

Clinical Impact of Non-Congenital Zika Virus Infection in Infants and Children

Stefan H. F. Hagmann¹

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Abstract

Purpose of Review While the Zika virus (ZIKV) has been noted for its distinct neurotropism and identified as a significant cause for a congenital infection syndrome, there has been increased recognition of the importance to better understand the clinical impact of non-congenital ZIKV infection in infants and children. This article reviews reports of perinatal and breast milk transmission of ZIKV and summarizes current clinical outcome data of pediatric non-congenital ZIKV infection.

Recent Findings Perinatal transmission and presence of infective ZIKV particles in breast milk have been reported. Most symptomatic non-congenital ZIKV infection in infants and children is mild and self-limited, but long-term follow-up studies are lacking.

Summary The mechanism and impact of perinatal and breast milk transmission is unclear. The current WHO infant feeding guidelines in areas of ZIKV transmission support breastfeeding. Unless any scientific data raise concern regarding transmission via breastfeeding, the current guidelines should continue to be followed. Prospective population-based cohort studies to investigate maternal, perinatal, infant, and child outcomes are needed.

Keywords Zika · Children · Non-congenital · Perinatal · Breast milk · Complications

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✉ Stefan H. F. Hagmann
shagmann@northwell.edu

¹ Division of Pediatric Infectious Diseases, Steven and Alexandra Cohen Children's Medical Center, Northwell Health, 269-01 76th Avenue, New Hyde Park, NY 11040, USA

Introduction

Zika virus (ZIKV) infection, now well recognized among the expanding list of pathogens known to cause congenital malformations in the developing fetus, has spread to more than 70 countries and to many areas where competent vectors are present. The World Health Organization (WHO) continues to call for high vigilance and pediatric health care providers may wonder whether Zika virus, just as the human immunodeficiency virus (HIV) in the 1990s, will lead to another paradigm shift in the pediatric health care landscape [1, 2].

ZIKV represents a previously obscure flavivirus with close relationship to Japanese encephalitis, West Nile, dengue, and yellow fever viruses, all of which are primarily transmitted by mosquitoes. ZIKV was originally discovered in Uganda in 1947 and has continued to expand its geographic range ever since, from equatorial Africa and Asia to the Pacific Islands, then further afield to South and Central America and the Caribbean.

It was primarily the unexpected increased incidence of microcephaly and other neurologic malformations in fetuses and newborns born to mothers infected with ZIKV during pregnancy in Brazil that led the WHO to declare the ZIKV epidemic a Public Health Emergency of International Concern [3]. Anatomic brain abnormalities in infants with congenital ZIKV infection have been described in detail and may include microcephaly, hydrocephaly/hydranencephaly, absent structures (e.g., corpus callosum), neuronal migration disorders, severe cortical thinning, cerebral calcifications, and brain asymmetry [4•]. In its maximal form, the severe anatomic abnormalities including severe microcephaly, partial collapse of the skull with overlapping sutures, occipital bone prominence, a small or absent anterior fontanel, and scalp rugae have been found to fulfill the criteria of a previously reported fetal brain disruption sequence [5, 6]. Because some of those

features are rarely seen with other congenital infections and seem specific to congenital ZIKV infection, the congenital Zika syndrome as a distinct clinical phenotype has been postulated [7].

The clinical manifestations and complications observed in newborns affected by congenital ZIKV infection are extensive and have been associated not only with many central nervous system, ocular, auditory, and motor and limb abnormalities but also possibly with distinct digestive and respiratory dysfunctions [4•, 8]. The full clinical spectrum will only become apparent through prospective long-term follow-up investigations of affected pregnant women and their infants regardless of symptoms at birth, as is currently being pursued by the National Institutes of Health-funded Zika in Infants and Pregnancy cohort study [9].

ZIKV's notable neurotropism and apparent capabilities to pass through the blood-brain barrier raises concerns that infants and young children infected with ZIKV perinatally or postnatally may also be at risk for neurodegenerative disease or developmental delay [2]. Compared to infants exposed to ZIKV in utero, there have probably been a multitude of infants and children exposed to ZIKV by a non-congenital route. However, only a few reports have been published on the clinical course and long-term outcomes of non-congenital ZIKV infection in children [10•]. This review will therefore focus on what is known about perinatal transmission routes and in particular, transmission through breastfeeding as well as the clinical impact of non-congenitally acquired ZIKV infection in infants and children.

Demonstration of Zika Virus in Breast Milk

ZIKV is primarily transmitted by mosquitos of the *Aedes* genus, especially *Aedes aegypti* [11]. However, with an increasing numbers of cases resulting from non-mosquito-borne transmission being reported, investigators have also attempted to better understand routes of nonvector transmission including potential breastfeeding-related transmission [12, 13•]. This seems to be especially important given the existing evidence, although limited, of perinatal and breast milk transmission of several arboviral infections including dengue virus (DENV) [14–18], chikungunya virus (CHIKV) [19, 20], West Nile virus (WNV) [21–23], and yellow fever virus (YFV) [24, 25].

A total of 5 studies have so far studied the presence and viability of ZIKV in breast milk of 9 women who had developed symptomatic ZIKV infection around the time of delivery or during the newborn's 1st year of life while breastfeeding (Table 1) [26•, 27–29, 30•]. Overall, in six of nine women examined (67%), ZIKV was identified in their breast milk by RT-PCR, and in four (44%), viable ZIKV could be demonstrated in cell culture suggesting infectivity (Table 1).

Altogether, those studies suggest that women who have had a ZIKV infection shortly before onset of lactation or while lactating may be very likely excreting ZIKV in their breast milk that retains viability and hence could serve as a source for mother-to-infant transmission.

Perinatal and Breastfeeding-Related Transmission of Zika Virus

The first two documented cases of perinatal transmission were reported in the context of the ZIKV outbreak in French Polynesia in 2013/2014 (Table 1: case #1 and #2). ZIKV infection was confirmed in two newborns by blood RT-PCR on day 3 and on day 4 of life, respectively. Only one became symptomatic and developed a rash, leukopenia, thrombocytopenia, and prolonged subclinical hepatitis (minor aminotransferase elevation, 2–3 times upper limit of normal, resolved by age 4 months). Their mothers had developed symptomatic ZIKV infection 2 days before and 3 days after delivery, respectively [26•]. The authors suspected that the infants' transmission most likely occurred by transplacental route or during delivery. As the breast milk was positive for ZIKV by RT-PCR breast milk transmission was considered but deemed less likely as the virus was not found replicative in the breast milk samples. Both infants were reexamined at age 32 and 30 months, respectively, and assessment with the Child Development Assessment Scale (CDAS) did not indicate any developmental neurocognitive problems [31•, 32]. However, the authors caution that the exclusion of late-onset cognitive or sensory deficits will require longer follow-up.

A third case of perinatal transmission was suspected in a newborn delivered from a mother who became symptomatic with ZIKV infection on the day of delivery (Table 1: case #3). The infant's blood RT-PCR result was described as “ambiguous” and absence of clinical symptoms was reported. According to a personal communication of the lead author recorded in a subsequent publication reviewing this case, no long-term complications were noted at 8 months of age [13•]. Potential breast milk transmission was considered as the inoculation of the breast milk samples onto Vero cells showed the presence of infective viral particles [27].

The most compelling evidence for potential breast milk transmission of ZIKV infection was reported in a 5-month-old infant who was exclusively breastfed when the mother developed a symptomatic ZIKV infection (Table 1: case #9). Breast milk samples revealed replicative ZIKV; whole genome sequencing and subsequent full genome comparison of the two ZIKV strains isolated from the breast milk and the infant's blood indicated >99% identity between the two strains [30•].

As ZIKV infection is frequently asymptomatic, ZIKV infection of newborns and infants during the perinatal period or

Table 1 Evaluation of ZIKV in breastfeeding mother-infant pairs

Author	Case #	Timing of transmission	Country of report	Age of mother (years)	Mother—clinical presentation and timing of symptom onset	Mother—ZIKV test results	Breast milk—ZIKV test results	Breastfeeding activity	Infant—ZIKV test results	Infant—clinical presentation and timing of symptom onset
Besnard M et al. [26 ^a]	1	December 2013	French Polynesia	Early 30s	Pruritic rash, started 2 days before delivery and lasted for 4 days	Blood and saliva RT-PCR (+) on day 2 of infant's life	RT-PCR (+), cell culture (-) on day 3 of infant's life	Started on day of delivery	Blood and saliva RT-PCR (+) on day 3 of life	Asymptomatic
	2	February 2014	French Polynesia	Early 40s	Pruritic rash, fever and myalgia, started 3 days after delivery	Blood RT-PCR (+) on day 1 of infant's life	RT-PCR (+), cell culture (-) on day 8 of infant's life	Started on day of delivery	Blood RT-PCR (-) at birth/day 3 of life, and (+) on day 4 of life	Rash, leukopenia, thrombocytopenia, and subclinical hepatitis ^a Asymptomatic
Dupont-Rouzeyrol et al. [27]	3	July 2015	New Caledonia	27	Fever and subsequent rash started on day of delivery	Blood RT-PCR (+) on day 3 of infant's life	RT-PCR (+), cell culture (+) on day 4 of infant's life	Started on day of delivery	Blood RT-PCR indeterminate	Asymptomatic
Cavalcanti MG et al. [28]	4	NA	Brazil	33	Fever, malaise, rash (appeared on day 2 of illness) when infant aged 11 months	Blood and urine RT-PCR (+) on day 4 of illness	RT-PCR (+), cell culture (+) on day 4 of illness	Breastfeeding held for 7 days when rash appeared	Urine RT-PCR (-)	Asymptomatic
	5	NA	Brazil	42	Fever, retro-ocular pain, conjunctival injection, rash, arthralgia when infant aged 2–3 months	Blood RT-PCR (-), Urine RT-PCR (+)	RT-PCR (-)	Breastfeeding throughout maternal illness	Not tested	Asymptomatic
	6	NA	Brazil	28	Fever, conjunctival injection, rash, arthralgia when infant aged 10–11 months	Blood and urine RT-PCR (+)	RT-PCR (-)	Breastfeeding throughout maternal illness	Blood RT-PCR (-)	^b
	7	NA	Brazil	33	Rash, arthralgia when pregnant (28 weeks)	Blood and urine RT-PCR (+), urine PCR remained (+) for 30 days	RT-PCR (-)	Breastfed for 4 months after birth ^c	Blood and urine RT-PCR (-), IgM anti-ZIKV (-)	Asymptomatic, no evidence of congenital disease
Sotelo JR et al. [29]	8	February 2016	Brazil	28	Fever, myalgia, arthralgia when pregnant (36 weeks), 2 weeks before delivery	Blood RT-PCR (+)	RT-PCR (+), cell culture (+) on day 9 of infant's life	Breastfeeding avoided	Placental tissue, amniotic fluid, umbilical cord blood, and urine RT-PCR (-)	Asymptomatic
Blohm GM, et al. [30••]	9	March 2016	Venezuela	?	Illness ^d when infant aged 5 months	Blood and urine RT-PCR (+)	RT-PCR (+), cell culture (+), full genome sequencing showed >99% identity with maternal strain	Exclusively breastfed	Blood and urine RT-PCR (+) (samples obtained 3 days after mother developed illness)	Asymptomatic

NA not available

^a Leukopenia 4.6×10^9 cells/L, thrombocytopenia: nadir 65×10^9 /ml on day 4 of life, alanine aminotransferase: maximum level 150 U/L at 2 months of age

^b Child had an illness with fever and rash [Chikungunya RT-PCR (+)], timing in relation to the maternal illness not specified in the publication

^c Publication did not specify when baby in relation of maternal illness was born

^d Symptoms of maternal illness not specified in publication

early infancy is probably frequently missed and hence underreported. There is still a significant amount of uncertainty about the mode of transmission that may occur at this crucial time. The understanding of the placental and blood-brain barrier at the end of gestation is incomplete as studies have shown conflicting results. While it was shown that primary human trophoblast cells of full-term placentae are resistant to infection with historic ZIKV strains (ZIKV strains from Uganda and Cambodia), a contemporary ZIKV strain from Puerto Rico was able to infect human placental macrophages and mature primary human trophoblast cells [33, 34]. With respect to potential breast milk transmission, research questions regarding the dynamics of ZIKV viral load in the breast milk, exposure duration, and a better understanding of how often breast milk transmission may happen in affected populations in ZIKV-endemic regions remain unanswered [13, 35]. The current WHO infant feeding guidelines in areas of ZIKV transmission support breastfeeding. Unless any scientific data raise concern regarding transmission via breastfeeding, the current guidelines should continue to be followed [36].

Clinical Characteristics of ZIKV Infection in Children Acquired Postnatally

Wherever incidence rates for ZIKV infection was studied during the more recent outbreaks, higher attack rates were noted for females compared to males and older age compared to

younger age [37–39]. Reasons for this observation are not clear and may be related to health care seeking behavior and testing preferences. Overall, it has been estimated previously that about 80% of ZIKV infections are asymptomatic [37, 40]. However, a more recent ZIKV seroprevalence study from French Polynesia estimated the proportion of asymptomatic infections to be 53% overall and only 29% for school children aged 6–16 years [41]. Descriptions of the spectrum of clinical characteristics of ZIKV infection specific to pediatric patients are still limited. For one, published reports of recent large outbreaks (e.g., in Yap and Colombia) summarized the clinical characteristics for children and adults combined only as aggregate information, thus precluding the opportunity to assess for differences in the clinical presentation and course of illness according to age [37, 38]. Moreover, in the report from Yap, young children <3 years were even excluded from the household survey component of the study that was meant to determine the extent of the outbreak and identify risk factors [37].

Karwowski et al. [42] summarized ten pediatric cases reported in six publications between 1954 and 2016 from Nigeria, Indonesia, Cambodia, The Philippines, New Caledonia, and Colombia [43–48]. The median age of the reported pediatric cases was 13.5 years, and only one child was a toddler (aged 3 years) (Table 2). While all had fever, arthralgia and conjunctivitis were reported in three and two children, respectively, and none reported a rash. Of note, gastrointestinal symptoms (i.e., abdominal pain, anorexia, nausea, vomiting, constipation, or diarrhea) were described for seven of the reported pediatric cases. One child had a

Table 2 Clinical characteristics of pediatric Zika virus infections

Author	Number of cases	Median age (range), years	Female gender, <i>N</i> (%)	Symptoms, <i>N</i> (%)				Neurological complications	Hospitalized
				Fever	Rash	Conjunctivitis	Arthralgia		
Karwowski MP et al. ^a	10	13.5 (3–16)	4 (40)	10 (100)	0 (0)	2 (20)	3 (30)	ID	ID
Goodman AB, et al. ^{b,c}	158	14 (0.1–17)	88 (56)	87 (55)	129 (82)	45 (29)	44 (28)	0 (0)	2 (1) ^d
Li J, et al. ^e	14	11 (0.5–16)	7 (50)	9 (64)	14 (100) ^f	4 (29)	2 (14) ^g	0 (0)	14 (100) ^h

ID incomplete data, see text

^a This report describes a total of 10 pediatric cases reported in 6 publications [39–44]. Other reported symptoms include malaise (*N* = 5), headache (*N* = 5), dizziness (*N* = 3), myalgia (*N* = 4), and sore throat (*N* = 2)

^b All cases were reported from the continental US, and they were travel-associated. Children living in Puerto Rico and other US territories were excluded

^c 70% had ≥ 2 of the four signs and symptoms, and 54% had fever and rash, 33% had \geq three of the primary signs and symptoms. Other reported symptoms include headache, myalgia, vomiting, diarrhea, retro-orbital pain, chills, and throat

^d One child (aged 4 years) required inpatient care for 3 days because of fever, cough, and poor oral intake, and another child (aged 1 year) was hospitalized for 1 day

^e ZIKV infections were locally acquired

^f At presentation only 50% had rash; the maximum duration of rash among patients with ZIKV infection only (*N* = 13) was 4 days. Other relevant symptoms reported included headache and myalgia reported by three patients, respectively

^g One of two had a coinfection with dengue

^h All had been admitted only because of temporary quarantine mandate in Singapore between 27 August and 5 September 2016

concurrent malaria infection, and one a concurrent DENV infection. No particular complications were noted in the context of those coinfections. However, another case was reported to have an episode of hypotension, and another case an episode of hematuria. Complete recovery was mentioned for four, while the course of a 15-year-old girl with sickle cell disease was complicated by ARDS, hemothorax, and splenic sequestration. ZIKV infection was confirmed by RT-PCR, while test results for DENV, CHIKV, YFY, and malaria were negative. She required intensive care and subsequently died. For five cases, no comment was made about outcome.

The largest population-based case series comes from the USA including a total of 158 confirmed or probable travel-associated pediatric cases (<18 years) that were reported to ArboNET, CDC's national arboviral disease surveillance system, until September 9, 2016 [10••]. Children living in Puerto Rico and other US territories were not included in this analysis. Most cases were reported from the state of Florida, New York, and California. The median age was 14 years, 142 (90%) were of school age (aged ≥ 5 years), 16 (10%) were 0–4 years old, and 5 teenagers (aged 16–17) were pregnant. Fever and rash were the predominant symptoms and signs, two children (aged 1 and 4 years) required hospitalization, and there was no mortality nor reported neurologic complications (Table 2). It was noted that there were no differences among age groups in the proportion of the clinical features observed. The authors acknowledge that the inclusion of only symptomatic cases in this report may be one of several limitations. Other limitations include a bias towards testing females of childbearing age, a lack of rigorous reporting system (the only optional reporting of symptoms is to ArboNET), and the lack of systematically collected clinical follow-up data [10••].

The most recently published case series of ZIKV infection in children comes from Singapore [49•]. It is the first pediatric case series of ZIKV infections from Southeast Asia. A temporary containment phase (27 August to 5 September 2017) led to the identification of 14 pediatric cases of locally acquired ZIKV infection that had been admitted to KK Women's and Children's Hospital, which at the time was the designated ZIKV quarantine hospital. With a median age of 11 years, most ($N = 9$) affected children in this series were of school age, followed by two preschool children (3.9 and 4.1 years old), two toddlers (1.3 and 2.2 years old), and only one infant (6 months old). Most children presented with fever and rash and half had concurrent cough or runny nose on presentation (Table 2). Of those with complete blood count testing on presentation ($N = 12$), a third had evidence of leukopenia with neutropenia ($N = 2$) or lymphopenia ($N = 4$), while all had normal platelet counts. One case of a 15-year-old boy with a DENV coinfection stood out as he had on day 3 of illness a single episode of hypotension that responded to intravenous hydration and developed thrombocytopenia with a nadir of $74 \times 10^9/L$. This case illustrates what has been shown

in vitro that DENV immunity may be associated with antibody-dependent enhancement of infection with ZIKV [50]. All children in this series recovered without any complications, and none died, required higher level of care or developed neurologic complications, although there was no long-term follow-up information available [49•].

In regard to neurologic complications, cases of ZIKV-associated Guillain-Barré syndrome and meningoencephalitis have apparently been reported occasionally among children during the outbreak in Brazil [10••], although no pediatric cases were reported from the recently reported seven countries case series [51]. In addition to the above described fatal case of a 15-year-old girl from Colombia, investigators have reported one other death in a 16-year-old girl from Brazil [10••]. She was hospitalized with headache, nausea, and petechial rash. ZIKV infection was confirmed by RT-PCR. More detailed information including DENV, CHIKV, and YFV test results were not available. No other deaths or complicated disease courses were reported in children that were studied in the context of the outbreaks on Yap Island or French Polynesia [37, 38].

Conclusions

There has been rapid progress into our understanding of the ZIKV's neurotropism and its effect on the fetal brain in utero since the beginning of the outbreak in the Americas. Most children with non-congenital ZIKV infection are asymptomatic or are affected by a generally mild and self-limited illness. However, there is lack of pediatric data describing the full clinical spectrum including effects on child development as a result of the congenital ZIKV infection. Also, lacking are descriptions of ZIKV infection in infants and children acquired by a non-congenital route. Two cases of perinatal ZIKV infection have been described in the literature with no evidence of neurocognitive deficits after approximately 30 months of follow-up. Recognition of the presence of infective ZIKV in breast milk raises concern about potential breast milk transmission of ZIKV in endemic areas. Nevertheless, only one likely case of breast milk transmission has been reported, based on the isolation of an identical ZIKV strain in a nursing mother and her infant. Better understanding is needed regarding the pathomechanisms and incidence of transmission related to breast milk in ZIKV-endemic regions. The current WHO infant feeding guidelines in areas of ZIKV transmission support breastfeeding. Unless any scientific data raise concern regarding transmission via breastfeeding, the current guidelines should continue to be followed. Prospective population-based cohort studies to investigate maternal, perinatal, infant, and child outcomes are urgently needed, as results of such research may likely influence future pediatric practice.

Compliance with Ethical Standards

Conflict of Interest Dr. Hagmann declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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