Chapter 2

Chikungunya Fever During Pregnancy and in Children: An Overview on Clinical and Research Perspectives

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Additional information is available at the end of the chapter

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Abstract

Chikungunya fever (CF) is an arboviral disease in worldwide expansion due to the plasticity of its pathogen and vector. Chikungunya virus (CHIKV), a positive-sense, single-stranded RNA alphavirus, is transmitted by *Aedes* (*Stegomyia*) *aegypti* and *Aedes albopictus* mosquitoes, two hegemonic anthropophilic day-biting mosquitoes capable of colonizing very different environments. This expert review discusses the molecular epidemiology, pathophysiology, clinical features, diagnosis, management, and prevention of CF during pregnancy, infancy, and childhood. Specifically, it will focus not only on the issue and challenges of perinatal mother-to-child transmission of CHIKV, its pathogenesis, and effects on neurodevelopment, but also on CHIKV-associated central nervous system disease in children, two previously ill-characterized features of the infection.

Keywords: Chikungunya virus, children, encephalitis, epidemiology, pregnancy

1. Introduction

Chikungunya fever (CF) is an arthropod-borne viral disease caused by the chikungunya virus (CHIKV) [1]. First described during an outbreak of dengue-like illness in the Newala district of the southern province of Tanganiyika (current Tanzania) in 1952–1953, the virus derives its name from the Makonde language and means "to become contorted" or "that which bends up" [2, 3]. These descriptors refer to the hallmark of the disease observed in adults, namely, severe incapacitating arthralgia, which was characterized as "frightening" in the seminal description of Robinson [4], as they lead to an inability to stand or walk [5]. In the majority of adult patients with CF, painful arthritis can continue for months and even years, yielding a significant persistent disease burden in affected populations [6–9]. CF is usually not life-threatening, although atypical and severe forms can occur during large-scale epidemics and

a slight increase of mortality has accompanied the peak of the outbreak in La Réunion island [10–15]. Indeed, CHIKV-associated mortality is considered rare (~1‰ infections), but occurs primarily among the elderly, as evidenced in La Réunion, India, or in Puerto Rico [15–17].

Genome-scale phylogenetic analyses of CHIKV suggest that the virus originated from Africa and was subsequently introduced from Africa into Asia [18]. Phylogenetically, CHIKV has evolved into three distinct clades across the past five centuries: Asian, East Central South African (ECSA), and West African lineages.

In its natural cycle, CHIKV is transmitted by the bite of female arboreal *Aedes* (*Stegomyia*) mosquitoes. The peridomestic *Ae. aegypti*, the well-known vector of yellow fever and dengue, was identified as the primary vector of CHIKV during its inaugural outbreaks, both in Africa [2] and Asia [19]. It is only during the last decade that *Ae. albopticus* (also known as the Asian tiger mosquito) has been recognized as a new propagating vector of CHIKV [20]. Originally native to Southeast Asia, *Ae. albopticus* has adapted successfully to cooler climates and spread worldwide [21]. Alongside the broadening geographic distribution of this new hegemonic vector, genetic adaptation through mutations in the envelope glycoproteins E1 and E2 has led to increased infectivity and dissemination of CHIKV in *Ae. albopictus* [22]. Moreover, rapidly increasing international travel exposures has contributed to the global expansion of CF. Over the last decade, ECSA CHIKV has been responsible for most of the recorded cases worldwide; however, in late 2013 somewhat surprisingly Asian CHIKV emerged in the Caribbean island of Saint-Martin [23] and further spread to the neighboring islands and to the Americas, causing over 1.6 million cases by November 13, 2015 [24].

In addition to horizontal mosquito-borne transmission, CHIKV can also be transmitted vertically, and mother-to-child transmission of CHIKV infection often leads to severe neonatal disease, mostly encephalitis, that may cause lifelong disabilities [25]. This expert review will discuss the molecular epidemiology, pathophysiology, clinical features, diagnosis, management, and prevention of CF in the pregnant woman and in children, with a particular focus on the issue and challenges of congenital infection.

2. Molecular epidemiology

2.1. The chikungunya virus

CHIKV is a positive-sense, single-stranded RNA virus (genus Alphavirus, family Togaviridae), whose genome encodes at the 5′ extremity four nonstructural proteins (nsP_1, nsP_2, nsP_3, and nsP_4 responsible for negative-strand RNA synthesis, helicase and protease activity, RNA-dependent RNA polymerase activity, respectively) and at the 3′ extremity three envelope glycoproteins (E1, responsible for membrane fusion; E2, responsible for receptor binding and virulence (E1 and E2 carrying the main epitopes); E3, which serves as a clade-specific signal sequence for translocation of the glycoprotein complex in the endoplasmic reticulum) [26]. The native monomeric capsid is of ~40 nm diameter and the mature enveloped virion of ~70 nm, with a genome weighing ~11.8 kB. In recent years, the ECSA clade has selected the A226V substitution for better fitness to *Ae. albopictus* [27].

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2.2. Chikungunya virus life cycle and modes of transmission

CHIKV is endemic in Africa where it circulates in sylvatic/enzootic cycle between arboreal mosquitoes (*Ae. furcifer*, *Ae. taylori*, *Ae. africanus*, and *Ae. luteocephalus*) and nonhuman primates and bats as reservoir hosts. Birds and other mammals have been found infected, but serve as occasional hosts without amplification of the virus [28]. In this context, the transmission depends on few mosquitoes and is usually clustered to sporadic cases [29].

In epidemic settings, the virus is transmitted by *Ae. albopictus* or *Ae. aegypti*, two day-biting anthropophilic vectors whose peak activity occurs early in the morning or in the evening, around or within human dwellings [20]. During the blood meal, *Aedes* mosquitoes acquire the virus from an infected person. In the subsequent extrinsic phase, the virus multiplies in the gut and migrates to the salivary glands (≥2 days depending on temperature) [30]. Further blood meals then transmit the virus to other individuals bitten (~4–5 feeds are needed to complete a successful blood meal for oviposition). *Aedes* spp. mosquitoes remain infectious throughout their whole life (30–45 days). Transmission between nonimmune human hosts is often massive and both sustained by densities of host and vector populations, very high titer viremias in humans, as well as by lack of protective host behaviors [29].

3. Pathophysiology

The onset of CF coincides with viremia (median duration: 5 days; range: 2–12 days). The mechanisms underlying acute CHIKV infection are still imperfectly understood [1]. Based on several animal models and meta-analysis of human immune signatures, once introduced into the dermis, it is believed that CHIKV disseminates in blood circulation causing a Th1-cytokine storm [31, 32]. CHIKV replicates in the liver hosted by endothelial and Küpffer cells, before reaching joint fibroblasts, muscle satellite, and skin epithelial cells, causing arthralgia, myalgia, and rash. Indeed, elective targeted sites where symptoms focus are typically infected, especially joint capsules, skeletal muscles, myotendinous insertions, and epidermis [1].

The intensity of the acute infection correlates with the CHIKV viral load [1]. The ability of CHIKV to disseminate through the body to the target organs is inversely correlated to the height of the host type-1 interferon (IFN) response. There is evidence that this CHIKV-specific innate immune response depends on the age and the maturity of the human host [33]. This can be shown in vulnerable persons by the breaking of two natural protective barriers, the blood brain barrier (BBB) and the skin barrier. Thus, infants and individuals >65 years of age are likely to exhibit severe or atypical localizations, including CHIKV-associated central nervous system (CNS) disease and severe bullous skin lesions. For example, the incidence of CHIKV-associated encephalitis is best described by an asymmetric U-shaped parabolic curve with the highest incidence occurring in infants below 6 months of age, the nadir being reached in young children (1–4 years of age), and a rise in seniors (≥65 years of age) to a figure five-fold lower than in infants [34]. Furthermore, skin blistering (rupture of bullous lesions) is almost exclusively observed in infants below 6 months of age [35].

B cells and neutralizing antibodies (abs) are critical for CHIKV clearance. Targeted epitopes for anti-CHIKV abs are located at C terminus of the E2 glycoprotein [36]. The contribution of

lymphoid (CD_4 and CD_8) and other cell types responsible for the adaptive immunity could be critical in residual arthralgia. Their immaturity may explain the rarity of chronic arthralgia before the age of 3 years. The role of myeloid cells is less clear in the acute and chronic stage of human CHIKV infection. At the acute stage, blood monocytes may be able to disseminate the virus toward the target tissues [37]. At the chronic stage, myeloid cells may be involved in the clearance of infected cell debris but whether CHIKV replication, lack of virus antigen clearance, or both contribute to rheumatism deserves further studies.

The long-term persistence of CHIKV in tissue macrophages (aka "host sanctuaries") as main driver for chronic inflammation has been postulated from a single clinical observation [38]. It is supported by the data from several animal models (i.e., "for example, see [31]").

4. Clinical features

4.1. Chikungunya fever during pregnancy

Pregnancy, a situation physiologically oriented toward a Th2-lymhocyte shift [39], has not been associated as a condition precipitating severe forms of infection in CF [40].

The consequences for the mother and the fetus of a CHIKV infection acquired during pregnancy have been investigated extensively on La Réunion island, both in the Groupe Hospitalier Sud-Reunion cohort study [41, 42], in the CHIMERE ("Chikungunya Mère-Enfant") cohort study [43], and in the 2004–2006 Family Allowance Office (41,665 deliveries) and Mother and Child Welfare (42,259 neonates) records [44]. To date, there is no reliable epidemiological data linking CHIKV exposure in the first trimester of gestation to an increased risk for miscarriage, nor to any type of congenital malformation [43, 44].

In the second trimester, CHIKV infection has been associated with only three cases of antepartum fetal deaths without clear evidence for the mechanism [45]. The CHIKV crossing of the placenta may be accidental and the timing of the infections (12 weeks + 4 days, 15 weeks, and 15 weeks + 5 days) coincides in the woman with the period of deep trophoblast invasion. We hypothesize Toll-like receptor (TLR) 3 expression and Th1 cytokines associated with CHIKV infection could have disturbed the spiral arteries remodeling, characteristic of this particular period. Our hypothesis is supported by the involvement of TLR3 in both the susceptibility to CHIKV infection and the impairment of vascular remodeling or fetal losses, as demonstrated in mouse models [46, 47].

In the third trimester, although 14 cases of stillborn fetuses have been reported associated with CF in pregnant women cohorts [42, 43], none was positive for CHIKV, which supports the nonpermissiveness of the human syncytiotrophoblast to CHIKV, as suggested by data from the IFN-$\alpha/\beta R^{-/-}$ mouse model and the absence of infection of BeWo cell line [33]. These findings are strengthened by the data retrieved from French population-based records [44]. The contribution of subclinical premature placental abruption has been proposed to support the exceptional cases of prepartum CHIKV infection in preterm neonates [48].

Importantly, CHIKV can be transmitted vertically with a probability ~50%, when the parturient woman has a high viral load during the early stage of labor [41–43]. Fetal heart rate

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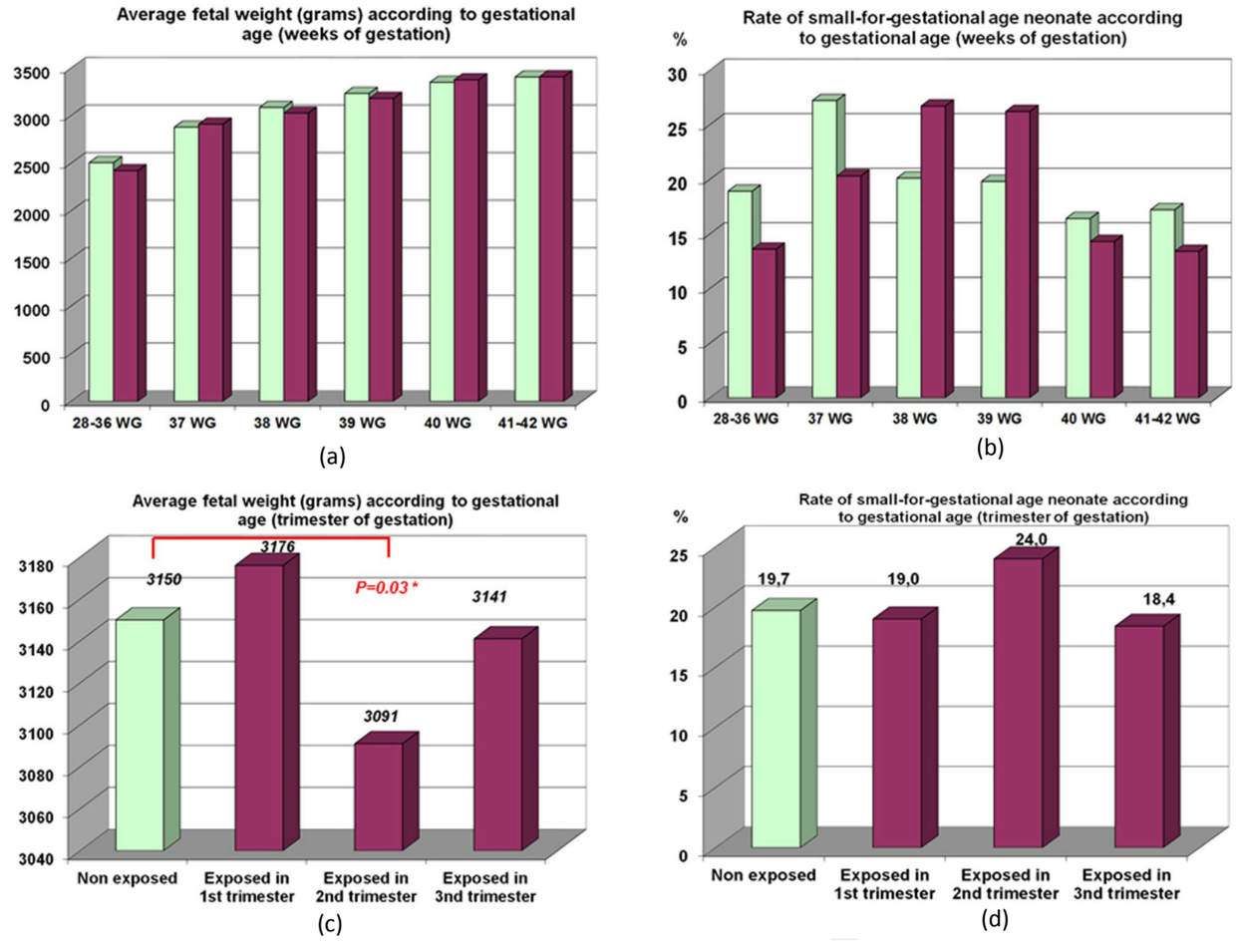
decelerations and meconium-stained amniotic fluid are common during labor [42, 49]. Neither postponing delivery nor cesarean has been shown to be protective. In this context, the alleged mechanism to explain the transmission to the neonate is the breakdown of the syncytiotrophoblast due to uterine contractions (aka the "placental breeches" hypothesis) [42] while placental microtransfusion has not been ruled out by a proper scientific investigation.

There is no increased risk to the pregnant mother for hypertensive disorders, gestational diabetes mellitus, or intrauterine growth restriction associated with maternal CF [43, 44, 50]. The relationships between average fetal birthweight, small-for-gestational age, and the timing of maternal CF during pregnancy are displayed in Figure 1.



Liveborn neonates were matched on birth gestational age and further compared according to the timing of maternal chikungunya fever during pregnancy. There was no statistical difference between exposed (purple) and unexposed (green) neonates in terms of small-for-gestational age incidence and the only observed difference was a non-clinically relevant lower mean birthweight in neonates exposed in the second trimester of pregnancy (*).

Figure 1. Average fetal birthweight, small-for-gestational age and the timing of maternal CF during pregnancy, Reunion island 2006 (i.e., "for details see [50].").

Contrary to dengue [51, 52], there is also no increased risk for obstetric hemorrhage (placental abruption), preterm birth or low birthweight [43, 44, 50].

4.2. Chikungunya fever in the neonate ("congenital chikungunya")

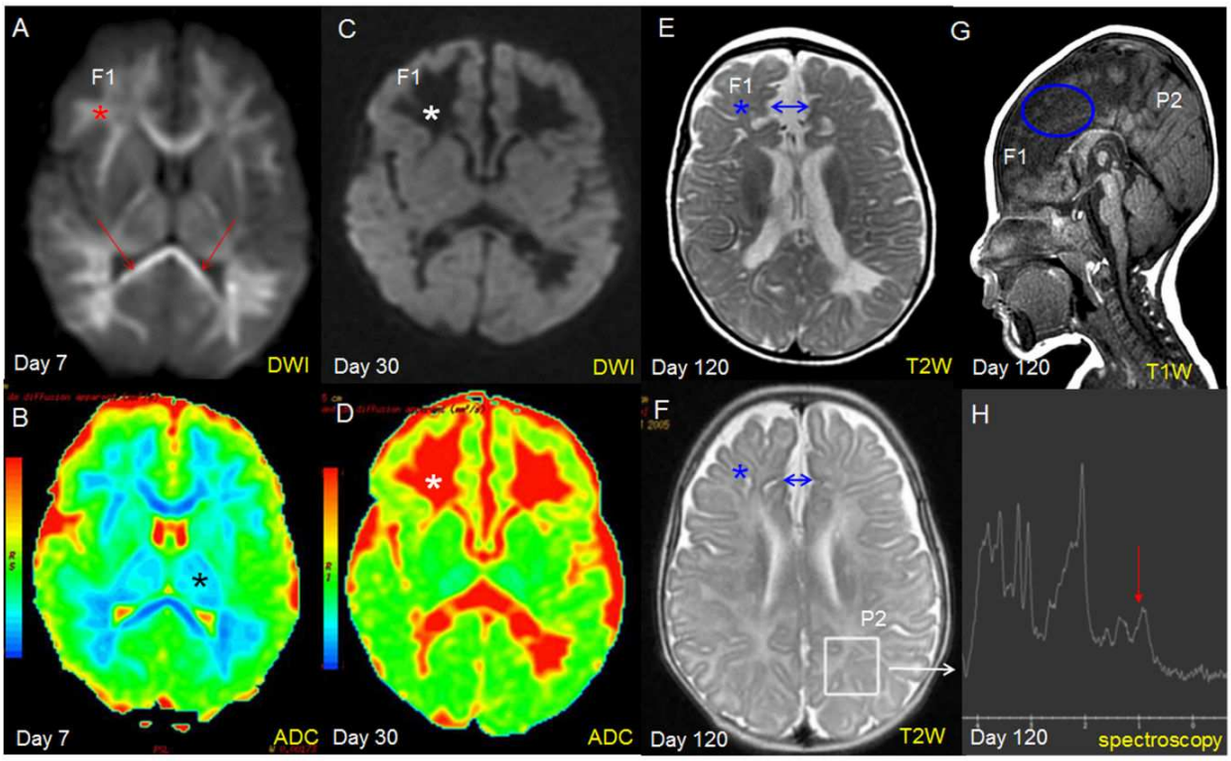
Perinatal mother-to-child CHIKV infection was first reported during La Réunion island outbreak in year 2005 [53]. It has been investigated extensively on the island using both a retrospective regional case series [54] and two prospective hospital-based cohort studies, one on a local basis, the GHSR child cohort study [42], and the other on a regional basis, the "CHIMERE child" cohort study [55, 56].

Children who are prenatally infected with CHIKV are born with very low or even undetectable viremia, which makes the hypothesis of placental microtransfusion unlikely as the expected neonatal viremia would parallel the one of the mother. On average, it takes 4–5 days (range: 3–7 days) for the viral load of CHIKV transmitted at birth to reach a level significant enough to cause clinical disease. Neonatal CHIKV infection almost invariably presents with fever, pain, and suckling difficulties often requiring enteral or parenteral nutrition [42]. Other common symptoms include limb edema, *petechiae*, and a skin rash such as maculopapular rash and intertriginous aphthous-like ulcers [25]. Further clinical features of neonatal CHIKV infection, although relatively infrequent in this age group, are cyanosis (slate coloration) and hyperpigmentation of the skin [35, 50, 55, 57–61]. Their topography includes centro-facial area (nose, lips), trunk, abdomen, extremities, and knuckles. Hyperpigmentation may persist for several weeks to months. Vesiculobullous skin lesions are exceptional [62]. Thrombocytopenia, lymphopenia, and mild to moderate increases of serum aspartate aminotransferase (AST or SGOT) are frequent observations [42, 54, 57–61].

Life-threatening complications occur in half of the neonates and display two main clinical pictures: CHIKV-associated CNS disease (formerly reported as encephalopathy) that in fact consists of an encephalitis [34] and a multiple organ dysfunction (MOD) syndrome that combines a circulatory collapse (hypovolemia and hyperkinetic profile on echocardiography), lethargy, hemorrhages (disseminated intravascular coagulation), uremia, and cytolysis [59]. These severe manifestations require intensive care support including mechanical ventilation (for airway protection or neurosedation) in a quarter of neonates, vasoactive amines, and platelet and red blood cell transfusions. Risk factors for severe disease are immaturity and low birthweight. Indicators for severity include a reduced core to skin temperature, low prothrombin rate, and low platelet count [42].

The most characteristic magnetic resonance imaging (MRI) findings of the early acute stage (day 7), subacute stage (day 30), and chronic stage (day 120) of CHIKV-associated encephalitis are presented in Figure 2.

Changes in the course of cerebral edema and the passage from the cytotoxic to the vasogenic phase occur around day 10 of onset of neurologic symptoms and may be monitored by transfontanellar ultrasonography using velocimetry for measuring the blood flow in the anterior cerebral artery trunks (pericallosal and calloso-marginal arteries). Other neuroradiologic features include scattered supratentorial parenchymal lesions such as basal ganglia and subcortical area bleeding, but also the possibility of cerebellar hematoma, as a reversible consequence of DIC syndrome [42, 55, 60].



At day 7 of life, diffusion-weighted imaging (DWI) reveals scattered hyper-intensity signals of the white matter (WM), as marked in the frontal lobe (red star) or in the posterior arm of the corpus callosum (red arrows) evocative of cytotoxic edema (A), apparent diffusion coefficient (ADC) reveals low-output areas (blue) of restriction evocative of parenchymal ischemia (B). At day 30, DWI reveals scattered hypo-intensity signals of the WM in the same areas evocative of vasogenic edema (C), ADC reveals high-output areas of reperfusion (red) evocative of blood brain barrier leakage (D). At day 120, T2-weighted (T2W) and T1-weighted imaging (T1-W1) reveal a scattered scalloped appearance of the WM (blue star), a dilatation of the interhemispheric sulcus (double blue arrow) indicative of WM mass reduction (E,F), focused in the frontal (blue oval) lobe (G), monovoxel spectroscopy reveals a lower N-acetyl aspartate peak signal (red arrow) in the left posterior parietal lobe (P2) evocative of axonal loss (H).

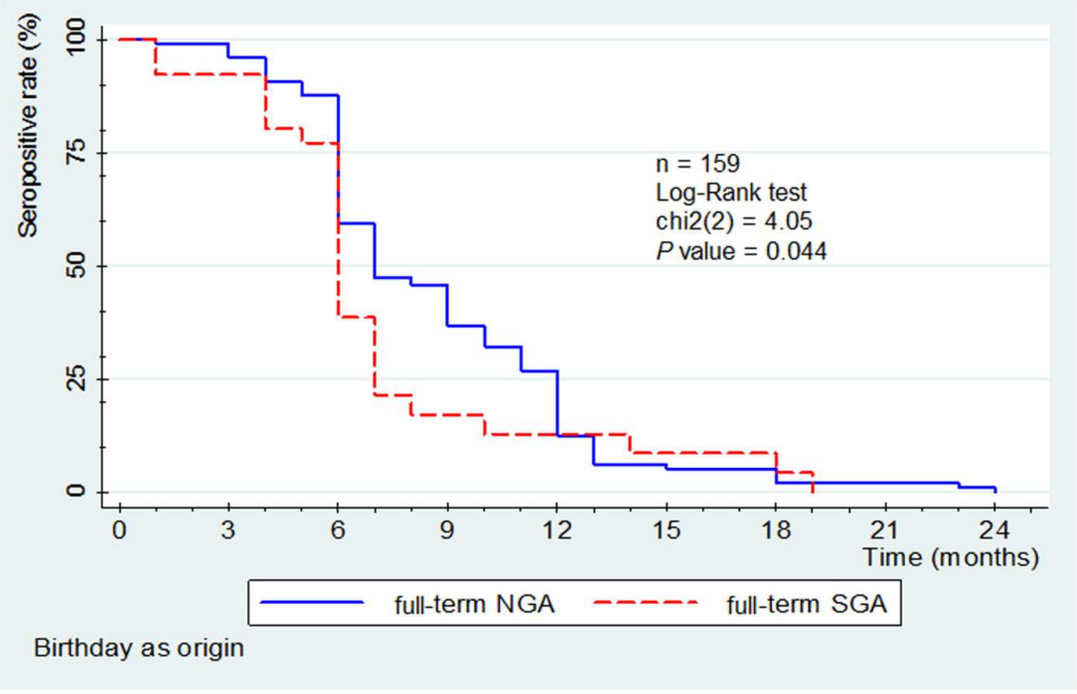
Figure 2. Typical course of cerebral edema over a 4-month period in a neonate with CHIKV-associated CNS disease previously defined as "severe encephalopathy" [42], reclassified as CHIKV-associated encephalitis [34], Reunion island, 2006.

Transient coronary arteries dilatation was reported for six neonates [55]. Cardiologic involvement in this context is evocative of myocardiopathy or myocarditis, it includes left ventricular hypertrophy (sometimes complicated by left ventricular dysfunction or septal dyskinesia) and pericardial effusion [55, 61].

To date, only few CHIKV-associated deaths in neonates have been reported [55, 61, 62]. For the neonates without neurological involvement, recovery was observed in 1–3 weeks without *sequelae*; however, future long-term studies will shed more light on the presence of subtle morbidities related to CF in these infants [63]. The neurodevelopmental outcome associated with perinatal mother-to-child CHIKV infection will be discussed in Section 4.5.

To investigate the potential for serological evidence of congenital infection in apparently healthy neonates born to women infected with CHIKV during pregnancy, we monitored the kinetics of transplacental CHIKV-specific IgG abs within the CHIMERE cohort study [55].

There was no evidence of asymptomatic congenital CHIKV infection as the 590 participating neonates were all negative for CHIKV-specific IgM at birth and the 368 children with CHIKV-specific IgG present at birth had undetectable levels of CHIKV-specific IgG by a mean of 7.7 months (range: 1–24 months). Seroreversion time (i.e., the time needed to clear transplacental IgG from infant blood or the duration until IgG is undetectable) was inversely correlated to the timing of exposure during pregnancy. Preterm-born infants seroversed earlier. Full-term small-for-gestational age seroreversed earlier than full-term normal-for-gestational age neonates (Figure 3).



These Kaplan-Meier curves illustrate the bodysize-dependent transfer of transplacental CHIKV-specific IgG antibodies: the seropositivity rate is lower in the first post-natal year and the seroreversion time is shorter in full-term small-for-gestational age neonates compared to full-term normal-for gestational-age counterparts.

Figure 3. Seroreversion time of transplacental CHIKV-specific IgG antibodies in full-term normal-for-gestational age (NGA) and full-term small-for-gestational age (SGA) infants, CHIMERE study, Reunion island 2008 (i.e., "for more details, see [55].").

These data corroborate a time-dependent and size-dependent placental transfer of maternal IgG: the longer the period of exposure to maternal IgG and the larger the placenta, the higher the load of the IgG transferred to the fetus, and the longer the seroreversion time and theoretically the child's individual protection. These issues may be helpful for maternal or postnatal immunization, should a vaccine become available.

4.3. Chikungunya fever in infants

To the best of our knowledge, only a few case series described the clinical manifestations of postnatally acquired CF in infants [64–71].

The largest pediatric series published to date, from Kerala, India, including 357 suspected and 35 confirmed cases, reported 140 infants of whom 57% had circulatory collapse and 80% febrile seizures [66]. In another series from Kerala including 56 infants with confirmed CHIKV infection, the main symptoms were fever (100%), skin rash (100%), acrocyanosis (75%), diarrhea (41%), atypical febrile seizures (39%), irritability (26%), lethargy/poor feeding (21%), and limb edema (11%) [67]. Note that the authors have dissected the sequence of skin involvement: abrupt onset of generalized erythematous rash (day 0 to 2 of fever), maculopapular rash (day 2 to 4), vesiculobullous lesions (day 3 to 6), peeling (day 6 to 10), and hypo- or hyperpigmentation (>day 10).

These data have been confirmed in La Réunion island where half of the infants below 6 months of age exhibited vesiculobullous skin lesions [68, 88]. Importantly, besides the susceptibility for neurological complications (six-fold higher incidence rate of encephalitis) [34], these vesiculobullous skin lesions have emerged as the most characteristic finding of CHIKV infection in this age group [25, 70, 72, 73]. Severe perianal involvement is a characteristic localization [67]. Blisters sometimes cover more than 30% of the body surface, and therefore management resembles that of severe burn patients [70]. Mucosal lesions have not been reported to date. Histopathologic examination of the blisters occurring in the course of CHIKV infection reveals intraepidermal cleavage (splitting beneath and within the stratum granulosum) with CHIKV-specific IgM deposits onto the basal layer or the dermal capillaries. On follow-up, long-term repigmentation is usually observed, sometimes with skin sequelae including discrete peripheral hyperpigmentation and keloid scars.

4.4. Chikungunya fever in children

As for children in the first year of life, fever is the main symptom in older children and is usually high grade (102/39–104/40 °F/°C) of sudden onset (<24 hours) and single-spiked [25, 64, 65, 74]. Febrile seizures are common but variably present in 14-80% of the cases. They also occur beyond the typical age range of 6 months to 6 years [25, 64, 69, 73, 74]. Other common symptoms accompanying fever include musculoskeletal pain (30–50%), skin rash (>30%), headache (15%), and photophobia (<10%) [25, 68, 74].

In contrast to adults, arthritis is uncommon in children [25, 74]: 9 of 22 (40%) children reported arthralgia and 6 of 22 (27%) reported arthritis during the Vellore epidemic, Tamil Nadu, India [64]. Residual arthralgia or arthritis is also far less frequent than reported in adults. In the TELECHIK population-based cohort study [75], they were reported in ~6% of children, two years after acute infection. Unfortunately, these data cannot be retrieved from observational studies or case series, either by lack of follow-up or inability to extract the pediatric data.

The most commonly reported skin manifestations were maculopapular exanthema (morbilliform or generalized) [35, 74, 76], pigmentary changes (diffuse or macular) [77], and intertriginous aphthous-like ulcers [75]. Itching is common. Vesiculobullous skin lesions are possible but rare beyond 1 year of age [77].

Hemorrhagic manifestations including epistaxis, gum, subconjunctival bleeding, and purpura are observed in ~10% of pediatric cases [25]. They are less severe than in children dengue fever.

CHIKV-associated sepsis is less common in toddlers (1–2 years) than in infants (<1 year) and exceptional in children (3–18 years) [64, 76, 78]. In infants, circulatory collapse should prompt cardiologic investigation, including echocardiography as cases of acute cardiac failure have been described during CF [79–81] and myocarditis demonstrated in a young adult [82].

Neurological symptoms have been notified in the acute phase of CF in 25–30% of hospitalized children on the island of La Réunion [25, 68, 69, 83] but were also observed in India [64–66, 74, 84–86]. Their burden will be described in the next section.

4.5. Chikungunya-virus-associated central nervous system (CNS) disease

CHIKV has long been suspected to be a neurovirulent pathogen [86]. Thus, the seminal publications of CHIKV-associated neuropathology came from India [64] and Cambodia [87].

Among the neurological manifestations complicating CHIKV infection, three distinct clinical patterns can be seen: (i) CHIKV-associated CNS disease, namely encephalopathy of chikungunya origin and CHIKV-associated encephalitis [34, 42]; (ii) CHIKV-associated peripheral nerve disease, including myeloradiculitis and polyradiculoneuritis, and (iii) a putative nonspecific neurobiologic disease (e.g., lethargy, irritability, altered mental status, mild cognitive disorders, fatigue, etc.) not entirely satisfying the two aforementioned conditions and presumably resulting from penetration of proinflammatory cytokines through the BBB. Although nonspecific neurological symptoms and CHIKV-associated CNS disease are deemed to be common in children, CHIKV-associated peripheral nerve disease (Guillain-Barré syndrome often referred as acute flaccid paralysis) seems exceptional [74, 87].

Indeed, hospital-based series have identified headaches, seizures, altered mental status such as confusion or delirium, and neck stiffness as common signs of CNS involvement [83, 84]. Status epilepticus, complex seizures, and encephalitis are being reported as the most serious complications of CNS involvement [25]. Importantly, while the overall burden of neurological manifestations seems to increase with age, the incidence of CHIKV-associated CNS disease peaks in children less than 5 years [34]. This is also highlighted by the fact that fatigue or mild neuropsychiatric symptoms (attention difficulties, sleep, memory, or mood disorders) were reported for 84% of school-age children participating to the TELECHIK cohort study, on average 2 years after acute infection [7].

We propose to represent the burden of neurological manifestations of CF in children using a pyramid (Figure 4), as done classically in public health for vector-borne zoonosis [88].

Little is known on the long-term outcome of CHIKV-associated CNS disease [34]. For example, the neurodevelopmental outcome of perinatal mother-to-child CHIKV infection in the CHIMERE cohort study revealed that 51% of infected neonates had a global neurodevelopmental delay (GND; Brunet-Lézine development quotient ≤ 85) at the age of 2 years [56]. The skill areas affected were coordination and language (57%), sociability (36%), and movement/

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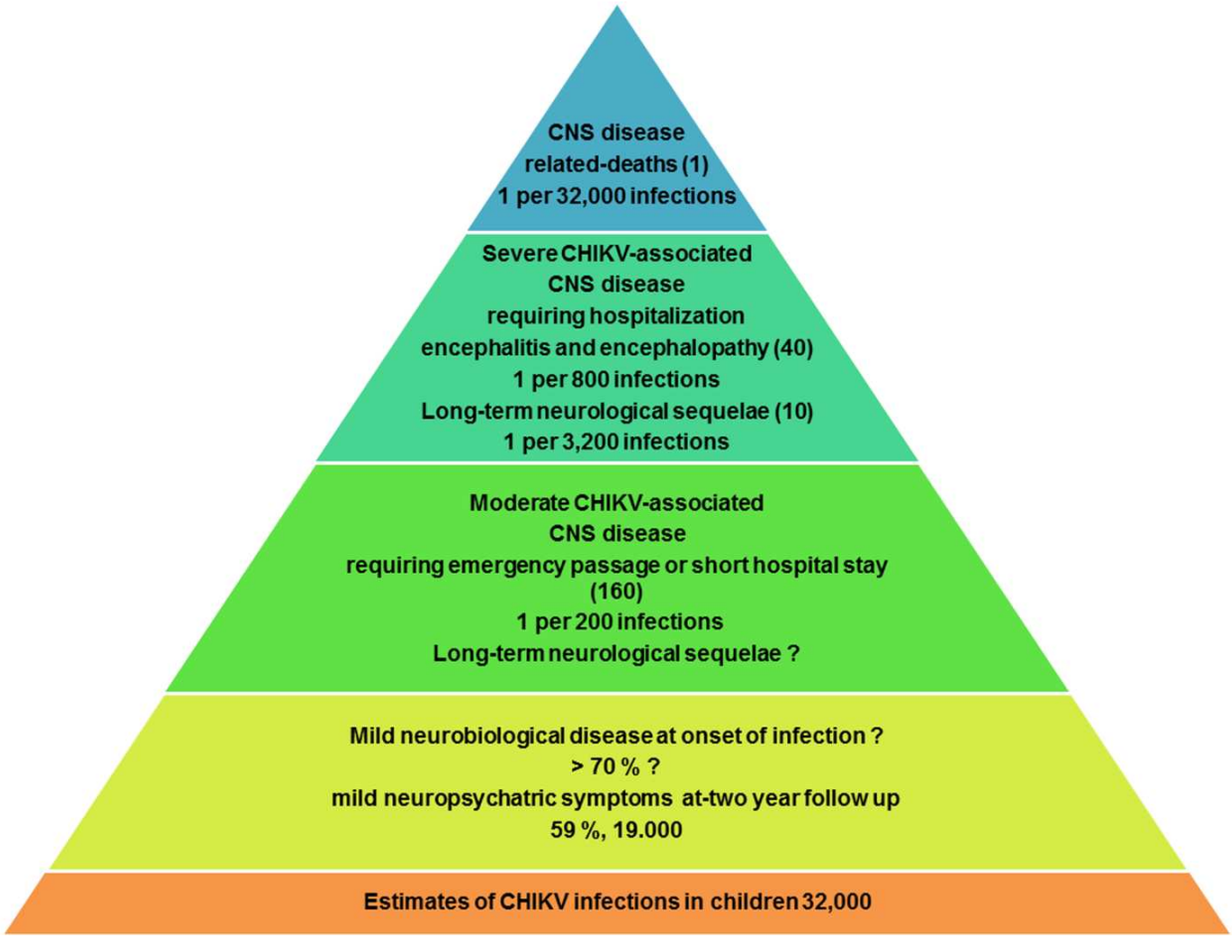

This pyramid presents the incidence data and proportions of clinical forms according to epidemiological standards for reporting the community burden of infectious diseases.

Figure 4. Burden of CHIKV-associated CNS disease in children, Southern Reunion island, 2009 (i.e., "source SEROCHIK, TELECHIK and ENCEPHALCHIK studies, see [11, 7, 34].").

posture (27%). Importantly, CHIKV infection was an independent predictor for GND after adjustment for maternal social status, infant's weight-for-gestational age, and head circumference, but also when controlling for preterm birth and breastfeeding. Five of the 12 neonates with CHIKV-associated "encephalopathy" developed a microcephaly of whom 4 matched the definition of cerebral palsy. Note that GND was observed in 38% of the CHIKV-perinatally infected neonates in which CNS disease was not previously suspected.

5. Diagnosis

5.1. Differential diagnosis

Even though viral diseases are a major public health concern, they are not given due recognition as a cause of fever in febrile children in resource limited settings [89]. The differential

diagnosis of a febrile child or pregnant woman with recent travel to or residency in tropical areas affected by CHIKV is broad and should include malaria, dengue, influenza, hepatitis, typhoid fever, leptospirosis, and rickettsial infections [25]. In addition, in areas, where these pathogens are present, infections with other alphaviruses, flaviviruses, filoviruses, and bunyaviruses should be considered. In infants, staphylococcal scalded skin syndrome [70] and Kawasaki syndrome [90] should additionally be considered and excluded as the two diagnoses require a specific treatment. Among those listed, dengue is the infection most capable of mimicking CF [25]. Clinical signs including fever pattern, arthralgia, and rash cannot reliably be used to distinguish dengue fever from CF [91]. However, rash appears earlier in the course of CF than it does in dengue fever, and dengue fever is more likely to be associated with bleeding. Pregnancy-induced hypertension, placental abruption, and preterm labor are more common in pregnant woman with dengue than with CF [51, 52].

5.2. Virological methods

After onset of CF, the viral load can rapidly reach up to 10^8 genome copies per ml of blood (even a maximum of 2.5×10^8 cps/ml in neonates) [1, 42]. During the first 5 days of infection, the CHIKV genome can be detected in the blood by reverse transcription polymerase chain reaction (RT-PCR). The virus may also be detected in the cerebrospinal fluid of children with CHIKV-associated CNS disease [25] and in blisters of infants with bullous skin lesions [62]. RT-PCR can be designed in multiplex assays to detect other arboviruses [92], which can be very useful for triage of patients [1]. Techniques have continuously improved over the years to allow diagnosis in 2 hours with a minimum cutoff for detecting circulating viremia as low as 40 genome copies/ml using a 5 ml blood sample in TaqMan real-time PCR [93].

5.3. Serological methods

CHIKV-specific IgM and IgG can be detected in serum by enzyme-like-immunosorbent assay (ELISA) immunocapture. CHIKV-specific IgM are detectable from 3 to 8 days after onset of infection (p.o.i.) and may persist for several months to up to 2 years. CHIKV-specific IgG are detectable from 4 to 10 days p.o.i. and may persist for years [1] and potentially lifelong. Although, improvement has diminished the possibility of cross-reactivity of IgG with other viruses of the Semliki antigenic serocomplex, it may still be useful to ensure a reliable diagnosis of CHIKV infection by using IgG seroconversion (increase by a factor ≥4). In areas where CHIKV and other closely related alphaviruses coexist, plaque reduction neutralization testing becomes a necessary adjunct to confirm CHIKV infection [94].

5.4. Diagnostic testing depends on timing of illness onset

The molecular assays (TaqMan real-time PCR, RT-LAMP assay, and reverse transcription PCR) are more sensitive in the early stage of CF (2–5 days p.o.i.) when CHIKV-specific IgM are not yet detectable. In the later stages of CF (>5 days p.o.i.), CHIKV-specific IgM is more sensitive than PCR. Experts recommend that ELISA IgM be used as an initial screening test

followed by one of the molecular assays in samples negative for IgM in the early stage of CF [95].

6. Therapeutic options

6.1. Pregnant women

There is no specific treatment for CF. CF in pregnant women should be treated with antipyretics and analgesics to prevent miscarriage, fetal demise, and limit the harmful consequences of fever, as well as this new competing risk for the neurodevelopmental outcome of preterm neonates.

6.2. Children

As in pregnant women, there is no specific treatment for CF. Management is symptomatic and focuses on adequate hydration, antipyretics, and analgesics (paracetamol/acetaminophen 60–80 mg/kg/day) [25]. Experts recommend withholding salicylates, steroidal, and nonsteroidal anti-inflammatory drugs (NSAIDs), as they may facilitate bleeding manifestations [73]. In La Réunion island, ibuprofen had been thought to precipitate infant blistering but the association was not statistically significant [96].

There are no antivirals that have been licensed to treat CF. Ribavirin and IFN-α have *in vitro* an antiviral activity against CHIKV [97], the first being able to alleviate chronic arthralgia and swelling [1]; however, neither one is recommended for use due to risk for side effects and nor the other has been tested in children. It is hoped that in the future, safe and effective antivirals will be able to offer specific CHIKV therapy.

Although persistent joint pain may be challenging to manage, NSAIDs together with corticosteroids or methotrexate successfully have been used in adults [25].

Passive immunotherapy has proven efficacious in the cure of CHIKV infections in animal models [98] and is currently being tested in neonates born to viremic mothers (i.e., "see ClinicalTrials.gov number NCT02230163") in French West Indies and French Guiana [1].

7. Prevention

7.1. Vaccination

By the end of year 2015, several promising vaccine candidates have reached late preclinical or phase-1 testing and two have been scheduled for phase-2 trials [99]. The licensure of vaccines will be challenging because of difficulties conducting affordable efficacy trials and predicting future markets [1].

7.2. Control of the vector

Preventive measures include community mobilization for eradication of breeding sites of Ae. mosquitoes [100], which primarily dwell in natural and artificial water-filled container habitats. During epidemics, peridomestic spraying of insecticides by residents and space spraying by vector controls teams are key for reducing adult mosquito populations.

7.3. Individual protection against mosquito bites

Appropriate clothing (long clothes for gardening and evening walks) may minimize skin exposure. Insect repellents containing DEET (N,N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester), or picaridin (1-piperidinecarboxylic acid and 2-(2-hydroxyethyl)-1-methylpropylester) are effective [101]. DEET is safe for use in pregnancy, though it is known to cross the placenta, and can be used in children of 3 months of age and older [102]. Its putative neurotoxicity remains controversial [103]. In addition, insecticide-treated nets are important for pregnant women, infants, and children who take daytime naps. Indeed, rest under treated nets for acute patients should be considered as a pillar of community protection and in the hospital setting during the period of viremia for at least 2 weeks. The effectiveness of both types of mechanical preventive measures has not been assessed.

8. Conclusions and perspectives

CF is a tropical arthropod-borne virus infection whose geographical distribution has grown steadily over the last decade as a result of global warming and globalization of transports. CHIKV can also be transmitted vertically from mother-to-child during the perinatal period when the parturient woman is highly viremic during labor. In the pediatric population, severe forms of CF may occur, and the CNS is particularly affected with encephalitis as the major syndrome of CHIKV-associated CNS disease. At pediatric ages, neonates and small infants below 6 months of age have the highest risk for case fatality and lifelong disabilities.

Several knowledge gaps remain for CF in both pregnant women and children including: (i) the effectiveness of postponing delivery and caesarian section; (ii) the genotype-specific virulence of CHIKV and its ability to cause perinatal mother-to-child infection, CNS infection, or other life-threatening complications; and (iii) are there possible interactions between CHIKV and other circulating arboviruses in Aedes mosquito vectors susceptible to explain the rise of arbovirus-related neurological disease? This question is critical both for CHIKV and Zika virus, a conqueror flavivirus which has supplanted CHIKV wherever it has tried to establish in recent years; (iv) the subtle long-term morbidities that CF may cause in children. The absence of autopsy data with reliable histopathological findings (immunochemistry staining) prevents understanding of the human CNS neuropathology.

Benchmarking of observational studies, meta-analysis of individual patient data, and well-designed clinical trials should be of paramount importance to address these knowledge gaps.

Future antivirals and vaccines may alleviate some of the disease burden, but for now vector control and human personal protection are the only means of CF prevention.

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