# Chikungunya in Children

*Nicole Ritz, MD, PhD,*† Markus Hufnagel, MD,‡ and Patrick Gérardin, MD, PhD§¶*

Chikungunya is an arthropod-borne viral disease caused by the chikungunya virus (CHIKV).[1] First described during an outbreak in southern Tanzania in 1952, the virus derives its name from the Makonde language and means "to become contorted" or "that which bends up." These descriptors refer to the hallmark of the disease in adults—namely, severe incapacitating arthralgia, which leads to an inability to stand or walk. CHIKV is a positive-sense, single-stranded RNA virus (genus *Alphavirus*, family Togaviridae) that is transmitted to humans by *Aedes* mosquito bites. In recent years, anthropophilic *Aedes aegypti* and *Aedes albopictus* have been identified as the main vectors. Originally native to Southeast Asia, *A. albopictus* (also called tiger mosquito) successfully has adapted to cooler climates and thereby propagated worldwide. Alongside the broadening geographic distribution of the vector, a genetic adaptation in the envelope glycoprotein E1 (A226V substitution) has led to increased infectivity and accelerated dissemination of CHIKV in *A. albopictus*.[2] In addition, international travel exposures have contributed to the global expansion of chikungunya.

From the *Pediatric Infectious Diseases Unit, University Children's Hospital Basel, The University of Basel, Switzerland; †Department of Pediatrics, The Royal Children's Hospital Melbourne, The University of Melbourne, Parkville, Australia; ‡Section of Pediatric Infectious Diseases and Rheumatology, Center for Pediatrics and Adolescent Medicine, University Medical Center Freiburg, Germany; §Neonatal Intensive Care Unit/Pediatric Intensive Care Unit, CHU Réunion, Groupe Hospitalier Sud Réunion, Saint Pierre cedex, La Réunion, France; and ¶UMR PIMIT "Processus Infectieux en Milieu Insulaire Tropical "(Université de La Réunion, Inserm U 1187, CNRS 9192, IRD 249), CYROI, Sainte Clotilde, La Réunion, France.

The authors have no funding or conflicts of interest to disclose.

Address for correspondence: Nicole Ritz, MD, PhD, University Children's Hospital Basel, Spitalstrasse 33, CH-4031 Basel, Switzerland. E-mail: nicole.ritz@unibas.ch.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).



ISSN: 0891-3668/15/3407-0789
DOI: 10.1097/INF.0000000000000716

## EPIDEMIOLOGY

Although CHIKV epidemics may have occurred since the 18th century, retrospective case reviews suggest that they may have been misclassified as dengue outbreaks.[3] CHIKV likely originated in Africa, where the virus circulates in a sylvatic/enzootic cycle involving forest-dwelling mosquitoes (*Aedes furcifer/taylori*, *Aedes africanus* and *Aedes luteocephalus*) and non-human primates or bats as reservoir hosts.[1] In fact, phylogenetic analyses show that CHIKV derives from an ancestor that over the course of 500 years evolved into 2 distinct phylogroups: the West African and the East Central South African (ECSA) clades.[3] The latter genotype was introduced to Asia 70–90 years ago and resulted in the Asian clade.[4] These studies further demonstrated that West African and ECSA genotypes share a degree of geographic overlap, and that within the ECSA clade, the Indian Ocean lineage and the Indian subcontinent lineage have emerged independently.[4] Between the 1950s and the 2000s, CHIKV has caused numerous outbreaks, mainly in Africa, Asia and the Pacific regions.[1,3] Since its 2004 reemergence on the east coast of Africa (along with its subsequent spread to the neighboring islands of the Indian Ocean, India, Southeast Asia and Pacific), CHIKV has caused 2–3 million autochthonous cases and thousands of imported cases, worldwide. This figure includes at least 3 small outbreaks in Europe: 1 in northern Italy in 2007 and 2 in France in 2010 and 2014. In all 3 outbreaks, the index case was a traveler returning from India and/or Cameroon. Subsequent autochthonous transmission of CHIKV occurred by means of local *A. albopictus.* In December 2013, chikungunya was reported for the first time in the Americas, with initial cases appearing in Saint Martin, an island in the northeast Caribbean. One year later (ie, as of December 5, 2014), the Pan American Health Organization reported chikungunya in 49 countries or territories—including the Caribbean, Central, South and North American regions—with a total burden of 975,678 suspected and 18,892 laboratory-confirmed cases.[5] These outbreaks highlight the significant risk of a chikungunya pandemic and the possibility of endemicity being established in countries with temperate climates.

## PATHOGENESIS

Following the bite of an infected *Aedes* mosquito, CHIKV is injected into the dermis and locally targets connective tissue, epithelial cells and fibroblasts where viral replication takes place. In addition, during the viremic phase (≤5–7 days), circulating monocytes are responsible for dissemination into the bloodstream. Secondary infection sites include muscles and joints where fibroblasts are the main target cells. CHIKV may also be identified in the epithelial and

The ESPID Reports and Reviews of *Pediatric Infectious Diseases* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

endothelial cells of many organs particularly in the liver, spleen and brain. The acute phase of infection is characterized by a strong type I interferon response by infected fibroblasts and other cell types. This response is usually short-lived, being primarily limited to the viremic phase, and it can be more pronounced in infants. The type I interferon response seems to be prolonged in adults with chronic arthritis. Adaptive immunity against CHIKV is less well understood and only develops after the first week when viral replication has been limited by innate immunity. CHIKV-specific immunoglobulins protect against infection, but both B and T cells may contribute to pathogenesis and long-term joint disease.[6]

## CLINICAL MANIFESTATIONS

To date, few observational studies have detailed the clinical features of chikungunya in children. However, the ones that do highlight the fact that children may have a different clinical presentation than adults (Table 1). The magnitude of symptoms and their diversity seem to describe a U-shaped curve, with a maximum occurring in young infants and the elderly and a minimum in older children. Furthermore, the rate of asymptomatic infection among children varies according to different outbreak reports (range 35–40%).

### Fever

After an incubation period of 2–4 days (range 1–12 days), adults typically present with sudden-onset fever, severe arthralgia, headache, photophobia and skin rash.[1] Fever is typically high-grade in both children and adults. In children, febrile seizures frequently are described and commonly occur beyond the typical age range of 6 months to 6 years. Typically, these seizures last for 3–5 days, with a maximum of 10 days.[7,8]

### Skin and Hemorrhagic Manifestations

Skin lesions are reported in approximately 50% of adults.[1] In children, however, studies from India and La Réunion suggest that they are less common, particularly in those younger than 2 years of age.[7,8] The skin lesions most frequently reported are pigmentary changes in the centrofacial area, maculopapular rash and intertriginous aphthous-like ulcers (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C112). The rash usually is present for 5 days, with hyperpigmentation sometimes following the rash. Infants younger than 6 months of age may exhibit extensive bullous skin lesions with blistering covering up to 35% of the body surface area.[9] Hemorrhagic manifestations including epistaxis, gingival bleeding and purpura are also observed in approximately 10% of pediatric cases.

**TABLE 1.** Differences in Clinical Manifestations of Chikungunya in Children and Adults

| Feature | Children | Adults |
|---|---|---|
| Fever | Sudden onset, high-grade (> 38.9°C), duration 1–8 d | |
| Skin manifestations | • Maculopapular rash (33–60%)<br>• Pigmentary changes (42%)<br>• Bullous rash/skin blistering in 38–48% of infants <6 mo of age | • Maculopapular rash on trunk and limbs (35–50%)<br>• Pigmentary changes (rare)<br>• Bullous rash/skin blistering or photosensitivity (rare) |
| Mucocutaneous manifestations | • Oral ulcers (rare) | • Oral ulcers (16%) |
| Musculoskeletal manifestations | • Myalgia, arthralgia (30–50%) | • Arthritis/arthralgia, symmetric, more commonly affecting distal joints (87–99%)<br>• Tenosynovitis (common)<br>• Back pain (more common)<br>• Myalgia (60–93%) |
| Chronic joint manifestations | • Arthralgias/arthritis persistent for 2 years (5–11%) | • Arthralgias persistent or recurrent for 1 year in up to 57%<br>• Arthralgias/arthritis, persistent for 3–5 years (12%) |
| Hemorrhagic manifestations | • Purpura, ecchymoses (10%)<br>• Severe bleeding from nose, gums, gut, and shock (up to 19% in neonates) | • Purpura, ecchymoses (occasional)<br>• Severe bleeding from nose, gums, gut, and shock (rare) |
| Neurological manifestations | • Headache (15%)<br>• Seizures, acute encephalopathy, meningoencephalitis (14–32%) | • Headache (40–81%)<br>• Encephalopathy, meningoencephalitis, acute flaccid paralysis, Guillain–Barre syndrome (<0.1%) |
| Asymptomatic disease | • 35–40% (rare in neonates and infants) | • 16–27% |

### Musculoskeletal Manifestations

Myalgia, arthralgia and arthritis often are present in adults with chikungunya but typically less so in children (between 30% and 50% of affected children).[7] In adult patients, finger, wrist, ankle, elbow and knee joints are the most commonly affected sites.[1] Swelling without other signs of synovitis typically is reported with a symmetric, distal, polyarticular pattern. Permanent destruction of affected joints is rarely reported. Other rheumatic manifestations include tenosynovitis, tendinitis or bursitis at the acute and subacute stages (<day 90). It is now widely recognized that in adults arthralgia may persist for years.

### Neurological Manifestations

Central nervous system (CNS) involvement potentially is more significant than previously documented, especially in children. During the chikungunya outbreak in La Réunion, 25% of children developed neurological symptoms, whereas in India 14% of all children presenting with suspected CNS infection had chikungunya.[10,11] Among these, a high proportion (40–50%) had severe manifestations, including status epilepticus, complex seizures and encephalitis. The incidence of encephalitis was U-shaped, with a significant burden for those younger than 1 year of age, as well as those older than 45 years (Gérardin P et al, personal communication, January 15, 2015). In La Réunion, 2 of the 22 children (9%) with neurological manifestations died. Long-term neurological symptoms were reported in both children and adults in a La Réunion study that included more than 1000 individuals, 28% of whom were below 20 years of age.[12] Two years after acute infection, cerebral disorders (including attention and memory difficulties) were reported in approximately 75% of CHIKV-infected subjects and sensorineural disorders (including blurred vision and hearing difficulties) in nearly 50%. These findings clearly show that chikungunya in children is not always a benign or nonfatal infection. Rather, it may result in long-term sequelae.

### Perinatal Infection

Perinatal CHIKV infection first was described during the La Réunion outbreak in 2005.[13]

Although intrauterine transmission of CHIKV was absent or exceptionally rare in early pregnancy, it rose to nearly 50% when mothers were viremic in the week just preceding delivery.[13] Infected neonates developed symptoms around day 4 (range: 3–7) of life. Signs most commonly included fever, rash and edema. Other frequent observations were petechiae, thrombocytopenia and lymphopenia. Complications included intracerebral hemorrhages, status epilepticus and multiorgan failure, which led to mechanical ventilation in

one quarter of the neonates.[13] The long-term outcome of survivors was poor: half the children exhibited diminished neurocognitive performance at 2 years of age.[14]

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of febrile children with recent travel to, or residency in, tropical areas is broad. It should include malaria, dengue, typhoid fever, influenza, hepatitis, leptospirosis and rickettsial infection. In addition, in areas where these viruses are present, infection with West Nile virus and other viruses belonging to the group of Flavivirus, Togavirus, Bunyavirus and Reoviruses should be considered, particularly if there is CNS involvement. Among the diseases listed, dengue is the infection most capable of mimicking chikungunya. In this regard, clinical signs including arthralgia and rash cannot reliably be used to distinguish between dengue and chikungunya.[15] Overall, however, rash appears earlier in the course of chikungunya than it does with dengue. Furthermore, thrombocytopenia more frequently is seen in patients with dengue; however, up to 50% of children with chikungunya also have mild thrombocytopenia.[15]

## DIAGNOSIS

Chikungunya should be suspected when a child presents with high-grade fever of acute onset, rash and/or arthralgia and/or edema not otherwise explained by a different infectious cause. A chikungunya diagnosis becomes more likely if the child has visited or lived in an endemic/epidemic area. However, it is important to keep in mind that cases may appear in places where chikungunya is not endemic. For laboratory confirmation of chikungunya, virological and serological tests are necessary. During the first 5 days of infection, the virus can be found in the blood by reverse transcriptase polymerase chain reaction. In samples obtained later, enzyme-linked immunosorbent assays may confirm the presence of IgM and/or IgG anti-chikungunya antibodies. IgM antibodies appear between days 2 and 7 after onset of disease, whereas IgG antibodies frequently are detected after the first week of illness. The World Health Organization, therefore, recommends both serological and virological testing of samples collected during the first week after onset of symptoms. IgM antibodies peak at 3–5 weeks after onset of symptoms and then decline 2 months later but still may persist for years. IgG antibodies are believed to be detectable lifelong.

## TREATMENT

There is no specific treatment for chikungunya. Management, therefore, focuses on adequate hydration, antipyretics and analgesics. Some experts recommend withholding salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs), as these may precipitate bleeding manifestations.[7] Others recommend excluding dengue fever before prescribing NSAIDs. Although the symptoms of patients with persistent joint pain may be challenging to manage, NSAIDs together with corticosteroids or methotrexate successfully have been used in adults. Ribavirin also has been shown to improve chronic arthralgia/arthritis in some adult patients, but its benefit in acute pediatric infection remains unknown.[1]

## PREVENTION

### Vaccines

In 2000, a live-attenuated CHIKV vaccine was developed by the US army and used in a randomized, double-blind, placebo-controlled trial. Seroconversion rates were high (98%), but the vaccine temporally was associated with arthralgia in 8% of vaccines.[1] For these reasons, further assessment of the vaccine was discontinued. Currently, alternative strategies for the development of a safe and efficacious chikungunya vaccine continue to be investigated.[16]

### Eradication of the Vector

Preventive measures include reduction of breeding sites for *Aedes* spp., which primarily dwell in natural and artificial water-filled container habitats. During outbreaks, insecticides and space spraying also may be used.

### Personal Protection Against Mosquito Bites

As with malaria, appropriate clothing minimizes skin exposure. It is important to consider that *Aedes* mosquitoes bite during the day. Insect repellents containing *N*,*N*-diethyl-3-methylbenzamide, IR3535 (3-[*N*-acetyl-*N*-butyl]-aminopropionic acid ethyl ester) or icaridin (1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester) should be applied to exposed skin. In addition, insecticide-treated mosquito nets are vital for infants and children who sleep during the daytime.

## ACKNOWLEDGMENTS

*N.R. is supported by a grant from the Rozalia foundation. The authors thank Natalie Diffloth for her suggestions in proofreading the manuscript.*

## REFERENCES

1. Burt FJ, Rolph MS, Rulli NE, et al. Chikungunya: a re-emerging virus. *Lancet* 2012;379:662–671.
2. Tsetsarkin KA, Vanlandingham DL, McGee CE, et al. A single mutation in chikungunya virus affects vector specificity and epidemic potential. *PLoS Pathog*. 2007;3:e201.
3. Powers AM, Logue CH. Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. *J Gen Virol*. 2007;88:2363–2377.
4. Volk SM, Chen R, Tsetsarkin KA, et al. Genome-scale phylogenetic analyses of chikungunya virus reveal independent emergences of recent epidemics and various evolutionary rates. *J Virol*. 2010;84:6497–6504.
5. Pan American Health Organization. *Number of reported cases of chikungunya fever in the Americas, December 5, 2014*; 2014. Available at: http://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931. Accessed January 16, 2015.
6. Schwartz O, Albert ML. Biology and pathogenesis of chikungunya virus. *Nat Rev Microbiol*. 2010;8:491–500.
7. Sebastian MR, Lodha R, Kabra SK. Chikungunya infection in children. *Indian J Pediatr*. 2009;76:185–189.
8. Ernould S, Walters H, Alessandri JL, et al. [Chikungunya in paediatrics: epidemic of 2005–2006 in Saint-Denis, Reunion Island]. *Arch Pediatr*. 2008;15:253–262.
9. Robin S, Ramful D, Zettor J, et al. Severe bullous skin lesions associated with Chikungunya virus infection in small infants. *Eur J Pediatr*. 2010;169:67–72.
10. Robin S, Ramful D, Le Seach' F, et al. Neurologic manifestations of pediatric chikungunya infection. *J Child Neurol*. 2008;23:1028–1035.
11. Lewthwaite P, Vasanthapuram R, Osborne JC, et al. Chikungunya virus and central nervous system infections in children, India. *Emerg Infect Dis*. 2009;15:329–331.
12. Gérardin P, Fianu A, Malvy D, et al. Perceived morbidity and community burden after a Chikungunya outbreak: the TELECHIK survey, a population-based cohort study. *BMC Med*. 2011;9:5.
13. Ramful D, Carbonnier M, Pasquet M, et al. Mother-to-child transmission of Chikungunya virus infection. *Pediatr Infect Dis J*. 2007;26:811–815.
14. Gérardin P, Sampériz S, Ramful D, et al. Neurocognitive outcome of children exposed to perinatal mother-to-child Chikungunya virus infection: the CHIMERE cohort study on Reunion Island. *PLoS Negl Trop Dis*. 2014;8:e2996.
15. Laoprasopwattana K, Kaewjungwad L, Jarumanokul R, et al. Differential diagnosis of Chikungunya, dengue viral infection and other acute febrile illnesses in children. *Pediatr Infect Dis J*. 2012;31:459–463.
16. Chang LJ, Dowd KA, Mendoza FH, et al; VRC 311 Study Team. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. *Lancet* 2014;384:2046–2052.

**Supplementary Figure 1:** Typical skin manifestations of chikungunya: **A)** Intertriginous aphthous-like in a three-month-old infant and B) Bullous skin lesions in an eight-week-old infant.