Chikungunya
What physicians need to know.
Epidemiology, case management, prevention

Pr Fabrice SIMON, MD, PhD
Department of Infectious Diseases and Tropical Medicine
LAVERAN Military Teaching Hospital - Marseille – France
simon-f@wanadoo.fr

I declare no conflict of interest

Chikungunya, a double disease

Arboviral disease
- Acute
- Epidemic
- Due to Aedes expansion
- Visible

Alphavirosis
- Joint tropism → rheumatic disorders
- Chronic outcome
- High post-epidemic burden
- Undermanaged
Chikungunya, first clinical descriptions

- Probably circulating for at least one century
- 1954, Tanzania, “the bending disease”
- Fever and intense pain in joints during acute stage, commonly persisting for months
- During 50 years, a benign infection in remote developing countries of poor interest in public health… = NEGLECTED
- And now, a global challenge!

Kennedy et al. J Rheumatol 1980;7:231-236

Chikungunya virus

ARN
Alphavirus
Togaviridae

3 subtypes
West African, East-Central-South African (ECSA), Asian

1950s-2000s : Africa
Selvatic cycle (like YF)
Primates
Forest Aedes spp.

1950s-2000s : Asia
Periurban and urban cycle (like DEN)
Humans
Aedes aegypti +/- Ae. albopictus


Chikungunya, 1954-2004, one million cases

Chikungunya 2005-2013, 3 to 5 millions cases

A real threat for continental Americas, Australia & Southern Europe

www.thelancet.com Vol 383 February 8, 2014

Chikungunya—coming to America

First reported in the early 1950s in the Makonde plains, straddling the border of Tanzania and Mozambique, the Chikungunya virus is more deadly than dengue, but less appreciated. The primary vector has been thought to be the Aedes aegypti mosquito, but a related species, A. albopictus, has also emerged as a potential player in the spread of the disease. A letter in today’s Lancet highlights the frightening capacity of genetic mutation in the propagation of specific viral variants. In this context, independent evolutionary adaptations in the two species of Aedes mosquitos might also contribute to the differential spread of distinct Chikungunya viral genotypes, including the east, central, and South African form and several Asian strains.

Once confined mainly to sub-Saharan Africa, southern Asia, and the Indian subcontinent, reported cases of autochthonous (locally originating) Chikungunya have occurred in Europe—such as Italy in 2007, Saint Martin in December, 2013, and in June 2015.

Chikungunya first autochthonous cases in the Caribbean
Chikungunya 2013-2017, > 2 millions in the Americas

- Autochtonous transmission in Florida
- Argentina, 2016
  > 1000 cases
- Brazil, 2014–
  385 000 confirmed & suspected cases in 2016
  Unusual mortality rate
  Ongoing spread expected

Chikungunya 2014, French Polynesia

- > 60 000 cumulated suspected cases
- Tahiti & Moorea...
- >20 deaths (> 65 y.o.)
### 2016-2017, some other outbreaks

- **Kenya, 2016**: >1700 c.
- **Somalia, 2016**
- **Southeast Asia, 2016**: Philippines > 400 c.
- **India, 2016**: > 26 000 c., incl. Karnātaka > 11 000c., Dehi > 10 000 c.
- **Pakistan, 2016-…**: > 3 000 c., incl. > 600 c. in Karachi.

### Toward a « pandemic » in tropical and temperate areas

![Map showing CHIK-susceptible areas](image)

### The Aedes pandemic, so many CHIK-susceptible areas

![Map showing Aedes distribution](image)
Chikungunya virus, a great traveler

Thousands chikungunya-infected travelers returning in their countries with acute or persisting symptoms...

**IMPORTED CASES AND EMERGENCIES**

Chikungunya in GeoSentinel experience

- 2006-2015: 720 cases
  - Female: 64%
  - 15%<25y., 55% 25 to 44y., 24% 45 to 64y., 6%>65y
  - Tourism (50%), VFR (30%)
  - 92% outpatients

Chikungunya, a major cause of travel-acquired rheumatism

<table>
<thead>
<tr>
<th>Disease</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated gonococcal infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis (Neisseria, Streptococcus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexually acquired Chlamydiae trachomatis, HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterically acquired Yersinia, Shigella, Campylobacter...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helminth-related rheumatism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taeniasis, hookworm, filariasis, strongyloides, anisakiasis...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis, parvovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coxsackie, rubella...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alphaviruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chikungunya, O Nyong Nyong, Ross River, Mayaro, Sindbis group, Semliki forest...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The natural history of chikungunya disease

- Three stages different in clinical features and treatment

**Acute**
- D1 to D21
- 40-80% spt
- High viremia to D5-D7
- Intense inflammation

**Post-acute**
- S4 to S12
- <10% spt
- Inflammation and transient immune changes
- Multifocal persistence of joint inflammation → musculo-skeletal disorders

**Chronic**
- From M4 to ...
- 40-60% spt
- Rare evolution toward a chronic inflammatory rheumatism
- Psycho-social consequences
- Up to 6-8 years

Acute stage: common features

- More than 60-80% of symptomatic cases
- Fever (90-96%) : high, 2-4 days
- Transient rash
- Multiple arthralgia +/- arthritides (95-100%)
  - Disabling in daily life

Hochedez et al. Eurosurveillance 2007; 12: 1

Acute stage: multiple joint and tendon involvement ++

- Bilateral, symmetrical, distal > 10 joints
- Synovitis + periarticular edema +/- joint effusion
- Multiple tendonitides

Simon et al. Medicine, 2007

Brutal multiple pain and disability

- Outbreak in Comoros, 2005 (seroprevalence: 53%)
  - 80% of CHIK-infected patients hospitalized/confined at home (mean: 6 days)
Other common clinical manifestations

Frequent varied symptoms in many outpatients:
- Cutaneous: 50%
- Digestive: 40%

Common biological changes

<table>
<thead>
<tr>
<th>CHIK+</th>
<th>CHIK-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>CHIK+</td>
</tr>
<tr>
<td>Temperature</td>
<td>37.3 (9)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (35.7%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>18 (43.5%)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>12 (28.6%)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>25 (59.5%)</td>
</tr>
</tbody>
</table>

Atypical hospitalized, complicated or severe acute cases

- Reunion island, Outbreak 2005-2006
- 2/3 of the population infected
Atypical hospitalized, complicated or severe acute cases

> 600 CHIK-infected pregnant women
Vertical peripartum transmission
→ 44 neonatal severe infections
(encephalitis, shock, myocarditis)
⇒ cerebral sequelae, death
224 atypical cases younger than 16 years

610 atypical adult cases:
222 severe (36%),
84 (14%) ICU, 65 deaths (10%)
Role of associated factors >> direct viral effects

Acute stage: harmful partners of CHIKV ++++

- Underlying diseases ++++
  - Decompensation of a chronic organ failure (heart, kidney, lung)
  - And/or overwhelming CHIKV infection
- Decubitus complications (elderly)++
- Iatrogenic +++
  - Drug misuse and overuse
- Co-infections +
Three newly described complications

- **Bullous epidermolysis and multivisceral failure on systemic lupus**
- **Sepsis And septic shock**
  - Atypical & severe
  - High lethality
  - Hyperleucocytosis
  - Renal failure
  - No other infection
- **Acute vascular purpura distal necrosis**

Chikungunya mortality

- **Case fatality rate close to that of seasonal flu**
  - From 0.3-1/1,000 in Reunion Island, 2006 and Martinique, 2014

- **Risk factors for chikungunya-associated severity and/or fatality**
  - Age ≥ 60 years, higher if ≥ 85 years
  - Hypertension
  - Underlying cardiac disorders
  - Use of NSAIDs
  - Alcohol abuse
  - Systemic lupus

Acute stage, high risk for clinical misdiagnosis

- **Zika**
- **Chikungunya**
- **Dengue**
- **Malaria**
- **Leptospirosis**
- **Bacterial sepsis**

Adapted from Simon et al, Schwartz, Infections in travelers, Ed 2009
### Diagnosis confirmation, RT-PCR and serology

- Non epidemic area ➔ biological testing for all cases
- During an outbreak ➔ atypical or complicated cases, high-risk patients, unfavourable outcome, end of the outbreak

**Simon F et al. French guidelines on chikungunya, Med Mal Infect 2015**

---

### Management of CHIK-suspected patients

**Simon F et al. French guidelines on chikungunya, Med Mal Infect 2015**

---

### Treatment

- **No efficient antiviral drug**

**Abdelnabi et al Antiviral Research 2015**

- **Painkillers +++** switch to class 2 if necessary (caution to toxicity)
  - NO NSAID BEFORE D10
  - NO CORTICOSTERIODS
  - Relative rest + anti-arthritic physiotherapy

- **Rehydration ++ & control of of underlying conditions**

- **Specific management for complicated/atypical cases or susceptible patients** (elderly, neonates, pregnant women)

**Abdelnabi et al Antiviral Research 2015**

**Simon F et al. French guidelines on chikungunya, Med Mal Infect 2015**
Prevention of CHIK diffusion in Aedes-colonized areas

- To avoid emergence
- Patients’ education
- Altruistic isolation of suspect acute cases
  - First week
  - Diurnal
  - Bednet
  - Repellents
- Local actions against breeding sites of Aedes

Post-acute stage (S4-S12): clinical features

- Clinical persistence or relapse after transient improvement
  - Common exacerbation at M2-M3
- General manifestations
  - Fatigue and depressive reaction
- Osteo-tendino-articular symptoms +++
  - Polymorph and associated
  - Initial sites +/- new sites with time

Toward chronicity

- Prevalence depending on the outbreak
  - After 3 months: up to 80 to 93%
  - After 2.5 years: about 50%
  - General and rheumatic overmorbidity up to 6 years
    - Intensity of the acute stage: pain, CRP, high viral load
    - Age > 45 yo, pre-existing joint disorders
### The post-CHIK persisting disorders in the literature

<table>
<thead>
<tr>
<th>Area (number of patients)</th>
<th>Year of Outbreak</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>De Andrade DC et al. BMC Infect Dis 2010</td>
</tr>
<tr>
<td>India Maharashtara (509)</td>
<td>2006</td>
<td>4.1%</td>
<td>1.6%</td>
<td>Chopra A et al. Epidemiol Infect 2012</td>
</tr>
<tr>
<td>India Karnataka Dakshina in Kannada district (203)</td>
<td>Jan-Aug 2008</td>
<td>75%</td>
<td>31%</td>
<td>Manimunda SP et al. Trans R Soc Trop Med Hyg 2010</td>
</tr>
<tr>
<td>Italy (250)</td>
<td>2007</td>
<td>66.5%</td>
<td>12 months</td>
<td>Moro ML et al. J Infect 2012</td>
</tr>
</tbody>
</table>

#### Waning with time
Not to zero…

#### Wide clinical spectrum

#### Heterogeneity of the methods
Lack of case-control studies

#### Chronic arthralgias - M6

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of Patients</th>
<th>Months after Onset</th>
<th>% Chronic Arthralgia</th>
<th>Disorder Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reunion Island, 2006</td>
<td>757 military policemen</td>
<td>6 months after onset</td>
<td>86%</td>
<td>Neck (54.1%), Shoulders (46.2%), Elbows (31.3%), Wrists (71.0%), Hands (82.1%), Back (26.5%), Hips (14.1%), Knees (13.3%), Heels (20.5%), Feet (60.7%)</td>
</tr>
</tbody>
</table>

762 answers, M 95%, mean age: 40 yo, 
→ 126 CHIK+ 
86% chronic arthralgia
Chronic joint stiffness – M6

Rheumatic overmorbidity after 2 years... even after recovery!

Chronic stage, up to 6 years...

### Rheumatic symptoms

<table>
<thead>
<tr>
<th></th>
<th>&gt;once/month 2008</th>
<th>&gt;once/month 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHIK+</td>
<td>CHIK+</td>
<td>CHIK+</td>
</tr>
<tr>
<td>Pain</td>
<td>83</td>
<td>70</td>
</tr>
<tr>
<td>Stiffness</td>
<td>82</td>
<td>53</td>
</tr>
<tr>
<td>Swelling</td>
<td>50</td>
<td>20</td>
</tr>
</tbody>
</table>

### Other symptoms

<table>
<thead>
<tr>
<th></th>
<th>&gt;once/month 2008</th>
<th>&gt;once/month 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHIK+</td>
<td>CHIK+</td>
<td>CHIK-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>21</td>
</tr>
</tbody>
</table>

Marimoutou C et al. BMC Musc Dis 2015

French gendarmes cohort
Reunion exposure, 2006
Follow-up 2008-2012 period

+ Increased medical consumption
+ Impaired QoL

Marimoutou C et al. Medicine 2012
Two categories of persisting rheumatic disorders

<table>
<thead>
<tr>
<th>Musculoskeletal disorders</th>
<th>Chronic inflammatory rheumatisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No synovitis</strong></td>
<td><strong>Presence of synovitis</strong></td>
</tr>
<tr>
<td>Localized +++</td>
<td>Rheumatoid arthritis ++</td>
</tr>
<tr>
<td>Multifocal ++</td>
<td>Unclassified polyarthritis +</td>
</tr>
<tr>
<td>Diffuse +</td>
<td>Spondyloarthritis</td>
</tr>
</tbody>
</table>

> 95%

> 95%

Multiple mechanical tendon disorders: FREQUENT (>95%)

- NO SYNOVITIS
  - Slow improvement of the distal tenosynovitis with time
  - Palmar and plantar fasciitis +++
  - New tendonitis on more proximal joints
    - Achilles's tendons, elbows
    - Shoulders, hips, knees
  - Contracture in axial muscles

Typical locations after 6 months

`Simon F et al. Medicine 2007 and personal data`
Post-CHIK chronic inflammatory rheumatisms: RARE (<5%)

- PRESENCE OF SYNOVITIS, not arthralgia only
- Subsequent evolution > 3 months after acute stage
- Fitting the criteria of the classical CIR definitions

Four post-CHIK chronic inflammatory rheumatisms (CIR)

- **Rheumatoid arthritis RA (ACR 2010 criteria)**
  - 1/3 with anti-CCP; bone erosions when delayed treatment; initial corticoresistance

- **Rheumatoid arthritis RA (ACR 2010 criteria)**
  - Remitting seronegative symmetrical synovitis with pitting edema RS3PE
  - Sensitive to NSAID or systemic corticotherapy; good outcome

- **Peripheral spondyloarthritis SA (ASAS 2011 criteria)**
  - Pseudo-psoriatic, multiple synovitis, enthesal inflammation (heels...)
  - Mostly exacerbation of pre-existing disease

- **Unclassified polyarthritis (non RA-SA chronic polyarthritis)**
  - Poor response to anti-inflammatory drugs; possible evolution to RA or SA

Persisting rheumatic disorders, clinical assessment

- The cornerstone of the diagnosis

- Specific clinical examination

- Level of pain and psychic load

- Functional impact and social consequences
Persisting rheumatic disorders: clinical management

Persisting rheumatic disorders, further investigations

- Biological testings
  - Confirmation of CHIK infection
  - Pre-treatment testings
  - Differential diagnosis (uricemia...)

- Imaging according the clinical features and hypotheses
  - Mostly useless for MSD
  - Follow the guidelines for rheumatologists


Persisting rheumatic disorders, diagnosis algorithm

Persisting rheumatic disorders, principles of treatment for all

Persisting symptoms

Persisting rheumatic disorders, drugs

- **Painkillers** ++
  - Acetaminophen, tramadol...; anti-neuropathic drug if test DN4+

- **NSAIDs** +++
  - Full dose if not CI, at night, prolonged liberation, switch if not sufficient after one week; total: 2-12 weeks

- **Oral corticosteroids: CAUTION**
  - For NSAID-refractory features only +++
  - Low dose, total < 4 weeks, relay with NSAIDs
  - High risk for clinical intense relapse and side effects

Persisting rheumatic disorders, physical therapies +++

- **To preserve articular amplitudes and muscle strength**

- **Activo-passive mobilisation and massages, ultrasounds**

- **Antalgic physiotherapy for refractory joints**
  - Arthritis, tenosynovitis ← cryotherapy/orthese (right)
  - Edema ← Scottish bath/pressure therapy/contention
  - Tunnel syndrome← infiltration (avoid surgery)
Post-acute stage, start self-rehabilitation

- Soft sport activities
- Repetition of soft movements to reduce stiffness

Post-CHIK chronic inflammatory rheumatisms, treatment

- Post-CHIK CIR: the target and the challenge +++
- Suspect after 12 weeks of a well-done treatment kit
- Specific management by a rheumatologist
  - Early diagnosis
  - Early start of specific treatment
  - Follow the guidelines for CIR!
  - No prolonged corticotherapy; special place for methotrexate
  - To date, no data to determine when to stop DMARDs
  - Psychological support

Chronic stage, the two opposite outcomes

Local inflammatory post-infectious → MSD

- Painkillers
- Anti-inflammatory drugs
- Spare tendons & muscles

Possibly destructive if delayed treatment
- Systemic auto-inflammatory → CIR
- Rheumatologist
- Early start of DMARDs
- Spare tendons & muscles

Resolutive
Prevention

- For all, avoid diurnal Aedes bites

- **Risk for severe acute complications**
  - Pregnant women in the last weeks of pregnancy
  - Patients with systemic lupus
  - Patients with chronic organ failure, even balanced
    ➔ Cancel the trip

- **Risk for increase of rheumatic disorders**
  - Patients with pre-existing spondyloarthritis
  - Patients with invalidating osteo-arthrosis
    ➔ Trip not recommended. If "mandatory", a spacesuit!

- **No available vaccine to date**
  - Eight candidates (2 in phase II)
Post-CHIK chronic rheumatic disorders, pathogenesis

Dupuis-Maguiraga, PLoS NTD 2012
Jaffer Bandjee et al. Microbes Infect. 2009;11:1206-18