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Chikungunya Infection in Hospitalized Febrile Infants Younger Than 3 Months of Age

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Background: Fever in infants younger than 3 months is generally a cause for concern because of the risk for a serious bacterial infection. The aim of this study was to describe clinical and biological features of Chikungunya infection in infants < 3 months of age hospitalized in Cayenne Hospital during the 2014-2015 outbreak.

Methods: We performed a preliminary retrospective study followed by a prospective study from March 2014 to February 2015. All infants younger than 3 months presenting with fever and hospitalized in Cayenne Hospital were included. The main diagnostic criteria were fever and positive Chikungunya PCR.

Results: One hundred and twenty infants were hospitalized with fever. The mean age was 46 days (SD± 22 days). The mean hospitalization duration was 7.4 days (SD± 6.1 days). Chikungunya infection was diagnosed in 26 children. The most important clinical findings were high (80.8% [77.5-84]) and prolonged fever (76.9%, [73.4-80.4]), irritability (96.2% [94.5-97.7]) and skin rash. (69.2%, [65.4-73]). Half of the infants presented edema of the extremities (hands and feet principally). However, in 15 %, Chikungunya infection was associated with a serious bacterial infection. Infants who presented with irritability, high fever and elevated PCT were at high risk for Chikungunya: OR 39, [9.2-243] ($p < 0.001$), with a specificity of 96.7 % and a negative predictive value of 89.4%. The area of the ROC curve was 0.96.

Conclusions: Our results confirm that Chikunguyna infection is a cause of high fever in infants younger than 3 months. Our data should be confirmed by larger studies.

Key words: Chikungunya virus, clinical triad fever-irritability-elevated procalcitonin, infants, French Guiana.

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Introduction

From July 2014 to April 2015, French Guiana, the biggest French overseas territory in South America was affected by a Chikungunya outbreak. This re-emerging arbovirus infection continues to increase because of non-immune populations, migrant populations, the adaptability of the virus, and possibly global warming increasing the number of potential vectors (1). The first cases of this tropical viral disease were reported in Tanzania in 1952 and gradually spread into Asia (India in particular). The re-emergence of the virus was marked by an intial epidemic in the Indian Ocean region. This outbreak appears to have followed a mutation in the viral genome allowing the virus to adapt to *Aedes albopictus*, which is considered an accessory vector. This mutation occurred simultaneously in several geographically distinct areas and was not limited to a distribution from a single mutant home (2). This mosquito had been identified in Europe in 1979 and its presence was responsible for the first European epidemic in southern Italy in 2006. The first French cases were reported during the great epidemic of 2005 on the island of Reunion where nearly a third of the population was infected. From there, the epidemic continued to increase: in 2010, there was the first metropolitan indigenous case in Southern France. In 2011, the French West Indies were affected, but it was not until July 2014 that the epidemic was officially declared in French Guiana. Given our experience of dengue epidemics (3), and to prevent severe complications, a proactive Chikungunya program was set up at the Emergency Department and the Infectious Diseases and Pediatrics Departments. Patients suspected of having Chikungunya went through a special process with physicians collecting standardized information, systematically rehydrating patients intravenously and hospitalizing those who had more severe illness or were from remote areas and unlikely to return for follow up.

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From mid-December 2014 to April 2015, 3,753 proven cases were reported in French Guiana, including 229 hospitalized cases. 14,460 potential cases were reported in general practice and in the health centers, which were regarded as sentinel networks. In the laboratory of Cayenne Hospital, there were 1,582 positive PCR results during the study period. After April 2015, the number of new cases globally decreased.

The clinical profile of Chikungunya infection in children has been well documented (4-8). After 5 to 8 days of incubation, children present with very high and poorly tolerated fever and often with a skin rash. Polyarthralgia is more moderate in infants than in adults (9), but some serious neonatal forms exist (10-13). Bullous skin rashes and encephalopathy have also been described (14, 15). Usually, infants less than 3 months are considered at risk for severe forms of Chikungunya infection as are newborns, the elderly and persons with weakened immune systems. In this study we aimed to investigate the incidence of severe forms of Chikungunya infection in young infants and to identify features that could allow differentiation from other causes of fever.

Methods

The study was carried out in Cayenne Hospital from March 1^{st,} 2014 to February 28th, 2015. It was a descriptive, monocentric study.

All infants younger than 90 days hospitalized for fever were included. We excluded infants who had a fever only the waning of hospitalization (it essentially was the premature newborns hospitalized in the neonatal unit)

The data collection was retrospective from March 1st until December 31st and prospective afterwards until the end of the study. Data was entered from computerized hospital records, or

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paper records when computer data was not available. We collected demographic data (age in days, sex, and hospitalization duration), clinical data (fever duration, past medical history, clinical symptomatology such as diarrhea, irritability, poor general condition, skin rash, edema of the extremities, hypotonia….), biologic data (absolute neutrophil count, CRP, PCT, urinalysis, lumbar puncture, stool viral and bacterial analysis, malaria smear, Chikungunya PCR, VRS, influenza, search for *Pneumococcus* in blood hemoculture and cerebrospinal fluid…) and therapeutic data (type of antibiotherapy, dosage and re-evaluation).

All data was collected after informed consent from the legal responsible and was subsequently anonymized.

The main criterion outcome was the positive Chikungunya PCR.

The analysis proceeded as follows:

- Description of clinical and biologic data in Chikungunya virus infection.
- Comparison between SBI children and children infected with Chikungunya virus regarding the following variables: sex, age, hospitalization duration, fever ≥ 39° and ≥ 48h, poor general condition, irritability, skin rash eruption, digestive symptomatology, hypotonia, and biological criteria (CRP, PCT, absolute neutrophil count).

Subsequently, we compared the Chikungunya group with the group of Non-Chikungunya infected infants, in order to identify the particularities of Chikungunya infection in our study population.

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Definitions

The fever was defined by a rectal temperature up to 100, 4°F (38°C).

The high fever was defined by a rectal temperature up to 102°F (39°C).

We defined irritability as an excessive, inconsolable crying despite attempts to comfort and console by the mother or the caregiver.

The poor general condition associated fever, lethargy and poor feeding.

Biologic methods

Here, CHIK infection was confirmed by real-time polymerase chain reaction. RealStar® Chikungunya RT-PCR Kit 2.0 **(**Altona Diagnostics) was used in 2 ml whole blood samples collected from children with ≤5 days of fever. PCR results were available in 1-2 days. Specimen for PCR were exactly similar to those for virus isolation, with a 100% sensitivity and specificity (16, 17).

Ethical and regulatory aspects

The data collection was part of the Chikungunya emergency plan and was mandated by the regional health authorities. The anonymized monocentric data issued from medical records was analyzed, which was authorized according to the Regulatory authorities (Commission Nationale Informatique et Libertés number TFN1490159N).

Data analysis

Data analysis was performed using Stata 13. Quantitative variables were categorized according to statistical criteria using the first and third quartiles and the median. Single comparisons were performed with T-student test for qualitative data and Exact Fisher test for quantitative data. All p-values < 0.25 were included in the multivariate of logistic regression model. We expressed results means, odds ratios and confidence intervals. The P-values < 0.05 were considered

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statistically significant. The final model included variables that were significantly associated with the failure event in a single covariable analysis.

Results

From, March 1, 2014 to February 28th, 2015, 719 children younger than 3 months attended Cayenne Hospital emergency department (Fig. 1).). One hundred and twenty children with fever (16.7%) were hospitalized: there were 67 girls and 53 boys (sex ratio: 1.3). The mean age was 46 days (± 22 days). The mean hospitalization duration was 7.4 days (± 6.1 days). We did not have any cases of malaria or dengue fever in our study population.

Chikungunya infection was diagnosed in 26 children. In 11 cases (42.3%), there was a simultaneous familial infection linked to the infant's diagnosis. In 4 cases (15.4 %), there was a simultaneous infection in neighbors linked to the infant's diagnosis.

The most important symptomatology was high (80.8% [77.5-84]) and prolonged fever (>7 days) (76.9% [73.4-80.4]), irritability (96.2% [94.5-97.7]) and skin rash. (69.2% [65.4-73]). Poor general condition with anorexia was found in 84.6% of cases [81.6-87.6]. Half of the infants presented edematous extremities (hands and feet principally). One third of infants presented vesiculobullous exanthem (Fig 2&3). However, in 15% of cases, Chikungunya infection was associated with a SBI (Fig. 1). Biologically, there was a moderate hepatic cytolysis in 84.6% [81.6-87.6] of the cases. Some patients had cholestasis, moderate transitory lymphopenia and neutropenia. Rare cases of coagulation diseases were found but prothrombin was always higher than 50% and platelets always up to 80.000G/L. Chikungunya cases are described in tables 1 and 2. Infants who presented irritability, high fever and skin rash were more likely to have

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Chikungunya infection: OR 39 [9.2-243] ($p < 0.001$). The specificity of the model was 96.7 % and the negative predictive value 89.4% (table 3)

When we compared the Chikungunya group and the Non-Chikungunya infected infants (table 2), the Chikungunya group were treated with fewer antibiotics and had a shorter hospitalization duration. However, its clinical initial presentation was remarkable, with irritability still significant in multivariate analysis (AOR: 36, [2-683], $p = 0.0017$).

CRP > 20mg/L was associated with SBI (OR: 0.3 [0.08-0.9], $p=0.02$) but PCT was associated with Chikungunya infection, OR: 3.6 [1.13-11.9], $p= 0.022$. The OR is remained significant in multivariate analysis, AOR: 4.9 [1.2-18], ($p = 0.036$). The Receiver Operating Characteristic (ROC) analysis was used to quantify how accurately our medical diagnostic test (fever-irritability-elevated PCT) can discriminate between Chikungunya and Non-Chikungunya infants. In our multivariate model, the area of the ROC curve was 0.96 (Figure 4).

Six children were transferred to the pediatric intensive care unit. The main manifestations were neurological symptoms (1 convulsion and 1 bulging fontanelle), dyspnea in 4 cases. No death or relapses were observed.

Discussion

The clinical presentation of the Chikungunya infection in our study was similar to that described in infants in the literature (6, 13, 15). Chikungunya infection in very young children was associated with high prolonged, poorly tolerated fever and irritability. This clinical form may be confused with systemic bacterial infection and treated with antibiotics, when in fact; it is a benign viral infection. However, during the 2005-2006 epidemic on Reunion Island, there were

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reports of rare severe forms involving both adults and children (16, 17). Nevertheless, we did not observe any severe forms as in the Réunion study (14).

The clinical triad: fever-irritability-elevated PCT was nearly 40 times more representative of Chikungunya infection ($p < 0.001$). The specificity and the NPV were high, and the area under the ROC curve was close to 1, confirming the quality of our model in this epidemic context. This triad may be particularly interesting for isolated centers that do not have easy access to blood testing. However, caution is required in the applicability to other contexts where malaria or dengue cases may have mimicked features of Chikungunya (18-20). The vesiculobullous exanthem, lymphopenia (but not neutropenia) were frequent as described in the literature (21).

In the literature, low platelet counts and coagulation disorders seemed to be more frequent whereas they concerned barely 8% of our population (7, 22). Liver abnormalities were relatively frequent both in our study and in the literature (7, 22).

Chikungunya could be associated with SBI in 15.4% [12.4-18.3]. Others have shown a higher risk of bacterial co-infection in Chikungunya infected young children (6).

Our results highlighted that CRP was significantly higher in the SBI group than the Chikungunya group. ($p= 0.02$). However, PCT was in favor of viral Chikungunya infection in univariate ($p = 0.022$) and multivariate analysis ($p = 0.036$). Some studies highlighted that PCT was a bacterial marker with a 96.3% NPV (23-27). However, other studies contradicted this result with no significant association between PCT and SBI (28, 29). We had a very low number of patients and our results should be confirmed by larger studies.

In our population, we did not have any complications or re-hospitalizations in the Chikungunya group, but as reported in the literature, mostly encephalopathy and multiorgan failure. (4, 7, 8, 14, 15).

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Figure legends

Fig. 1 Infants younger than 3 months of age consulting in the Emergency Department of Cayenne Hospital (from 03/01/2014 to 02/28/ 2015).

Fig 2. Erythema eruption in an infant with Chikungunya infection

Fig 3. Bullous eruption in an infant with Chikungunya infection

Fig 4. ROC curve testing our multivariate model. The area under the ROC curve was close to 1, confirming the quality of the model. The ROC analysis is used here to quantify how accurately our medical diagnostic test (fever-irritability-elevated PCT) can discriminate between Chikungunya and Non-Chikungunya infants.

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Table 1: Clinical and biological description of Chikungunya sick patients.

Variables	N=26 (100%)	IC 95%
Temperature		
T°>48 hours	20 (76.9)	[73.4-80.4]
T°>39°C	21 (80.8)	[77.5-84]
Irritability	25 (96.2)	[94.5-97.7]
Impaired general condition	22 (84.6)	[81.6-87.6]
Skin rash	18 (69.2)	[65.4-73]
Peripheric edema	13 (50)	[45.9-54.1]
Digestive abnormalities	7 (26.9)	[23.2-30.6]
Lymphopenia	12 (46.2)	[42-50]
Hepatic cytolysis	22 (84.6)	[81.6-87.6]
Cholestasis	16 (61.5)	[57.5-65.6]
Low platelets	4 (15.4)	[12.4-18.3]
Coagulation impairment	2 (7.7)	[5.5-9.9]
Low sodium	5 (19.2)	[16-22.5]

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Table 2. Chikungunya sick infants characteristics compared to those without CHIK

Variables	CHICK +(N=26)	CHICK - (N=94)	*P*	Sensitivity % (IC95 %)	Specificity % (IC95 %)	PPV %	NPV %
Sex							
- Female	16 (61.5)	51 (54.3)	*0.5*				
- Male	10 (38.5)	43 (45.7)					
Median age, days (IQ)	49 [34-55]	45 [28-65]	*0.2*				
Temperature °>39°							
Yes	21 (80.8)	35 (37.2)	***<0.001***	80.77 (62-91)	62.77 (53-72)	37.5	92.19
No	5 (19.2)	59 (62.8)	**OR: 7 [2.5-20.5]**				
T°>48 h			***<0.001***	76,9 (58-89)	81,9 (73-89)	54	92,8
Yes	20 (76.9)	17 (18)	**OR: 15**				
No	6 (23.1)	77 (82)	**[5-43]**				
Impaired general condition			***<0.001***	84.6 (66-94)	59.6 (49-69)	36.7	93.33
Yes	22 (84.6)	38 (40.4)	**OR: 8**				
No	4 (15.4)	56 (59.6)	**[2.6-25.4]**				
Irritability			***<0.001***	96.15 (81-99)	71.3 (61-79)	48	98.5
Yes	25 (96.2)	27 (28.7)	**OR: 62**				
No	1 (3.8)	67 (71.3)	**[8.00-481.00]**				
Skin rash	18 (69.2)	12 (12.8)	***<0.001***	69,23 (50-84)	87,23 (79-93)	60	91,11
Yes	8 (30.8)	82 (87.2)	**OR: 15.4**				
No			**[5.50-43.10]**				
Low sodium							
Yes	3 (11.5)	12 (12.8)					
No	23 (88.5)	82 (87.2)	*0.9*				
Digestive abnormalities	7 (27)	27 (28.7)					
Yes	19 (73)	67 (71.3)					
No			*0.7*				
CRP(IQ)	18.8 [7.6-28.0]	12.6 [3.7-38.2]	*0.3*				
PCT(IQ)	1.26 [0.54-2.36]	0.27 [0.14-0.63]	***0.001***	80,95 (60-92)	65.6 (53-76)	47,22	90,91
			OR: 8.1				
PNN(IQ)	5.05 [4.20-7.10]	4.95 [2.40-8.10]	**[2.4-27.2]** *0.2*				

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Table 3. Multivariate analysis

Variables	CHICK + (N=26)	CHICK - (N=94)	*P*
Impaired general condition	22	38	***0.02*** **AOR: 11 [1.4-90]**
Irritability	25	27	***0.000*** **AOR: 78 [7-872]**
PCT(IQ)	1.26 [0.54-2.36]	0.27 [0.14-0.63]	***0.003*** **AOR: 16 [2.6-107]**

Sensitivity	Specificity	PPV	NPV
%	%	%	%
66,7	96,7	87,5	89,4

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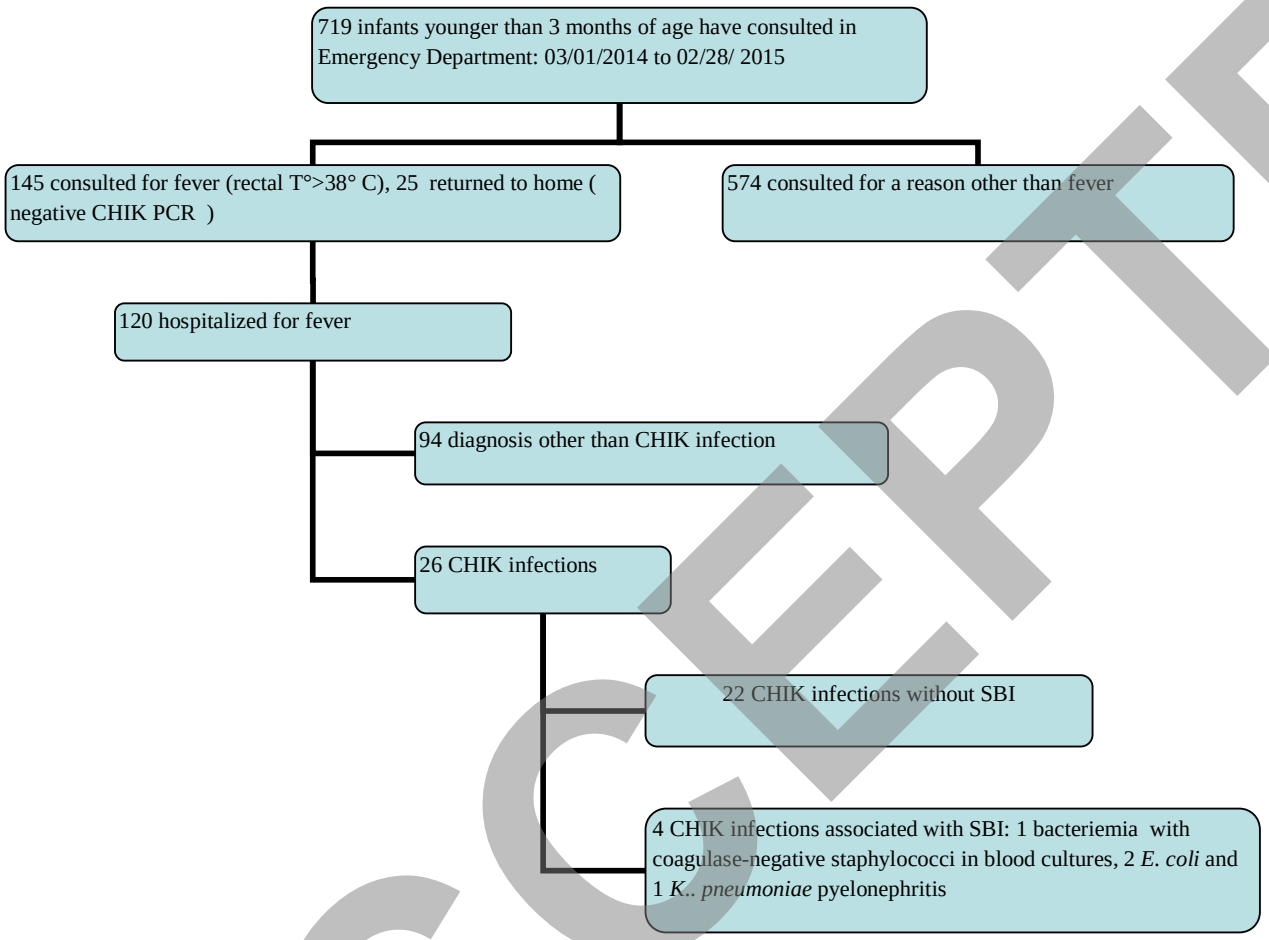


Fig. 1 Infants younger than 3 months of age consulting in the Emergency Department of Cayenne Hospital (from 03/01/2014 to 02/28/ 2015)

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Fig 2. Erythema eruption in an infant with Chikungunya infection



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Fig 3. Bullous eruption in an infant with Chikungunya infection

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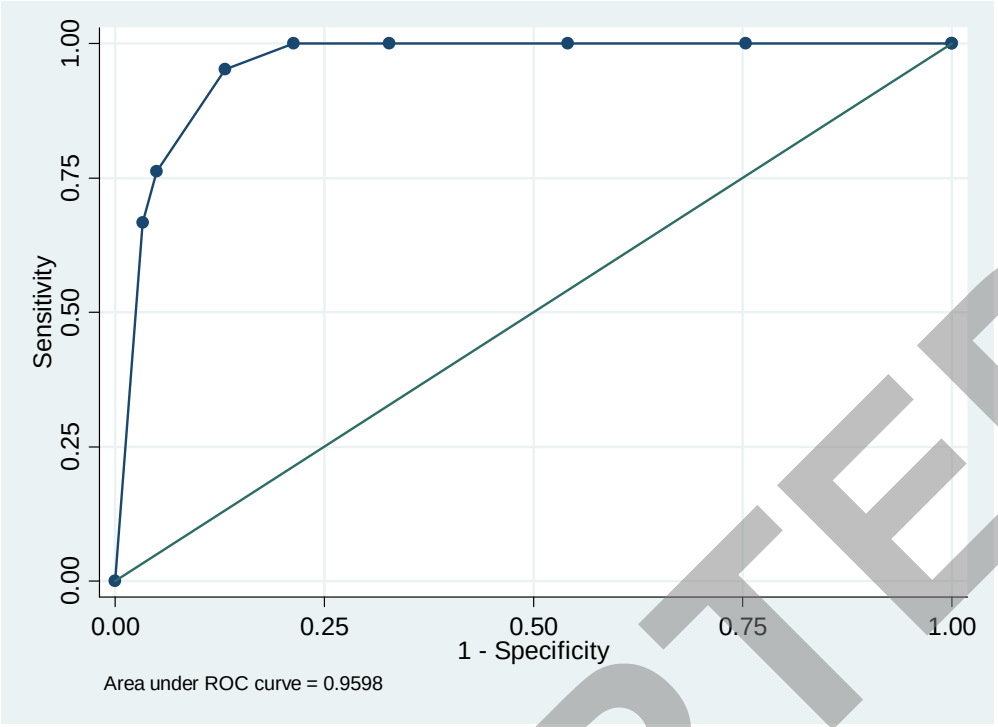


Fig 4. **ROC curve testing our multivariate model. The area under the ROC curve was close to 1, confirming the quality of the model. The ROC analysis is used here to quantify how accurately our medical diagnostic test (fever-irritability-elevated PCT) can discriminate between Chikungunya and Non-Chikungunya infants.**

ACCEPTED

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