CHIKUNGUNYA IN TRAVELERS

Lessons from epidemiological and clinical aspects

Philippe PAROLA, MD, PhD
University Hospital of Marseille, France
EuroTravNet Coordinator

EuroTravNet - The ECDC Collaborative Network for Travel and Tropical Medicine – www.eurotravnet.eu
WHAT IS CHIKUNGUNYA VIRUS?

1950s: Africa
sylvatic cycle involving wild primates
+ forest dwelling *Aedes* spp. mosquitoes
( similar to yellow fever virus).

1950’s: Asia
associated with the urban *Aedes aegypti*
possibly supplemented by *A. albopictus*:
• absence of an animal reservoir
• direct H to H transmission by urban mosquito
• similar to dengue cycle


Dr. Ph. Parola Lecture at ASTMH meeting 2009
CHIKUNGUNYA

a Makonde word meaning “that which bends up”:

a reference to the inability of some patients to walk upright due to the severe crippling pains in the acute stages

Many patients remain in severe pain for months.

Knowledge of its clinical features based on the descriptions of South African teams in the late 1970’s:
  + brief fever +/- headache +/- myalgias +/- evanescent rash

Long been considered as benign

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

Dr. Ph. Parola Lecture at ASTMH meeting 2009
potential for major epidemics that re-emerge after an unpredictable period of silence

1999–2000: Democratic Republic of the Congo, an estimated 50,000 persons infected after 39 years without any isolation of the virus

2001–2003: Indonesia, after a near 20-year hiatus of epidemic CHIKV activity


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September 18th, 2006: an estimate of 266,000 residents infected (population 770,000)

Peak end of January: 45,000 cases / week!

248 death certificates mentioning “CHIKV” as the possible cause of death!!! > 61 years old +++


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Chikungunya epidemic in India: a major public-health disaster

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths reported/ (estimated)</th>
<th>Mortality rate per 100 000 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Réunion (France)</td>
<td>258 000</td>
<td>237</td>
<td>91.8</td>
</tr>
<tr>
<td>India reported by government</td>
<td>1391165</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>India conservative estimate</td>
<td>1391165</td>
<td>(1194)</td>
<td>91.8</td>
</tr>
<tr>
<td>India moderate estimate</td>
<td>6.5 million</td>
<td>(6389)</td>
<td>91.8</td>
</tr>
<tr>
<td>India full estimate</td>
<td>6.5 million</td>
<td>(19168)</td>
<td>275.6†</td>
</tr>
</tbody>
</table>

*Assuming under reporting—actual numbers estimated as five times the reported number. †Assuming mortality in India is three times that in Réunion.

Table: Reported cases, deaths, and estimated deaths in Réunion and India
First report of chikungunya from the Maldives.


Ministry of Health, Malé 20379, Republic of Maldives.

An outbreak, characterised by fever, arthralgia and myalgia, in Malé and other islands of the Maldives began in December 2006. The illness was suspected as being due to chikungunya virus based on clinical symptoms and the prevailing chikungunya epidemic in the Indian Ocean region. The Department of Public Health initiated an investigation and collected blood samples from 67 patients; 21% were IgM-positive for chikungunya and 96% were PCR-positive. Six percent were positive for dengue by enzyme immunoassay and 4% had evidence of dual infection. This is the first time that chikungunya fever has been confirmed in the Maldives. A total of 11,879 suspected and confirmed cases affecting 61% of inhabited islands (attack rate ranging from 0% to 72% on individual islands) were reported by the end of the epidemic in April 2007.
OTHER REEMERGENCES

Reemergence of Endemic Chikungunya, Malaysia

Sazaly AbuBakar,* I-Ching Sam,*
Pooi-Fong Wong,* NorAziyah MatRahim,*
Poh-Sim Hooi,* and Nuruliza Roslan*

Chikungunya virus infection recently reemerged in Malaysia after 7 years of nondetection. Genomic sequences of recovered isolates were highly similar to those of Malaysian isolates from the 1998 outbreak. The reemergence of the infection is not part of the epidemics in other Indian Ocean countries but raises the possibility that chikungunya virus is endemic in Malaysia.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 1, January 2007
LETTERS

Chikungunya Outbreak, Singapore, 2008

To the Editor: Chikungunya

Yee S. Leo, Angela L.P. Chow, Li Kiang Tan, David C. Lye, Li Lin, and Lee C. Ng

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 5, May 2009
Circulation of Chikungunya Virus in Gabon, 2006–2007

Christophe N. Peyrefitte,1 Maël Bessaud,1,2 Boris A.M. Pastorino,1 Patrick Gravier,1,3 Sébastien Plumet,1 Olivier L. Merle,1 Isabelle Moltini,1 Emilie Coppin,1 Fabienne Tock,1 William Dariey,1 Lénaïck Ollivier,4 Frédéric Pages,5 Ronan Martin,2 Frédéric Boniface,2 Hugues J. Tolou,1 and Marc Grandadam1

18 000 suspected cases  829 hospitalized  No death

Dr. Ph. Parola Lecture at ASTMH meeting 2009
20,000 estimated cases in Thailand by May 15, 2009
Archive Number: 20091022.3633
Published Date: 22-OCT-2009
Subject: PRO/EDR> Chikungunya (41): Viet Nam (HN) susp., RFI

CHIKUNGUNYA (41): VIET NAM (HANOI) SUSPECTED, REQUEST FOR INFORMATION
***********************************************************************

A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Tue 20 Oct 2009
Source: Thanh Nien News [edited]
<http://www.thanhniennnews.com/healthy/?catid=8&newsid=53234>

Dengue look-alike infects Hanoi
-----------------------------
Viet Nam is verifying an outbreak in Hanoi of a mosquito-borne virus
that closely resembles the dengue fever virus, a health ministry
official said on Monday [19 Oct 2009].

So far, 60 percent of patients with classic dengue symptoms have
tested negative for dengue, according to Vu Sinh Nam, deputy director
general of the Preventive Health and Environment Department.
CHIKUNGUNYA (31): INDIA (ANDHRA PRADESH)

A ProMED-mail post

ProMED-mail is a program of the International Society for Infectious Diseases

Date: Mon 7 Sep 2009
Source: Desimete.com [edited]

The spate of seasonal diseases in twin cities took another turn, with authorities on Sunday [6 Sep 2009] confirming the presence of chikungunya in twin cities [of Hyderabad].

The Nallakunta Fever Hospital had received a patient with chikungunya like symptoms from Amberpet. Laboratory tests revealed that the patient has tested positive for chikungunya.
LESSONS FROM THE (ON GOING ?) OUTBREAK

The vector(s) - The Virus

Clinical Aspects

Travelers – Vectors & Risk of Globalisation

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Most likely first hypothesis: Invasion of a region where the population is immunologically naive for CHIKV

+ Where a vector, *Aedes albopictus* is proliferating profusely.

+ one more thing !!!
The Asian tiger mosquito *Aedes albopictus* : the implicated vector in Reunion
AEDES ALBOPICTUS

Artificial

Natural

Domestic

Breeding sites

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Aire de distribution de Ae albopictus en hiver à la Réunion (juillet-août 2006):

DRASS La Réunion, Jean Sébastien Dehecq, Julien Thiria, collab. IRD, Hélène Delatte
Trophic preferences of *Ae. albopictus* from la Réunion Island

Dr. Ph. Parola Lecture at ASTMH meeting 2009

Delatte at al. unpublished results
Aedes albopictus was the only potential vector collected.
SCIENTIFIC NOTE

FIRST RECORD OF Aedes albopictus IN GABON

T. COFFINET, J. R. MOUROU, B. PRADINES, J. C. TOTO, F. JARRAVAL, R. AMALVICT, M. KOMBILA, P. CARNEVALE, and F. PAGÈS

Aedes albopictus Mosquito: The Main Vector of the 2007 Chikungunya Outbreak in Gabon

Frédéric Pagès, Christophe N. Peyrefitte, Médard Toung Mve, Fanny Jarjaval, Sylvain Brisse, Isabelle Iteman, Patrick Gravier, Dieudonné Nkoghe, Marc Grandadam

1 Institut de médecine tropicale du Service de santé des armées, Unité d’entomologie médicale, UR-MITE UMR 6238, Marseille, France; 2 Institut de médecine tropicale du Service de santé des armées, Unité de virologie tropicale, Marseille, France; 3 Ministère de la Santé publique, Libreville, Gabon; 4 Institut Pasteur, plate-forme génomique, Paris, France; 5 Service médical du 6e BIMA, Libreville, Gabon
Outbreak of chikungunya fever in Thailand and virus detection in field population of vector mosquitoes, Aedes aegypti (L.) and Aedes albopictus Skuse (Diptera: Culicidae).


National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.

We investigated chikungunya fever outbreak in the southern part of Thailand. Human plasma specimens obtained from suspected patients and adult wild-caught mosquitoes were detected for chikungunya virus employing reverse transcriptase-polymerase chain reaction technique. Chikungunya virus was detected in about half of the blood specimens whereas a range of 5.5 to 100% relative infection rate was found in both sexes of the vector mosquitoes, Aedes aegypti (L.) and Ae. albopictus Skuse. The infection rate in Ae. albopictus was higher than in Ae. aegypti, with relative infection rate in male of both species being higher than in female. The appearance of chikungunya virus in adult male mosquitoes of both species reveals a role of transovarial transmission of the virus in field population of the mosquito vectors. These findings have provided further understanding of the relationship among mosquito vectors, chikungunya virus and epidemiology of chikungunya fever in Thailand.
THE VIRUS

Novel Chikungunya Virus Variant in Travelers Returning from Indian Ocean Islands

Philippe Parola,*†‡ Xavier de Lamballerie,‡§† Jacques Jourdan,¶ Clarisse Rovery,* Véronique Vaillant,# Philippe Minodier,* Philippe Brouqui,*† Antoine Flahaut,** Didier Raoult,†‡ and Rémi N. Charrel‡§

Emerging Infectious Diseases Vol. 12, No. 10, October 2006

Dr. Ph. Parola Lecture at ASTMH meeting 2009
East Central South African CHIKV genotype

Patient: 22nd Feb 2006.
Complete genome sequence: Feb 28th
• released immediately in GenBank
• information posted on PROMED
• can be sent to any scientist who has access to BSL-3 facilities
• sent to 15 scientist in France, Germany, UK, Italy, Portugal, USA, Hong-Kong, Australia

Phylogenetic analysis of CHIKV virus isolates based on a 1044-nucleotide fragment located in the E1 gene

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Very high viral loads in CHIKV infection: viral loads are 100,000 times higher than in Hepatitis C

1µL of CHIKV viremic serum contains a number of virions equivalent to 100 mL of HCV infected serum!

nosocomial infection! Needle-stick injury or mucous membrane exposure.
Biological and virological parameters (2)

Sudden onset
Arthralgias, rash, fever
Headaches, buccal erosions

Inoculation
Clinical symptoms

mean D-3 D0 D4-D7 D15

Incubation time
(1 to 12 days)

Viral RNA until D5
(RT-PCR)

Dr. Ph. Parola Lecture at ASTMH meeting 2009
### Indian Ocean: 92 sequences from 89 patients

<table>
<thead>
<tr>
<th>Date</th>
<th>Sequences</th>
<th>A226</th>
<th>V226</th>
</tr>
</thead>
<tbody>
<tr>
<td>March to June 2005</td>
<td>19</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>September to December</td>
<td>27</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>January to March 2006</td>
<td>46</td>
<td>6</td>
<td>40</td>
</tr>
</tbody>
</table>

Switch from A226 to V226 between the 2 epidemic waves
Comparative full genome analysis revealed E1: A226V shift in 2007 Indian Chikungunya virus isolates


Division of Virology, Defence R&D Establishment (DRDE), Jhansi Road, Gwalior 474 002, MP, India
Circulation of Chikungunya Virus in Gabon, 2006–2007

Christophe N. Peyrefitte, Maël Bessaud, Boris A.M. Pastorino, Patrick Gravier, Sébastien Plumet, Olivier L. Merle, Isabelle Moltini, Emilie Coppin, Fabienne Tock, William Daries, Lénaïck Ollivier, Frédéric Pages, Ronan Martin, Frédéric Boniface, Hugues J. Tolou, and Marc Grandadam

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Short report

Chikungunya virus adapts to tiger mosquito via evolutionary convergence: a sign of things to come?
Xavier de Lamballerie*1, Eric Leroy2, Rémi N Charrel1, Konstantin Ttsetsarkin3, Stephen Higgs3 and Ernest A Gould1

Abstract

Since 2004, several million indigenous cases of Chikungunya virus disease occurred in Africa, the Indian Ocean, India, Asia and, recently, Europe. The virus, usually transmitted by Aedes aegypti mosquitoes, has now repeatedly been associated with a new vector, Ae. Albopictus. Analysis of full-length viral sequences reveals three independent events of virus exposure to Ae. Albopictus, each followed by the acquisition of a single adaptive mutation providing selective advantage for transmission by this mosquito. This disconcerting and current unique example of "evolutionary convergence" occurring in nature illustrates rapid pathogen adaptation to ecological perturbation, driven directly as a consequence of human activities.
Two Chikungunya Isolates from the Outbreak of La Reunion (Indian Ocean) Exhibit Different Patterns of Infection in the Mosquito, *Aedes albopictus*

Marie Vazeille¹, Sara Moutailler², Daniel Coudrier², Claudine Rousseaux³, Huot Khun⁴, Michel Huerre⁴, Julien Thiria⁵, Jean-Sébastien Dehecq⁵, Didier Fontenille⁶, Isabelle Schuffenecker⁷, Philippe Despres⁸, Anna-Bella Failloux²

A single new mutation (E1-A226V) present in the CHIKV isolates in all places

providing selective advantage for CHIKV transmission by *Ae. albopictus*.
A Single Mutation in Chikungunya Virus Affects Vector Specificity and Epidemic Potential

Konstantin A. Tsetsarkin, Dana L. Vanlandingham, Charles E. McGee, Stephen Higgs

Department of Pathology, University of Texas Medical Branch, Galveston, Texas, United States of America

Chikungunya virus (CHIKV) is an emerging arbovirus associated with several recent large-scale epidemics. The 2005–2006 epidemic on Reunion island that resulted in approximately 266,000 human cases was associated with a strain of CHIKV with a mutation in the envelope protein gene (E1-A226V). To test the hypothesis that this mutation in the epidemic CHIKV (strain LR2006 OPY1) might influence fitness for different vector species, viral infectivity, dissemination, and transmission of CHIKV were compared in *Aedes albopictus*, the species implicated in the epidemic, and the recognized vector *Ae. aegypti*. Using viral infectious clones of the Reunion strain and a West African strain of CHIKV, into which either the E1–226 A or V mutation was engineered, we demonstrated that the E1-A226V mutation was directly responsible for a significant increase in CHIKV infectivity for *Ae. albopictus*, and led to more efficient viral dissemination into mosquito secondary organs and transmission to suckling mice. This mutation caused a marginal decrease in CHIKV *Ae. aegypti* midgut infectivity, had no effect on viral dissemination, and was associated with a slight increase in transmission by *Ae. aegypti* to suckling mice in competition experiments. The effect of the E1-A226V mutation on cholesterol dependence of CHIKV was also analyzed, revealing an association between cholesterol dependence and increased fitness of CHIKV in *Ae. albopictus*. Our observation that a single amino acid substitution can influence vector specificity provides a plausible explanation of how this mutant virus caused an epidemic in a region lacking the typical vector. This has important implications with respect to how viruses may establish a transmission cycle when introduced into a new area. Due to the widespread distribution of *Ae. albopictus*, this mutation increases the potential for CHIKV to permanently extend its range into Europe and the Americas.
The first local outbreak was due to a wild-type virus and occurred in an area where *Aedes aegypti* mosquitoes were the primary vector.

Strains isolated during subsequent outbreaks showed alanine to valine substitution (A226V) and largely spread in areas predominated by *Ae. albopictus* mosquitoes.
LESSONS
CLINICAL ASPECTS
A previously unknown case mix in Reunion
Main Clinical findings in patients with viremia:

95.5% asymmetrical polyarthralgia
  affecting the lower 98% and small joints 75%

Asthenia 89%, headache 70%, digestive trouble 63%, myalgia 59%,
exanthems 48%, conjunctival hyperhemia 23%, adenopathy 9%
Seldomly: vertigo, cutaneous dysesthesia, pharyngitis, haemorrhage.
Chondrocostal arthralgia, entesiopathies

Laboratory findings:
Lymphopenia 88% - Leukopenia 38% - Thrombocytopenia 37% -
Increased ASAT-ALAT 32%

Prospective study of Chikungunya virus acute infection in the Island of La Réunion during the 2005-2006 outbreak.

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SKIN MANIFESTATIONS

« dengue-like » rash
SKIN MANIFESTATIONS: « new aspects »

Keratolysis

Dyshidrotic eczema like lesions

The French Task Force on Research on Chikungunya

Dr. Ph. Parola Lecture at ASTMH meeting 2009
SKIN MANIFESTATIONS: « new aspects »

Purpuric

Eythema nododum like

The French Task Force on Research on Chikungunya

Dr. Ph. Parola Lecture at ASTMH meeting 2009
SKIN MANIFESTATIONS: « new aspects »

Hyperpigmentation

Ulcerous

The French Task Force on Research on Chikungunya

Dr. Ph. Parola Lecture at ASTMH meeting 2009
SKIN MANIFESTATIONS: « new aspects »

- Petechial
- Vesicular and Bullous

The French Task Force on Research on Chikungunya

Dr. Ph. Parola Lecture at ASTMH meeting 2009
SKIN MANIFESTATIONS
Bullous Epidermolysis in Children

The French Task Force on Research on Chikungunya

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Hospital-based surveillance: 123 severe features respiratory failure, cardiovascular decompensation, meningoencephalitis, severe acute hepatitis, severe cutaneous effects, other central nervous system problem, kidney failure.

50% of severe cases: > 65 years of age. 1/3 Died!

Causal relationship between CHIKV and most complications?
- Underlying diseases and/or iatrogenic complications
- Direct role of CHIKV limited to rare acute central neurological or cardiac complications?

Miscellaneous ocular complications recently described in India: recovery is common
Acute myocarditis reported in adults and in children
• 2 – 4 % hospitalized
• Neonatal transmissions
• Severe diseases
• Fatal Cases
• Case-fatality rate (CFR) :
  • 1/1,000 population

SEVE FORMS IN REUNION ISLAND
CHIKV IN REUNION ISLAND: crude death rate

likely responsible for most of the excess deaths observed during the first 4 months of 2006

A total of 2,944 excess deaths occurred during the chikungunya epidemic when compared with the average number of deaths in the same months during the previous 4 years.
Higher risk

for abortion in the first trimester
for mother-to-child transmission in the last trimester

Epidemic peak in Reunion Island: attack rate 8.3% of pregnant women.

50% of the mothers with ongoing CHIKV infection in the setting of delivery transmitted the disease to their offspring

Mother-to-child CHIKV virus transmission:
+++ in the context of intrapartum maternal viremia often lead to severe neonatal infection.

Cesarean section: no protective effect on transmission.

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NEONATAL INFECTIONS

Associated with

- Fever
- poor feeding / Pain / distal edema
- Various skin manifestations.

Severe illness observed:
- mainly encephalopathy
- pathologic MRI findings (brain swelling; cerebral hemorrhages)
- possible evolution towards persistent disabilities.

Multidisciplinary Prospective Study of Mother-to-Child Chikungunya Virus Infections on the Island of La Réunion

Patrick Gérardin, Georges Barau, Alain Michault, Marc Bintner, Hanitra Randrianainavo, Ghassan Choker, Yann Lenglet, Yasmina Touret, Anne Bouvier, Philippe Grivard, Karin Le Roux, Séverine Blanc, Isabelle Schuffenecker, Thérèse Coudert, Fernando Arezana-Seisdedos, Marc Lecuit, Pierre-Yves Robillard
LESSONS FROM IMPORTED CASES
Chikungunya Infection

An Emerging Rheumatism Among Travelers Returned From Indian Ocean Islands. Report of 47 Cases

Fabrice Simon, MD, Philippe Parola, MD, PhD, Marc Grandadam, PhD, Sabrina Fourcade, MD, Manuela Oliver, MD, Philippe Brouqui, MD, PhD, Pierre Hance, MD, Philippe Kraemer, MD, Ali Mohamed, MD, Xavier de Lamballerie, MD, PhD, Rémi Charrel, MD, PhD, and Hugues Tolou, MD, PhD

Medicine

Volume 86, Number 3, May 2007
CHIKV INFECTION IN FRANCE

First cases hospitalized as early as 2005

Marseilles: +++
70,000 inhabitants originating from Comoros Islands
the « capital » or the « 5th Island » of the Comoros


Dr. Ph. Parola Lecture at ASTMH meeting 2009
Incidence of Chikungunya-infected returned travellers, Marseilles - France, 03-2005 to 04-2006

2005

2006

Period

Mauritius
Seychelles
Reunion Island
Comoros Archipelago

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ACUTE STAGE: THE RASH

Simon et al. Medicine, 86 (3), May 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
ACUTE STAGE: THE RASH

Simon et al. Medicine, 86 (3), May 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
ACUTE STAGE: THE RASH

common oedema of the face accompanying the rash

Simon et al. Medicine, 86 (3), May 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
ACUTE STAGE: ARTHRITIS (1)

Commonly involves more than 10 joint groups.

Can be edematous, asymmetrical, or atypical (Baker’s cyst)

Frequently associated with disabling acute tenosynovitis

Intense pain provoked by pressure on the anterior part of the wrists: highly evocative.

Unusual locations are possible, e.g., sterno-clavicular, temporomandibular, while hips are relatively spared.

Axial involvement is common at any level.

Often in association with periarticular inflammatory oedema

Simon et al. Medicine, 86 (3), May 2007
ACUTE STAGE: ARTHRITIS (3)

After a 4-day anti-inflammatory treatment

Simon et al. Medicine, 86 (3), May 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Chikungunya Virus–Induced Myopericarditis: Toward an Increase of Dilated Cardiomyopathy in Countries with Epidemics?

Fabrice Simon,* Philippe Paule, and Manuela Oliver

**Figure 1.** Horizontal long-axis cardiac magnetic resonance image of the patient 10 minutes after injection with gadolinium, showing subepicardial-delayed enhancement in the apical and apicolateral walls of the left ventricle and the lateral wall of the right ventricle (arrows).


Dr. Ph. Parola Lecture at ASTMH meeting 2009
Common early laboratory findings in both mild and severe cases:

- **Elevated enzymes**: LDH, lactate dehydrogenase, ASAT, ALAT, CPK, and gamma glutamyl transaminase GGT = 50%.
- **Mild thrombocytopenia** 50%.
- **Leucopenia** 75%.
SECOND PHASE OF CHIKV INFECTION

Not constant

Seems affected by age and underlying diseases
rheumatic or traumatic +++

Early exacerbation

Relapses

Long-lasting rheumatism

Simon et al. Medicine, 86 (3), May 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
SECOND PHASE OF CHIKV INFECTION

Temporary increase of
handicap
joint pain and stiffness
+/- dysesthesia in the extremities

Transitory peripheral vascular disorders, such as Raynaud syndrome

Chronic hypertrophic tenosynovitides +++
+/- nerve tunnel syndromes in wrists or ankles

Dr. Ph. Parola Lecture at ASTMH meeting 2009
CHIKV-induced chronic rheumatism

Several clinical components +/- associated
• exacerbation of pain on movement in previously injured joints and bones
• finger and toe polyarthritis with morning pain and stiffness

Handicap in handling objects during daily life can be major, leading to prolonged sick leave

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Severe subacute tenosynovitis/bursitis on hands, wrists and ankles

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Tenosynovitis and Vascular Disorders Associated with Chikungunya Virus–Related Rheumatism

To the Editor—

Philippe Parola,¹ Fabrice Simon,² and Manuela Oliver²
intense focus of tracer uptake particularly on the left side in the left metacarpo-phalangeal, wrist and the first distal interphalangeal joints

Persisting Mixed Cryoglobulinemia in Chikungunya Infection

Manuela Oliver¹, Marc Grandadam², Catherine Marimoutou³, Christophe Rogier³, Elisabeth Botelho-Nevers⁴, Hugues Tolou², Jean-Luc Moalic¹, Philippe Kraemer⁴, Marc Morillon⁵, Jean-Jacques Morand⁶, Pierre Jeandel³, Philippe Parola⁷, Fabrice Simon⁵*

¹ Laboratoire de Biochimie, Hôpital d'Instruction des Armées Laveran, Marseille, France, ² Unité de Virologie Tropicale, Institut de Médecine Tropicale du Service de Santé des Armées, Marseille, France, ³ Comité Recherche, HIA Laveran, Marseille, France, ⁴ Service de Pathologie Infectieuse et Tropicale, Hôpital d'Instruction des Armées Laveran, Marseille, France, ⁵ Laboratoire de Biologie, HIA Laveran, Marseille, France, ⁶ Service de Dermatologie, HIA Laveran, Marseille, France, ⁷ Service des Maladies Infectieuses et Tropicales, Centre Hospitalo-Universitaire Nord, Assistance Publique Hôpitaux de Marseille, Marseille, France
TREATMENTS

• Analgesics
• Local and/or systemic NSAIDs
• Physiotherapy
• Short-term systemic corticotherapy
• Chloroquine phosphate?

Infectious Disorders - Drug Targets 2009

Antiviral Treatment of Chikungunya Virus Infection

X. de Lamballerie* and R. N. Charrel

Unité des Virus Emergents, UMR190 IRD / Université de la Méditerranée / Assistance Publique-Hôpitaux de Marseille, Faculté de Médecine, 27 Bd. J. Moulin, 13005 Marseille, France

Dr. Ph. Parola Lecture at ASTMH meeting 2009
FOLLOW-UP IN IMPORTED CASES

For most patients who complained of persistent incapacitating pain:
• severe discomfort in daily life lasting weeks to months
• particularly while walking and using the hands
• 3 reported depression

Among patients who have been followed up to 1, 3, and 6 months after disease onset,

88%, 86%, and 48% were symptomatic respectively.

Simon et al, Medicine, 2006
Rheumatic symptoms lasted for at least 15 months in 57% of 147 participants.

- 63% reported permanent trouble
- 37% had recurrent symptoms.

Factors such as age >45 years, severe initial joint pain, and presence of underlying osteoarthritis comorbidity were associated with nonrecovery over the 15-month period.
Robinson in 1955, about CHIKV infection:

“absence of adenopathy, the frequent dissociation of the rash and the secondary rise of the temperature, the lack of post-orbital pain, or pain on moving the eyes, and the long continuance of chronic joint pains”.

Here, more keys to differentiate:

- “two-phased” disease evolution
- multiple peripheral tenosynovitis
- typical pain on pressure to the wrists
- delayed onset of Raynaud syndrome

Simon et al. Medicine, 86 (3), May 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
The Risk of CHIKV Globalisation

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Indian Ocean islands: popular tourist destinations.

WTO, 2004:
719,000 tourists arrived in Mauritius,
430,000 in Reunion Island
229,000 in Madagascar
121,000 in the Seychelles in 2004.

European tourists +++

During the past months several CHIKV-infected visitors returned home to countries.

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Chikungunya Infection
An Emerging Rheumatism Among Travelers Returned From Indian Ocean Islands. Report of 47 Cases

Fabrice Simon, MD, Philippe Parola, MD, PhD, Marc Grandadam, PhD, Sabrina Fourcade, MD, Manuela Oliver, MD, Philippe Brouqui, MD, PhD, Pierre Hance, MD, Philippe Kraemer, MD, Ali Mohamed, MD, Xavier de Lamballerie, MD, PhD, Rémi Charrel, MD, PhD, and Hugues Tolou, MD, PhD

Imported cases of chikungunya by month of onset, Pitié-Salpêtrière Hospital, France 2005-2006

Hochedez et al.
Emerg Infect Dis. 2006;12:1565-7
Eurosurveillance 2007, 12: 1
Chikungunya Fever, Hong Kong

To the Editor: Vol. 12, No. 11, November 2006

Chikungunya Virus Infection in Traveler to Australia

To the Editor: Vol. 13, No. 3, March 2007

Two Imported Chikungunya Cases, Taiwan

To the Editor: Vol. 14, No. 8, August 2008

Dr. Ph. Parola Lecture at ASTMH meeting 2009
the Asian tiger mosquito: the implicated vector in Indian Ocean. Originally indigenous to South-east Asia, the Western Pacific and Indian Ocean, but has recently spread to Africa, the Middle-East, Europe and the Americas, mainly because of transportation of dormant eggs in tyres.
Remember imported cases including viremic patients!

Introduction (dates)

Theoric possibilities
- Highest risk
- Moderate risk
- Less risk

Risk map: Knudsen et al., 1996, maj F Schaffner

Dr. Ph. Parola Lecture at ASTMH meeting 2009
WHAT IS THE RISK OF GLOBALISATION?

Would ecological conditions in southern Europe and north America support the development of a productive and persistent viral cycle in local vectors, during the period of activity of *Ae. Albopictus*??

Capability of *Ae. albopictus* to transmit vertically and thus to transfer CHIKV to the next generation (and the next season) ??

- If viremic patients arrive in places during the summer, when *Aedes albopictus* is prevalent and active, they might serve as a source of an outbreak

« If viremic patients arrive in Italy, France, or elsewhere in southern Europe during the summer, however, they could cause a European outbreak » Parola et al. Emerg Infect Dis October 2006

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Figure 1. Weekly density of *Aedes albopictus* in Rome. Percentage of positive traps out of 650 traps (bars, left axis), and mean number of eggs by positive traps (black line, right axis).
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Reason for travel</th>
<th>Country of origin</th>
<th>Date of return (length of stay, d)</th>
<th>Date of first medical assessment after return (delay, d)</th>
<th>Last date of fever (length of fever, d)</th>
<th>Fever on date of return?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>M</td>
<td>32</td>
<td>Business</td>
<td>Réunion</td>
<td>Feb 23 (93)</td>
<td>Feb 25 (2)</td>
<td>Feb 26 (4)</td>
<td>Yes</td>
</tr>
<tr>
<td>2†</td>
<td>F</td>
<td>39</td>
<td>Tourism</td>
<td>Mauritius</td>
<td>Feb 28 (10)</td>
<td>Feb 28 (0)</td>
<td>Feb 28 (4)</td>
<td>Yes</td>
</tr>
<tr>
<td>3‡</td>
<td>M</td>
<td>46</td>
<td>Tourism</td>
<td>Mauritius</td>
<td>Mar 7 (10)</td>
<td>Mar 7 (0)</td>
<td>Mar 6 (5)</td>
<td>No</td>
</tr>
<tr>
<td>4‡</td>
<td>M</td>
<td>32</td>
<td>Tourism</td>
<td>Madagascar</td>
<td>Mar 7 (15)</td>
<td>Mar 8 (1)</td>
<td>Mar 4 (4)</td>
<td>No</td>
</tr>
<tr>
<td>5§</td>
<td>M</td>
<td>49</td>
<td>Tourism</td>
<td>Mauritius</td>
<td>Mar 08 (16)</td>
<td>Mar 15 (7)</td>
<td>Mar 4 (5)</td>
<td>No</td>
</tr>
<tr>
<td>6‡</td>
<td>M</td>
<td>66</td>
<td>Tourism</td>
<td>Madagascar</td>
<td>Mar 24 (15)</td>
<td>Mar 24 (0)</td>
<td>Mar 27 (5)</td>
<td>Yes</td>
</tr>
<tr>
<td>7§</td>
<td>M</td>
<td>36</td>
<td>Tourism</td>
<td>Mauritius</td>
<td>Apr 4 (15)</td>
<td>Apr 5 (1)</td>
<td>Apr 1 (6)</td>
<td>No</td>
</tr>
<tr>
<td>8*</td>
<td>F</td>
<td>43</td>
<td>Resident</td>
<td>Madagascar</td>
<td>Apr 10 (−)</td>
<td>Apr 11 (1)</td>
<td>Mar 2 (6)</td>
<td>No</td>
</tr>
<tr>
<td>9†</td>
<td>F</td>
<td>46</td>
<td>Tourism</td>
<td>Réunion</td>
<td>Jan 30 (16)</td>
<td>Apr 13 (73)</td>
<td>NA (2)</td>
<td>–</td>
</tr>
<tr>
<td>10†</td>
<td>F</td>
<td>44</td>
<td>Visit relatives</td>
<td>Mauritius</td>
<td>Apr 17 (33)</td>
<td>Apr 19 (2)</td>
<td>Apr 7 (12)</td>
<td>No</td>
</tr>
<tr>
<td>11†</td>
<td>F</td>
<td>36</td>
<td>Tourism</td>
<td>Mauritius</td>
<td>Apr 30 (11)</td>
<td>May 3 (3)</td>
<td>May 3 (3)</td>
<td>Yes</td>
</tr>
<tr>
<td>12‡</td>
<td>M</td>
<td>31</td>
<td>Tourism</td>
<td>Réunion</td>
<td>Apr 21 (30)</td>
<td>May 4 (13)</td>
<td>Apr 5 (6)</td>
<td>No</td>
</tr>
<tr>
<td>13‡</td>
<td>M</td>
<td>44</td>
<td>Visit relatives</td>
<td>Cameroon</td>
<td>May 3 (24)</td>
<td>May 22 (19)</td>
<td>May 7 (6)</td>
<td>Yes</td>
</tr>
<tr>
<td>14*</td>
<td>M</td>
<td>35</td>
<td>Tourism</td>
<td>Seychelles</td>
<td>May 31 (9)</td>
<td>Jun 1 (1)</td>
<td>Jun 1 (2)</td>
<td>Yes</td>
</tr>
<tr>
<td>15*</td>
<td>M</td>
<td>38</td>
<td>Tourism</td>
<td>Mauritius</td>
<td>May 10 (11)</td>
<td>Jun 12 (2)</td>
<td>May 7 (4)</td>
<td>No</td>
</tr>
<tr>
<td>16‡</td>
<td>F</td>
<td>58</td>
<td>Missionary work</td>
<td>Central African Republic</td>
<td>Jun 24 (14 y)</td>
<td>Jul 10 (16)</td>
<td>Apr 26 (12)</td>
<td>No</td>
</tr>
<tr>
<td>17*</td>
<td>F</td>
<td>57</td>
<td>Business</td>
<td>India</td>
<td>Sep 8 (31)</td>
<td>Sep 9 (1)</td>
<td>Sep 10 (4)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*GISPI (Gruppo di Interesse e Studio delle Patologie di Importazione) centers: Torno.
†GISPI center: Udine.
‡GISPI center: Negar. NA, not available.
§GISPI center: Brescia.
¶GISPI center: Triggiano.
Infection with chikungunya virus in Italy: an outbreak in a temperate region

Lancet 2007; 370: 1840–46

G Rezza*, L Nicoletti*, R Angelini, R Romi, A C Finarelli, M Panning, P Cordioli, C Fortuna, S Boros, F Magurano, G Silvi, P Angelini, M Dottori, M G Ciufolini, G C Majori, A Cassone, for the CHIKV study group†

August 2007:
local health authorities of the province of Ravenna, Italy: unusually high number of cases of febrile illness in Castiglione di Cervia and Castiglione di Ravenna, two small villages divided by a river.

Serological testing + PCR in patients: Chikungunya fever.

CHIKV detected by PCR in local Aedes albopictus
Table 1: Demographic characteristics of the 205 individuals infected with CHIKV

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–19</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>20–39</td>
<td>26 (13%)</td>
</tr>
<tr>
<td>40–59</td>
<td>62 (30%)</td>
</tr>
<tr>
<td>60–70</td>
<td>78 (38%)</td>
</tr>
<tr>
<td>≥80</td>
<td>27 (13%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>99 (48%)</td>
</tr>
<tr>
<td>Female</td>
<td>106 (52%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presumed place of infection</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castiglione di Cervia or Castiglione di Ravenna</td>
<td>171 (83%)</td>
</tr>
<tr>
<td>Cervia</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>21 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification of cases</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory confirmed</td>
<td>175 (85%)</td>
</tr>
<tr>
<td>Clinically defined (untested)</td>
<td>40 (15%)</td>
</tr>
</tbody>
</table>

Index case

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Figure 3: Phylogenetic analysis of the partial nucleotide sequence (1011 nucleotides) of the E1 gene of CHIKV strains identified in Italy and in different parts of the world.
Who’s next ??

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Short note

Chikungunya: A risk for Mediterranean countries?

Marie Vazeille\textsuperscript{a}, Charles Jeannin\textsuperscript{b}, Estelle Martin\textsuperscript{a}, Francis Schaffner\textsuperscript{b,1}, Anna-Bella Failloux\textsuperscript{a,*}
Aedes albopictus colonization progress
in Alpes-Maritimes
(metropolitan french department)

Oviposition traps results
- Positive (at least one time)
- Negative

Supposed colonized area
- 2004
- 2005
- 2008
- 2007

Dr. Ph. Parola Lecture at ASTMH meeting 2009
Table 1
Infection rates towards chikungunya virus of mosquito populations collected in southern France in October 2006

<table>
<thead>
<tr>
<th>Species</th>
<th>Site of collection</th>
<th>% Infection (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aedes albopictus</td>
<td>Alpes maritimes</td>
<td>77.1 (35)</td>
</tr>
<tr>
<td>Aedes caspius</td>
<td>Sainte-Marie de la Mer</td>
<td>25 (16)</td>
</tr>
<tr>
<td>Aedes detritus</td>
<td>Sainte-Marie de la Mer</td>
<td>67.3 (49)</td>
</tr>
<tr>
<td>Aedes vexans</td>
<td>Sainte-Marie de la Mer</td>
<td>0 (13)</td>
</tr>
<tr>
<td>Culex pipiens</td>
<td>Montpellier</td>
<td>0 (11)</td>
</tr>
</tbody>
</table>

N, number of females tested.
A French Air France Hostess returning from a 2-day stay in Singapore (2 Mar 2009 evening to 4 Mar 2009 evening) PCR +
The USA ??
Chikungunya Virus in US Travelers Returning from India, 2006

Robert S. Lanciotti,* Olga L. Kosoy,* Janeen J. Laven,* Amanda J. Panella,* Jason O. Velez,* Amy J. Lambert,* and Grant L. Campbell*

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 5, May 2007
Update: Chikungunya Fever Diagnosed Among International Travelers
United States

37 imported cases of CHIK fever in 2006 were unprecedented in the United States

From India: 86%

Morb Mortal Wkly Rep March 30, 2007 / 56(12);276-277
Susceptibility of Florida Mosquitoes to Infection with Chikungunya Virus

Michael H. Reiskind, Kendra Pesko, Catherine J. Westbrook, and Christopher N. Mores*

Florida Medical Entomology Laboratory, University of Florida, Vero Beach, Florida

Abstract. Chikungunya virus (CHIKV) has caused recent, large epidemics on islands in the Indian Ocean, raising the possibility of more widespread CHIKV epidemics. Historically, CHIKV has been vectored by Aedes aegypti, but these outbreaks likely also involved Ae. albopictus. To examine the potential for an outbreak of CHIKV in Florida, we determined the susceptibility to CHIKV of F1 Ae. aegypti and Ae. albopictus from Florida. In addition, we also evaluated two well-characterized laboratory strains (Rockefeller and Lake Charles) of these species. We determined infection and dissemination rates as well as total body titer of mosquitoes 7 days post-exposure (pe) (Ae. albopictus) and 3, 7, and 10 days pe (Ae. aegypti). All mosquito strains were susceptible to both infection and dissemination, with some variation between strains. Our results suggest Florida would be vulnerable to transmission of CHIKV in urban and rural areas where the two vector species occur.
Vector Competence of Australian Mosquitoes for Chikungunya Virus.

van den Hurk AF, Hall-Mendelin S, Pyke AT, Smith GA, Mackenzie JS.

1 Virology, Forensic and Scientific Services, Queensland Health, Coopers Plains, Queensland, Australia.

Abstract Chikungunya virus (CHIKV) is a globally emerging arbovirus responsible for unprecedented outbreaks in the western Indian Ocean, the Indian subcontinent and Italy. To assess the receptivity of Australia to CHIKV, we exposed 10 Australian mosquito species to a 2006 strain of CHIKV isolated from a viremic traveler from Mauritius. In susceptibility trials, the infectious dose required to infect 50% of the mosquitoes was 10(2.6) cell culture infectious dose (CCID(50))mosquito for Aedes procox, 10(1.7) CCID(50)mosquito for Aedes albopictus, 10(2.1) CCID(50)mosquito for Aedes vigilax, and 10(2.6) CCID(50)mosquito for Aedes aegypti and Aedes notoscriptus. When exposed to blood meals containing between 10(3.5) and 10(4.1) CCID(50)mosquito of CHIKV, infection rates in these five species, plus Coquillettidia linealis, were >81%. Subsequent transmission rates ranged between 20% for Aedes notoscriptus and 76% for Aedes vigilax. In contrast, Culex spp. were poor laboratory vectors, with infection and dissemination rates <20% and <12%, respectively. Although Australia has efficient laboratory vectors, the role a mosquito species plays in potential CHIKV transmission cycles will also depend on its geographical and temporal abundance, longevity, and association with humans.
ACKNOWLEDGMENTS

French Task Force on Research on Chikungunya


Clinicians and Virologists In Marseille

F. Simon, P. Brouqui, P. Minodier, M. Grandadam, M. Oliver, P. Hance, R. Charrel, H. Tolou

Clinicians and Friends In Reunion and Comoros

Dr. Ph. Parola Lecture at ASTMH meeting 2009