onset of symptoms between D3 and D7
- Severe forms: 50% (1 death, D6, NEC)
- Specific manifestations
  - Skin (rash, epidermolysis, bullae)
  - Myocarditis
  - Encephalopathy/encephalitis
- Viremic mother and symptomatic in the 4 days before delivery
- Starting symptoms: 4 days (median) [range: 3-7 days]
- MTCT rate ≈ 50%

### CHIKV Neonatal Infection

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Number of cases /44 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperalgic syndrom</td>
<td>38 (86)</td>
</tr>
<tr>
<td>Rash</td>
<td>23 (52)</td>
</tr>
<tr>
<td>Edema in the extremities</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Meningo–encephalitis</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Dermatosis bullosae</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Manifestations observées chez 44 nouveaux-nés, avril 2005-mars 2006, La Réunion. (Dominguez M et coll.)

50% of severe forms, 50% with neurologic sequelae
Skin manifestations in neonates

- **Edema**
- **Erythroderma**
- **Vesicular and bullous rash**
1.3 Lethality

General Morbility and Mortality
CHIK Outbreak, Reunion Island
Reunion Island, unexpected mortality

- **Excess of mortality during the first 4 months of 2006**

- **CHIK mortality rate, Reunion, 2005-2006**
  - 0.3 / 1,000 population
  - Elderly population (comparable with seasonal influenza)
  - 203 death certificates: CHIK as a direct or indirect cause of death

- **Lethality: ~ 1 / 1,000 cases**

Increased Mortality Rate Associated with Chikungunya Epidemic, Ahmedabad, India

Dileep Mavalankar,* Priya Shastri,* Tathagata Bandyopadhyay,* Jeram Parmar,* and Karaikurichi V. Ramani*

Figure. Monthly chikungunya cases, expected deaths, and reported deaths, Ahmedabad, India, 2006. Error bars show 99% confidence intervals. Jul–Dec, differences were statistically significant.
Lethality (per 1000 cases)
EW 7, Feb 2015

- Martinica: 1.13
- Barbados: 1.07
- Islas Vírgenes (EUA): 1.05
- Guadalupe: 0.82
- Suriname: 0.82
- Puerto Rico: 0.52
- San Martín (Francia): 0.49
- Guayana Francesa: 0.05
- Colombia: 0.02
- República Dominicana: 0.01

Average: 0.19
### Lethality (per 1000 cases)
### Countries that reported deaths, EW 7, 2015

<table>
<thead>
<tr>
<th>Countries</th>
<th>Num of cases</th>
<th>Incidence</th>
<th>Deaths</th>
<th>Lethality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominican Rep.</td>
<td>539,183</td>
<td>5182.4</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Colombia</td>
<td>177,213</td>
<td>366.7</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>French Guyana</td>
<td>18,499</td>
<td>7429.3</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>San Martin (France)</td>
<td>6,073</td>
<td>17,016</td>
<td>3</td>
<td>0.49</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>29,047</td>
<td>786.8</td>
<td>15</td>
<td>0.52</td>
</tr>
<tr>
<td>Suriname</td>
<td>1,224</td>
<td>224.5</td>
<td>1</td>
<td>0.82</td>
</tr>
<tr>
<td>Guadalupe</td>
<td>81,630</td>
<td>17,517.2</td>
<td>67</td>
<td>0.82</td>
</tr>
<tr>
<td>Virgin Islands (USA)</td>
<td>1,912</td>
<td>1813.3</td>
<td>2</td>
<td>1.05</td>
</tr>
<tr>
<td>Barbados</td>
<td>1,872</td>
<td>645</td>
<td>2</td>
<td>1.07</td>
</tr>
<tr>
<td>Martinica</td>
<td>73,715</td>
<td>18,246.3</td>
<td>83</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Lethality in the countries reporting deaths: 0.19
Lethality in the Region: 0.14
2. Chronic Manifestations
2.1 Overview
Acknowledgment

This is a result of the multi disciplinary experience conducted by the French military department of health on Chikungunya.
Clinical evolution of arboviral infections

Acute Infection

- General signs
- Organ damage

Recovery without sequelae

Evolution

Cure with sequelae
Evolving towards a chronic condition....

- Up to 3 months: 80 to 93%
- Up to 15 months: 57%
- After 2.5 years: 47%

Factors related to chronic disease:
- Intensity of the acute phase: pains, CRP, high viremia
- Age > 45 years, pre-existing joint conditions
- Cardiovascular comorbidities

Heterogeneity of studies: pain, arthralgia, arthritis...

Moiton, M.P. et al. BEH thématique, 2008; 38-40
Marimoutou C et al. ASTMH 59th Annual Meeting, Atlanta, USA, 2010

<table>
<thead>
<tr>
<th>AREA (number of patients)</th>
<th>YEAR OF OUTBREAK</th>
<th>%</th>
<th>TIME AFTER CHIK ONSET</th>
<th>CHRONIC DISORDER</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reunion (106)</td>
<td>2005-2006</td>
<td>52%</td>
<td>17 months</td>
<td>Chronic pains (BPI questionary)</td>
<td>de Andrade DC et al. BMC Infect Dis 2010</td>
</tr>
<tr>
<td>Reunion (88)</td>
<td>2005-2006</td>
<td>63.6%</td>
<td>18 months</td>
<td>Persistent arthralgia (yes/no)</td>
<td>Borgherini G et al. Clin Infect Dis 2008</td>
</tr>
<tr>
<td>India Maharashtara (509)</td>
<td>2006</td>
<td>4.1%</td>
<td>12 months</td>
<td>Persistent rheumatic non-specific pain</td>
<td>Chopra A et al. Epidemiol Infect 2012</td>
</tr>
<tr>
<td>India Karnataka Dakshina in Kannada district (203)</td>
<td>2006</td>
<td>75%</td>
<td>1 month, 1 month</td>
<td>Rheumatoid arthritis</td>
<td>Manimunda SP et al. Trans R Soc Trop Med Hyg 2010</td>
</tr>
<tr>
<td>India Otoor village in Kerala (1396)</td>
<td>2008</td>
<td>55%</td>
<td>1 month, 1 month</td>
<td>Musculoskeletal pain</td>
<td>Mathew AJ et al. Int J Clin Pract 2011</td>
</tr>
<tr>
<td>Indian Ocean and South East Asia (69)</td>
<td>Jan-Oct 2006</td>
<td>69%</td>
<td>2 months, 6 months</td>
<td>Persistent arthralgia</td>
<td>Taubitz W et al. Clin Infect Dis 2007</td>
</tr>
<tr>
<td>Italy (250)</td>
<td>2007</td>
<td>66.5%</td>
<td>12 months</td>
<td>Myalgia, asthenia, arthralgia</td>
<td>Moro ML et al. J Infect 2012</td>
</tr>
<tr>
<td>Japan (15 imported cases)</td>
<td>2005</td>
<td>6/15 (40%)</td>
<td>12 months</td>
<td>Persistent arthralgia 1/6 erosive arthritis and tenosynovitis</td>
<td>Mizuno Y et al. J Infect Chemother 2011</td>
</tr>
<tr>
<td>Réunion (180)</td>
<td>2005-2006</td>
<td>31%</td>
<td>14 months</td>
<td>Fully recovered from acute symptoms Long-term arthralgia, 75% with stiffness, 43.5% triggered by a change in ambient temperature, 8% triggered by physical effort.</td>
<td>Schilte C et al. PLoS Negl Trop Dis. 2013;7(3):2137.</td>
</tr>
<tr>
<td>Mauritius</td>
<td>2006</td>
<td>136/173 (78%)</td>
<td>27.5 months</td>
<td>Persisting musculoskeletal symptoms 5% (7/136) ACR rheumatoid arthritis criteria</td>
<td>Essackjee K et al. Postgrad Med J. 2013;89(1054):440-7.</td>
</tr>
</tbody>
</table>

The percentage of affected decreases over time:
- 88 to 100% within 6 weeks.
- 12% at 3-5 years

Never 0 %
Chronic impact on mood – M30

Marimoutou C et al. ASTMH 59th Annual Meeting, Atlanta, USA, 2010
Long-term impact of Chikungunya?

- Cured or not? Subjective criteria
  - Physical state «not cured», quality of life «cured»
  - Fear of relapse ➔ remission

- Possible chronic evolution:
  - Joint damage OR
  - Chronic joint inflammation
Chikungunya Réunion Island, real impact 2005-2014

Cummulative symptomatic cases

Alphavirus : endemic
The chikungunya epidemic, A double impact

The CHIK

The shock

The check
2.2 In the Americas
Post-Chikungunya Rheumatoid Arthritis, Saint Martin

Maud Foissac, Emilie Javelle, Simon Ray, Bruno Guérin, Fabrice Simon

Author affiliations: Hospital Jacques Puel, Rodez, France (M. Foissac, S. Ray, B. Guérin); Laveran Military Teaching Hospital, Marseille, France (E. Javelle, F. Simon)

DOI: http://dx.doi.org/10.3201/eid2103.141397
Conclusions
Conclusions

1. CHIKV causes lethality and increases the mortality → monitoring should be improved

2. Probability of mother to child transmission is 50% during delivery → preventive interventions needed

3. Chronic manifestations are relevant → impact of the chronic cases should be assessed. Patients need follow up.