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Consequences of a recent past dengue infection for acute and long-term chikungunya outcome: A retrospective cohort study in Curaçao

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ABSTRACT

Background: Dengue and chikungunya co-infections are an emerging threat to public health in tropical and subtropical areas. This study investigates acute and long-term clinical presentation patterns of chikungunya against a backdrop of preceding dengue infection and determines predicting factors for long-term chikungunya sequelae.
Methods: A retrospective cohort study was performed in 2015, including 299 previously confirmed chikungunya cases, of which 162 subjects were assessed for dengue serology at disease onset.
Results: Those with previous dengue infection (35.2% of the examined population) had a similar acute disease presentation, and suffered (not statistically significantly) more frequently from long-term musculoskeletal and neuropsychological symptoms compared to chikungunya-only patients. Patients with a preceding dengue infection (vs. those without) (OR = 4.17; p = 0.004), female sex (OR = 3.17; p = 0.034) and pre-existing joint disease (OR = 2.95; p = 0.031) had a higher risk of developing aggravated long-term chikungunya. Chronic disease (sequelae lasting > 90 days) was predicted by an age between 41 and 60 (OR = 3.07; p = 0.009) and concomitant cardiovascular disease (OR = 4.08; p = 0.010), but not by a preceding dengue infection.
Conclusions: This study suggests several predicting factors of, and a possible link between preceding dengue and chikungunya infection and aggravated long-term sequelae, which should be interpreted in the light of the limitations of this study.

1. Introduction

Dengue and chikungunya are arboviruses transmitted by the day-biting mosquitoes *Aedes aegypti* and *Aedes albopictus* [1,2]. The vectors of these viruses currently circulate in large parts of the world, rendering 40% of the world population susceptible to these diseases [3]. Chikungunya led to devastating epidemics when introduced in the Americas at the end of 2013 [4,5]. In the same regions, dengue is endemic with an increasing spread to previously unaffected areas [6]. Concomitant dengue and chikungunya infection have been reported in several regions worldwide, in particular in Africa and Asia [7]. However, considering the high transmission rates of both diseases, co-infections of dengue and chikungunya are surprisingly little reported [8,9]. Saint Martin, a Caribbean island where the first locally transmitted chikungunya cases were reported in the Caribbean and America, also described the first co-infections of dengue and chikungunya in these regions [10].

Curaçao became affected by the epidemic of chikungunya up from mid-2014. The outbreak rapidly spread and at the end of the epidemic in January 2015, an estimated 50,000 to 75,000 inhabitants were infected [IG, unpublished]. This epidemic took place in a naïve population for chikungunya against the backdrop of well-established dengue transmission, with outbreaks during the rainy season [11]. All four dengue virus serotypes co-circulate in Curaçao [11].

Abbreviations: CLTCS, Curaçao Long-Term Chikungunya Sequelae; ADC N·V., Analytical Diagnostic Centre

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Dengue and chikungunya lead to similar acute clinical presentations, typically starting with an abrupt onset of fever, which may be accompanied by a range of symptoms such as rash, headache, myalgia and arthralgia [1,2]. Disease may evolve into severe conditions and cause death in the case of dengue [2], while chikungunya is recognized for its debilitating long-lasting musculoskeletal symptoms, which may persist for years [12–14]. The clinical spectrum of dengue and chikungunya co-infections is not well described, and focuses on acute disease manifestations or complications. These studies do not show substantial differences in disease presentation [15–17]; however, complicated disease was described in co-infected patients [17].

To assess the knowledge gap concerning infections of chikungunya and dengue, this study investigated the impact of a preceding dengue infection on acute and chronic chikungunya disease presentation and analysed predicting factors for chronic sequelae.

2. Study methods

During June and July 2015, a retrospective cohort study was set up including laboratory confirmed (by serology (ELISA), reverse transcription polymerase chain reaction (RT-PCR) or indirect fluorescent antibody (IFA)) chikungunya cases infected during the 2014 epidemic in Curaçao. Participant recruitment procedures and study site were described elsewhere [18]. Briefly, adult participants' data was provided by general practitioners, working in 14 practices across Curaçao. Assessment of long-term chikungunya sequelae was performed in the homes of participants as part of a cross-sectional survey study.

2.1. Study objectives

This study has different objectives. These objectives have distinct inclusion criteria (see Fig. 1), and therefore the sample size differs per objective. The objectives with their inclusion criteria are presented in Fig. 1 and are as follows:

- Objective 1: To analyse acute clinical presentation of preceding dengue infection and chikungunya-only disease. Inclusion criteria: subjects with clinical data of acute disease presentation and available dengue serology (n = 94);
- Objective 2: To analyse predicting factors of chronic disease outcomes: (a)severe disease development and (b) disease persistence > 90 days. Inclusion criteria: subjects with clinical data of acute disease presentation (n = 159);
- Objective 3: To analyse chronic clinical presentation of preceding dengue infection and chikungunya-only disease. Inclusion criteria: subjects with available dengue serology (n = 162).

2.2. Data collection

Individuals were surveyed using a structured questionnaire assessing socioeconomic variables, co-morbidities, chronic chikungunya sequelae and chikungunya disease status; the latter being assessed using the formerly described Curaçao Long-Term Chikungunya Sequelae (CLTCS) score, where individuals with chronic chikungunya sequelae were classified as 'recovered', 'mildly affected' or 'highly affected' [18]. Trained, experienced local interviewers applied the questionnaire, which was piloted and adapted in Dutch, and translated to Papiamentu, Spanish and English [18].

The Ministry of Health of Curaçao is responsible for disease surveillance. During outbreaks, physicians are requested to report any suspected case to the Ministry of Health. Data from acute disease presentation was acquired via general practitioners, who assessed suspected chikungunya cases using a standardized form for chikungunya surveillance (Table 1) and referred them for dengue serology. Enzyme-linked immunosorbent assay (ELISA; DxSelect™, Focus Diagnostics) of acute samples and, if available, convalescent samples was performed by the Analytical Diagnostic Centre (ADC N·V.) in Curaçao according to the manufacturer's protocol, to detect dengue-specific IgM and IgG.

2.3. Classification of dengue serology

Classification of serologic outcomes was determined as presented in Table 2.

We expected that a positive IgM for dengue and laboratory confirmed dengue could influence clinical manifestations. Therefore, patients diagnosed with an acute or presumptive/recent dengue infection were merged into one group, to which we hereinafter refer as 'preceding dengue'. On the other hand, the 'past dengue' and the 'negative cases' were merged and are hereinafter referred to as chikungunya-only (i.e. no preceding dengue infection).

2.4. Data analysis

Data analysis procedures were described elsewhere [18]. Briefly, odds ratios of acute and chronic symptoms were calculated and adjusted for confounding factors using a binary logistic regression. Possible confounding of acute or chronic clinical presentation between individuals with chikungunya-only and a preceding dengue disease

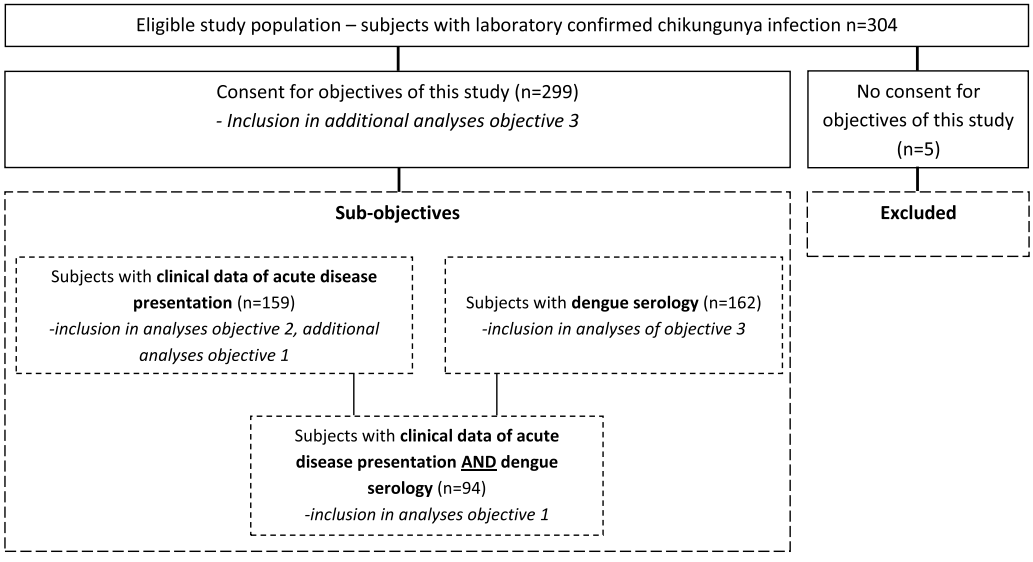

Fig. 1. Flowchart inclusion procedure of the study population.
Objective 1: To analyse acute clinical presentation of preceding dengue infection and chikungunya-only disease.
Objective 2: To analyse predicting factors of chronic disease outcomes: (a) severe disease development and (b) disease persistence > 90 days.
Objective 3: To analyse chronic clinical presentation of preceding dengue infection and chikungunya-only disease.
Additional analyses: these analyses are presented in Appendix A, and were additionally performed since the sample size in the main manuscript was limited. The additional analyses also include the sample which was not tested for dengue. Therefore, these results should be interpret with caution.

Table 1
Univariate analysis of acute clinical presentation of chikungunya, comparing individuals with vs. without preceding dengue infection.

	Chikungunya-only infection (n = 58)		Preceding dengue infection (n = 36)*		Adjusted OR[a] (95% CI)	Adjusted p-value[a]
	n	(%)	n	(%)		
Acute symptoms (n)[b]						
Fever (n = 56; n = 36)	54	(96.4)	32	(88.9)	0.35 (0.06–2.13)	0.253
Headache (n = 57; n = 36)	50	(87.7)	30	(83.3)	1.10 (0.64–5.60)	0.890
Orbital pain (n = 53; n = 35)	38	(71.7)	21	(60.0)	0.72 (0.90–12.26)	0.512
Myalgia (n = 56; n = 35)	53	(94.6)	34	(97.1)	2.96 (0.27–32.31)	0.373
Arthralgia (n = 56; n = 36)	53	(94.6)	34	(94.4)	1.65 (0.22–12.52)	0.628
Arthritis (n = 55; n = 35)	35	(63.6)	26	(74.3)	1.62 (0.61–4.32)	0.335
Rash (n = 57; n = 35)	27	(47.4)	15	(42.9)	1.04 (0.43–2.55)	0.637
Nausea/vomiting (n = 57; n = 36)	19	(33.3)	12	(33.3)	0.98 (0.39–2.44)	0.962
Diarrhoea (n = 56; n = 36)	14	(25.0)	7	(19.4)	0.75 (0.26–2.18)	0.603
Cold shivers (n = 55; n = 36)	29	(52.7)	17	(47.2)	0.89 (0.37–2.17)	0.801
Cough (n = 57; n = 35)	16	(28.1)	2	(5.7)	0.14 (0.03–0.71)	**0.017**
Haemorrhagic tendencies (n = 57; n = 35)	3	(5.3)	0	(0.0)	–	0.168*
Icterus (n = 56; n = 35)	1	(1.8)	1	(2.9)	0.51 (0.02–11.39)	0.669

p-values in bold are statistically significant.
*Fisher's exact test.
[a] p-value and OR corresponds to the comparison of 'preceding dengue infection' vs. 'chikungunya-only infection', adjusted for concomitant diabetes mellitus and cardiovascular disease.
[b] number of subjects in the 'chikungunya-only infection' group and the 'preceding dengue infection' group, respectively.

episode due to age, sex and co-morbidity was explored (Table 3). Variables associated with a preceding dengue infection at a $p \leq 0.200$ level were considered as confounding variables, namely concomitant diabetes mellitus and cardiovascular disease (for acute and chronic clinical presentation) and age (for chronic clinical presentation) (Table 3). The same procedures were performed in the additional analyses presented in Appendix A.

A multivariate binary logistic regression was performed to investigate predicting factors of chronic chikungunya (sequelae lasting longer than 90 days), and 'highly severe' chronic chikungunya disease outcomes, based on the CLTCS-score. The 'highly severe' disease status was chosen, because it reflects a chronic chikungunya disease status associated with severely reduced quality of life [18]. The multivariate analyses included all clinical and general characteristic variables which were associated with the dependent variables at a significance level of $p < 0.20$. To obtain more insights and power, additional analyses of acute and chronic disease presentation were performed in Appendix A. These analyses followed the same procedures as the main manuscript, but included the participants without available dengue serology and should therefore be interpreted with caution.

2.5. Ethics statement

The study was approved by the Medical Ethical Board of the Sint Elisabeth Hospital (METC SEHOS) Curaçao (Reference number: 2015–002). All participants enrolled consented in writing.

3. Results

In June and July 2015, 304 laboratory-confirmed chikungunya cases were included in a cohort study (Fig. 1). The socio-economic characteristics of the individuals were described previously [18]. Of the 304 individuals, 299 consented to participate in the present study of which 162 were tested for dengue exposure. Fifty-seven participants were defined as having had a preceding dengue infection. Of those, 11 had a laboratory confirmed dengue and 46 a 'presumptive/recent

Table 2
Categorisation of ELISA assessments.

Acute sample		Convalescent sample			Classification	Binary categorisation for analyses
IgM	IgG	IgM	IgG	n (%)[a]		
P	N	P	P	1 (0.6)	Acute dengue	Preceding dengue infection and chikungunya
N	P	P	P	6 (3.7)	Acute dengue	Preceding dengue infection and chikungunya
N	N	N	P	2 (1.2)	Acute dengue	Preceding dengue infection and chikungunya
P	N	–	–	1 (0.6)	Acute dengue	Preceding dengue infection and chikungunya
N	P	N	P	1 (0.6)	Acute dengue[b]	Preceding dengue infection and chikungunya
P	P	–	–	38 (23.5)	Presumptive/recent dengue	Preceding dengue infection and chikungunya
P	P	N	P	2 (1.2)	Presumptive/recent dengue	Preceding dengue infection and chikungunya
P	P	P	P	4 (2.5)	Presumptive/recent dengue	Preceding dengue infection and chikungunya
–	–	P	P	2 (1.2)	Presumptive/recent dengue	Preceding dengue infection and chikungunya
N	P	N	P	26 (16.0)	Past dengue	Chikungunya-only
N	P	–	–	70 (43.2)	Past dengue	Chikungunya-only
–	–	N	P	6 (3.7)	Past dengue	Chikungunya-only
N	N	N	N	1 (0.6)	Confirmed dengue negative	Chikungunya-only
N	N	–	–	2 (1.2)	Presumptive dengue negative	Chikungunya-only

P = positive test outcome; N = negative test outcome; [a]Total subjects with dengue serology: n = 162; [b]This concerned one case. Because values of the convalescent sample rose by more than 5 times, this sample was considered as IgG seroconversion.Classification: Patients were defined as having an 'acute dengue infection', 'presumptive/recent dengue' or 'past dengue'. A dengue infection was assumed as a 'laboratory confirmed dengue' based on a conversion of IgM or IgG in paired samples, or on a positive IgM in a previously naïve individual (i.e. negative IgG) in the acute sample. Participants were defined as having had a 'preceding dengue' infection when IgM was positive in one of the samples (i.e. in the acute or convalescent sample). Cases were defined as 'past dengue' when IgM was negative and IgG positive. When IgG and IgM tests were negative in acute (and convalescent) sample(s), cases were defined as (laboratory confirmed) 'dengue negative'.

Table 3
Analysis of possible confounders on acute and chronic disease presentation.

	Sample with dengue serology and clinical data on acute disease presentation (n = 94)					Sample with dengue serology (n = 162)				
	Chikungunya-only infection (n = 58)		Preceding dengue infection (n = 36)		p-value[a]	Chikungunya-only infection (n = 105)		Preceding dengue infection (n = 57)		p-value[a]
	n	(%)	n	(%)		n	(%)	n	(%)	
Age										
18–40	16	(27.6)	6	(16.7)		30	(28.6)	9	(15.8)	
41–60	35	(60.3)	24	(66.7)		55	(52.4)	37	(64.9)	
> 61	7	(12.1)	6	(16.7)	0.484*	20	(19.0)	11	(19.3)	0.171
Sex										
Male	14	(24.1)	9	(25.0)		27	(25.7)	12	(21.1)	
Female	44	(75.9)	27	(75.0)	0.925	78	(74.3)	45	(78.9)	0.507
Co-morbidity										
Joint disease	8	(13.8)	6	(16.7)	0.704	15	(14.3)	10	(17.5)	0.584
Cardiovascular disease[c]	9	(15.5)	10	(27.8)	0.150	15	(14.3)	13	(22.8)	0.171
Neurologic disease	1	(1.7)	1	(2.8)	1.000*	2	(1.9)	3	(5.3)	0.346*
Diabetes mellitus	4	(6.9)	8	(22.2)	0.053*	9	(8.6)	11	(19.3)	**0.047**

p-values in bold are statistically significant.
*Fisher's exact test.
[a] p-value corresponds to the comparison between the groups 'chikungunya-only infection' and 'preceding dengue infection'.
[b] Cardiovascular disease group includes hypercholesterolemia and hypertension.

dengue infection' (Fig. 1). Prevalence of chikungunya with a preceding dengue infection (which included the 46 'presumptive/recent', and the 11 laboratory confirmed participants) was thereby 35.2% (57/162).

3.1. Acute clinical presentation

To understand if the acute disease presentation of chikungunya was influenced by a preceding dengue infection, symptoms assessed by general practitioners were compared and adjusted for concomitant diabetes mellitus and concomitant cardiovascular disease (Table 1). Cough was more frequently reported in individuals with only chikungunya (chikungunya: 18.1% [n = 16] vs. preceding dengue infection: 5.7% [n = 2]; adjusted p-value = 0.017). No other symptoms of acute presentation were associated with having a chikungunya-only or preceding dengue, neither in the additional analyses in Tables A1, A2.

3.2. Predicting factors of disease outcomes

Clinical characteristics of long-term chikungunya sequelae were assessed between 92 and 419 days after onset of acute disease. Uni- and multivariate analyses were performed to identify predicting factors of two disease outcomes: 1) chikungunya disease persistence > 90 days, and 2) development of a 'highly affected' CLTCS-disease status. In 66.5% (n = 105) of the cases, chikungunya disease persisted > 90 days and 25.8% (n = 41) were 'highly affected' at time of interview. Time-between-interview and disease onset was assessed as potential confounder, but showed a similar distribution for the 'recovered and mildly affected' and 'highly affected' individuals (Mean = 267 days, SD = 75 days vs. Mean = 258 days, SD = 57 days; T-test: p = 0.431). In the univariate analysis, disease outcomes were compared with socio-economic characteristics, co-morbidity and clinical presentation at acute disease presentation (Table 4). Variables associated at a level of $p \leq 0.20$ were included in the multivariate analysis. The final models of the multivariate analysis are presented in Table 5. An age between 41 and 60 (OR = 3.07; p = 0.009) (baseline category: age of 18–40) and concomitant cardiovascular disease (OR = 4.08; p = 0.010) were independent predictors of chikungunya disease longer than 90 days. 'Highly affected' disease status was predicted by female sex (OR = 3.17; p = 0.034), concomitant joint disease (OR = 2.91; p = 0.031) and preceding dengue (OR = 4.17; p = 0.004) (although the baseline category 'no dengue serology' was used).

3.3. Long-term sequelae

Clinical chronic chikungunya presentation of the 162 individuals was compared between those with and without a preceding dengue infection, adjusted for age, concomitant diabetes mellitus and concomitant cardiovascular disease. Participants with a preceding dengue infection at disease onset reported higher proportions of most chronic symptoms (Table 6, Fig. 2, Table A3), but no significant associations were found. Chronic joint pain in lower extremities was associated with a preceding dengue infection (OR = 1.86; p = 0.044) in the additional analyses in Table A3.

4. Discussion

In June and July 2015, a retrospective cohort study was performed to investigate the influence of a preceding dengue infection on chikungunya disease development. Chikungunya and a preceding dengue infection covered 35.2% of the subjects serologically tested for both diseases, which is amongst the highest incidences reported to date. As reviewed by Furuya-Kanamori and colleagues, the vast majority of studies report incidences of 'co-infections' up to 10% of the study population [19]. Most of these studies assessing 'co-infection' relied, like the present study, (partly) on ELISA-IgM assessment when estimating concomitant prevalence of chikungunya and dengue. It is important to note here that ELISA-IgM assessment alone is not specific enough to define co-infection.

Very few studies describe acute clinical disease presentation of chikungunya and a preceding dengue infection [8,20]. Even fewer of these included chikungunya-only infections and show, like the present study, no major differences with preceding or co-infected subjects in acute disease presentation [15–17] but reported complicated disease manifestations [17]. It is notable that patients with chikungunya and a preceding dengue infection were assessed as having more myalgia (OR = 3.0) and arthritis (OR = 1.6). This contradicts the findings of the study by Taraphdar et al. where patients with a preceding dengue infection and chikungunya presented with milder musculoskeletal manifestation than the chikungunya-only infected population [15]. Acute chikungunya (without preceding dengue) presented more often with

Table 4
Univariate analysis of chikungunya disease outcome parameters: disease persistence longer than 90 days and highly affected CLTCS-disease status.

	0-90 days (n = 53)		> 90 days (n = 105)		p-value[a]	Recovered & mildly affected (n = 118)		Highly affected (n = 41)		p-value[b]
	n	(%)	n	(%)		n	(%)	n	(%)	
Age										
18–40	18	(34.0)	15	(14.3)		28	(23.7)	6	(14.6)	
41–60	24	(45.3)	71	(67.6)		65	(55.1)	30	(73.2)	
> 61	11	(20.8)	19	(18.1)	**0.008**	25	(21.2)	5	(12.2)	0.126
Sex										
Male	15	(28.3)	23	(21.9)		33	(28.0)	5	(12.2)	
Female	38	(71.7)	82	(78.1)	0.374	85	(72.0)	36	(87.8)	**0.041**
Education										
Illiterate/primary school	11	(20.8)	23	(21.9)		24	(20.3)	10	(24.4)	
Secondary school	16	(30.2)	37	(35.2)		39	(33.1)	14	(34.1)	
Intermediate vocational education	16	(30.2)	27	(25.7)		37	(31.4)	7	(17.1)	
University (of applied sciences)	10	(18.9)	18	(17.1)	0.895	18	(15.3)	10	(24.4)	0.269
Occupation										
Unemployed/student/housewife/voluntary	9	(17.0)	12	(11.4)		16	(13.6)	5	(12.2)	
Paid job (domestic or manual)	22	(41.5)	53	(50.5)		54	(45.8)	22	(53.7)	
Paid job (not domestic or manual)	16	(30.2)	23	(21.9)		30	(25.4)	9	(22.0)	
Retired	6	(11.3)	17	(16.2)	0.708*	18	(15.3)	5	(12.2)	0.853
Income (n1 = 156; n2 = 157)										
0-999 ANG	4	(7.7)	9	(8.7)		10	(8.5)	3	(7.5)	
1000-2499 ANG	19	(36.5)	39	(37.5)		39	(33.3)	19	(47.5)	
2500-4999 ANG	20	(38.5)	45	(43.3)		52	(44.4)	14	(35.0)	
> 5000 ANG	9	(17.3)	11	(10.6)	0.691	16	(13.7)	4	(10.0)	0.314*
Co-morbidity										
Joint disease	3	(5.7)	19	(18.1)	**0.033**	12	(10.2)	10	(24.4)	**0.023**
Cardiovascular disease[c]	5	(9.4)	31	(29.5)	**0.004**	25	(21.2)	11	(26.8)	0.457
Neurologic disease	0	(0.0)	2	(1.9)	0.551*	2	(1.7)	0	(0.0)	1.000*
Diabetes mellitus	5	(9.4)	12	(11.4)	0.702	11	(9.3)	6	(14.6)	0.382*
Dengue assessment										
Preceding dengue infection	22	(41.5)	43	(41.0)		21	(17.8)	10	(24.4)	
Past dengue/dengue negative	21	(39.6)	36	(34.3)		42	(35.6)	16	(39.0)	
No dengue serology	22	(41.5)	43	(41.0)	0.664	55	(46.6)	15	(36.6)	**0.014**
Acute symptoms										
Fever (n1 = 51&101; n2 = 112&41)	45	(88.2)	95	(94.1)	0.219*	102	(91.1)	39	(95.1)	0.516*
Headache (n1 = 52&105; n2 = 41&117)	41	(78.8)	85	(81.0)	0.755	92	(78.6)	35	(85.4)	0.350
Orbital pain (n1 = 51&99; n2 = 113&38)	28	(54.9)	64	(64.6)	0.246	66	(58.4)	26	(68.4)	0.274
Myalgia (n1 = 52&103; n2 = 116&40)	48	(92.3)	97	(94.2)	0.733*	107	(92.2)	39	(97.5)	0.454*
Arthralgia (n1 = 52&104; n2 = 116&41)	51	(98.1)	97	(93.3)	0.270*	109	(94.0)	40	(97.6)	0.681*
Arthritis (n1 = 51&97; n2 = 108&41)	30	(58.8)	61	(62.9)	0.629	63	(58.3)	29	(70.7)	0.164
Rash (n1 = 53&102; n2 = 115&41)	21	(39.6)	46	(45.1)	0.514	48	(41.7)	20	(48.8)	0.435
Nausea/vomiting (n1 = 52&104; n2 = 116&41)	12	(23.1)	41	(39.4)	**0.042**	35	(30.2)	18	(43.9)	0.110
Diarrhoea (n1 = 51&104; n2 = 115&41)	11	(21.6)	22	(21.2)	0.953	24	(20.9)	9	(22.0)	0.884
Cold shivers (n1 = 51&103; n2 = 114&41)	22	(43.1)	50	(48.5)	0.527	51	(44.7)	21	(51.2)	0.475
Cough (n1 = 53&102; n2 = 115&41)	8	(15.1)	16	(15.7)	0.923	16	(13.9)	8	(19.5)	0.394
Haemorrhagic tendencies (n1 = 53&102; n2 = 115&41)	2	(3.8)	2	(2.0)	0.607*	4	(3.5)	0	(0.0)	0.574*
Icterus (n1 = 53&101; n2 = 115&40)	2	(3.8)	0	(0.0)	0.117*	2	(1.7)	0	(0.0)	1.000*

p-values in bold are statistically significant.
*Fisher's exact test.
[a] p-value corresponds to the comparison between the groups '0–90 days' and ' > 90 days'.
[b] p-value corresponds to the comparison between the groups 'recovered and mildly affected' and 'highly affected'.
[c] Cardiac disease group includes hypercholesterolemia and hypertension; n1 refers to the number of subjects of the '0–90 days' and ' > 90 days' group respectively; n2 refers to the number of subjects of the 'Recovered & mildly affected' and 'Highly affected' group respectively.

cough when compared to chikungunya with recent dengue (OR = 7.1; p = 0.017). Cough is a relatively infrequent symptom at acute disease and might differentiate between a chikungunya-only infection and a chikungunya with recent dengue, although we could not find a patho-physiological explanation for this finding. Compared to other studies on acute chikungunya disease presentation, this study reported similar proportions of fever [21–25], arthralgia [21–24,26] and rash [22–25] while myalgia [21,23,24,26] and headache [21,23–25] were reported in higher proportions. These results indicate that differentiating between chikungunya-only infections and infections of chikungunya with recent dengue at acute presentation remains difficult and depends on laboratory assessment.

This is the first study describing that chikungunya with preceding dengue at acute disease presentation is a predicting factor (OR = 4.1) for severe chronic disease development. This independent association was most prominent when compared to the subjects without available dengue serology, but not significant (OR = 1.9; p = 0.159) when compared to the chikungunya-only subjects. It is likely that the group without available dengue serology consisted mainly of 'past dengue' or 'dengue negative' subjects, whilst a lower proportion would have had dengue before. Therefore, we conclude that the latter bias may only have led to an underestimation of differences between the two groups. The independent association of dengue infection preceding chikungunya and developing a 'highly affected' chronic disease status was reflected in the chronic clinical presentation, where the vast majority of chronic symptoms was reported in higher proportions in this group (i.e.

Table 5
Final model of variables independently associated with chikungunya disease outcome parameters: a) duration longer than 90 days vs. 0–90 days; b) highly affected vs. recovered & mildly affected at time of interview.

	OR (95% CI)	p-value
Chikungunya disease > 90 days		
Age		
18–40	1	0.018
41–60	3.07 (1.32–7.11)	0.009
> 61	1.31 (0.44–3.89)	0.625
Co-morbidity: cardiovascular disease		
No	1	
Yes	4.08 (1.39–11.93)	0.010
Highly affected disease status		
Sex		
Male	1	
Female	3.17 (1.09–9.23)	0.034
Co-morbidity: joint disease		
No	1	
Yes	2.95 (1.11–7.86)	0.031
Dengue assessment		
Preceding (/acute) dengue infection	1	0.016
Past dengue/dengue negative	0.52 (0.21–1.29)	0.159
No dengue serology	0.24 (0.09–0.63)	0.004

arthralgia, myalgia, fatigue, insomnia and neuropsychological symptoms). In particular the higher proportions of chronic joint pain in the lower extremities, which have previously been associated with the 'highly affected' disease status [18], may be responsible for this association. The outcomes of the analyses on predicting factors and chronic disease manifestations might suggest that a preceding dengue infection aggravates chronic (chikungunya) sequelae. However, the results of this study alone are not sufficient enough to draw a strong conclusion about this.

Several studies that focused on predicting chikungunya disease persistence have identified age [27–29], sex [29], co-morbidity [27,30], or acute disease presentation [27–30] as determinants, but did not assess preceding/co-infection of dengue. This study also identified age, co-morbidity (joint disease and cardiovascular disease) and female sex as predicting factors for longer or worse disease outcome. These predicting factors may aid in assessing the need to follow up chikungunya patients. Furthermore, they may guide further fundamental research on the poorly understood pathophysiology of chikungunya and dengue co-infections.

In this manuscript, we assessed the influence of (preceding) dengue on chikungunya sequelae. It is important to note that diagnosis of chikungunya was based on laboratory testing and clinical evaluation by a physician. When both IgM serology of dengue and chikungunya were positive following acute disease, it was hard to say which of the two diseases caused the acute disease manifestations in this case, and in which order these diseases afflicted the patient. However, it is likely that chikungunya played the most significant role in the acute phase, considering the opinion of the physician and that asymptomatic disease is less common in chikungunya than in dengue. Therefore, we choose to refer to these cases as 'chikungunya with preceding dengue'.

An important limitation of this study was the small sample size of participants tested for dengue (162/299), with consequent implications for the power and representativeness of the study. Parallel analyses were done on acute and long-term clinical presentation to obtain higher power in the analyses (presented in Appendix A). The results of Table A1-A3 should be interpreted with caution, because it is likely that some of the subjects without dengue serology had a preceding dengue infection. Since little is known about clinical presentation of chikungunya with preceding dengue infection in other contexts than in Curaçao, generalization of this study should be limited. Due to the recruiting procedures, a referral bias can be present in this study. Also, in some cases laboratorial assessment relied on serology of one sample, which may have lowered the probability to determine a dengue infection. Further, ELISA-based serological assays of dengue are less reliable than RT-PCR or viral isolation and might cross-react with (vaccines of) various flaviviruses (e.g. Japanese encephalitis, yellow fever). However, based on the epidemiological situation of Curaçao at the time of the study, we have no reasons to assume that cross-reaction has significantly influenced the results of this study.

Chikungunya sequelae were prominent in the population with a preceding dengue infection (which included patients with an acute dengue infection) and chikungunya disease, suggesting survival of chikungunya virus during concurrent dengue infection. Though severe

Table 6
Chronic chikungunya clinical presentation: preceding dengue infection vs. chikungunya-only infection.

	Chikungunya-only infection (n = 105)		Preceding dengue infection (n = 57)		Adjusted	Adjusted
	n	n	n	(%)	OR[a] (95% CI)	p-value[a]
Joint pain in the …						
upper extremities	45	(42.9)	24	(42.1)	0.80 (0.40–1.59)	0.525
lower extremities	42	(40.0)	31	(54.4)	1.65 (0.84–3.24)	0.148
Back/neck	31	(29.5)	17	(29.8)	0.92 (0.44–1.91)	0.826
Weakness in the …						
upper extremities	39	(37.1)	23	(40.4)	0.98 (0.49–1.95)	0.943
lower extremities	69	(34.3)	25	(43.9)	1.39 (0.70–2.74)	0.351
back/neck	26	(24.8)	15	(26.3)	0.95 (0.44–2.06)	0.902
Myalgia[b]	31	(29.8)	23	(40.4)	1.36 (0.67–2.74)	0.394
Fatigue	35	(33.3)	21	(36.8)	1.15 (0.58–2.31)	0.686
Insomnia	29	(27.6)	21	(36.8)	1.47 (0.72–3.01)	0.292
Sombreness	16	(15.2)	10	(17.5)	1.02 (0.42–2.51)	0.958
Loss of vitality	26	(24.8)	18	(31.6)	1.21 (0.58–2.56)	0.610
Numbness	13	(12.4)	12	(21.1)	1.74 (0.66–3.68)	0.225
Paraesthesia	13	(12.4)	11	(19.3)	1.40 (0.56–3.51)	0.474
Nausea	16	(15.2)	6	(10.5)	0.58 (0.21–1.67)	0.312
Vomiting	4	(3.8)	1	(1.8)	0.42 (0.04–4.24)	0.460
Abdominal pain[b]	9	(8.7)	7	(12.3)	1.22 (0.40–3.70)	0.731
Skin diseases	8	(7.6)	5	(8.8)	1.12 (0.33–3.78)	0.856
Hair loss	11	(10.5)	6	(10.5)	0.90 (0.31–2.64)	0.851

*Fisher's exact test.

[a] p-value and OR corresponds to the comparison of 'preceding dengue infection' vs. 'chikungunya-only infection', adjusted for age and concomitant diabetes mellitus and cardiovascular disease.

[b] Total of 'chikungunya-only infection' group: n = 104.

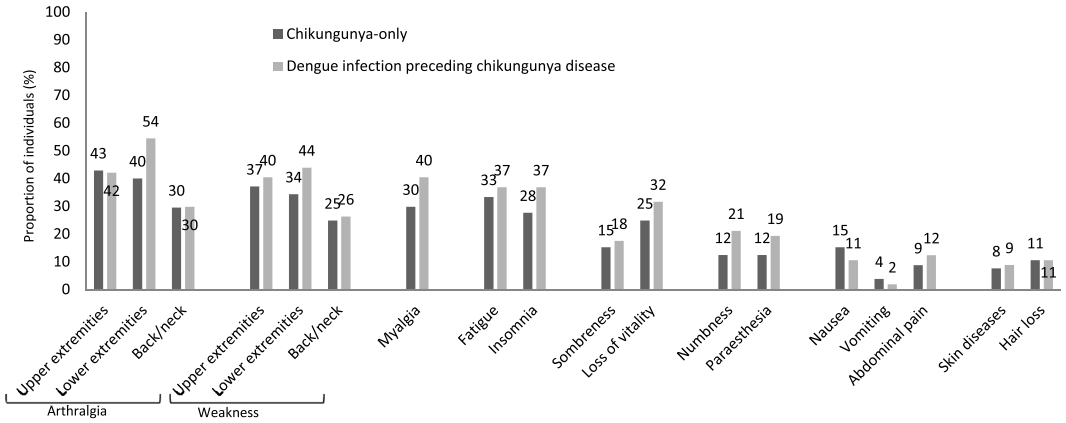

Fig. 2. Chronic chikungunya clinical presentation: Chikungunya-only infection vs. preceding dengue infection.

dengue disease manifestations were not assessed in this study, they have been described during co-infection with chikungunya [17]. Under which circumstances these sequelae present might be understood through further research regarding (pathophysiology of) chikungunya and (preceding) dengue (co-)infections. For example, clinical manifestations might be influenced by order of infection or viral load of the two viruses.

The high incidence of dengue infection preceding chikungunya disease and the presence of concurrent infection advocate for a critical clinical assessment of patients presenting with fever-like diseases in a chikungunya epidemic against the backdrop of a high dengue endemicity. As co-infections are not easily distinguishable from chikungunya-only infections based on acute clinical presentation, concomitant dengue might be missed in diagnosis. In the latter case, dengue disease can still develop into severe disease conditions. Hence, when a patient presents with acute fever in an area where dengue and chikungunya circulate, it is important to perform laboratory diagnosis to confirm presence of these viruses. Additionally, this will provide valuable information for further chronic disease development, as patients with preceding dengue infection and chikungunya disease might have higher chances to develop a severe long-term disease associated with decreased long-term quality of life [18].

This study described several risk factors for prolonged and severe long-term chikungunya sequelae. Furthermore, it presents clinical presentation of preceding dengue infection with chikungunya and suggest that there might be a link between preceding dengue infection and aggravated chronic sequelae. However, considering the limitations of this study, this possible link should be further investigated before a conclusion can be drawn. The possible consequences, but little knowledge on the consequences of the ongoing spread of these viruses, raise an urgent call to investigate the clinical presentation and pathophysiology of co-circulating (i.e. chikungunya, dengue and Zika) arboviruses.

Conflicts of interest

All authors declare no conflicts of interest.

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Appendix A

The analysis performed in this document includes also the subjects who were not serologically assessed for dengue. This group was included in the 'Chikungunya infection'-group, and concerned 137 individuals (of which 65 had data available on acute disease presentation) (See flowchart in Fig. 1). The remaining individuals were classified as was described in the main manuscript. At interpretation of these data, this limitation should be taken into account.

Table A1
Univariate analysis of acute clinical presentation chikungunya, comparing individuals with vs. without preceding dengue infection.

	Chikungunya infection (n = 123)		Preceding dengue infection and chikungunya (n = 36)		Adjusted OR[a] (95% CI)	Adjusted p-value[a]
	n	(%)	n	(%)		
Acute symptoms (n)[b]						
Fever (n = 117; n = 36)	109	(93.2)	32	(88.9)	0.71 (0.19–2.63)	0.603
Headache (n = 122; n = 36)	97	(79.5)	30	(83.3)	1.36 (0.50–3.72)	0.364
Orbital pain (n = 116; n = 35)	71	(61.2)	21	(60.0)	0.92 (0.42–2.03)	0.841

(*continued on next page*)

Table A1 (*continued*)

	Chikungunya infection (n = 123)		Preceding dengue infection and chikungunya (n = 36)		Adjusted OR[a] (95% CI)	Adjusted p-value[a]
	n	(%)	n	(%)		
Myalgia (n = 121; n = 35)	112	(92.6)	34	(97.1)	4.33 (0.48–39.50)	0.193
Arthralgia (n = 121; n = 36)	115	(95.0)	34	(94.4)	1.11 (0.20–6.20)	0.904
Arthritis (n = 114; n = 35)	66	(57.9)	26	(74.4)	1.96 (0.83–4.63)	0.126
Rash (n = 121; n = 35)	53	(43.8)	15	(42.9)	1.12 (0.51–2.46)	0.782
Nausea/vomiting (n = 121; n = 36)	41	(33.9)	12	(33.3)	0.96 (0.43–2.16)	0.927
Diarrhoea (n = 120; n = 36)	26	(21.7)	7	(19.4)	0.95 (0.37–2.47)	0.923
Cold shivers (n = 119; n = 36)	55	(46.2)	17	(47.2)	1.04 (0.48–2.25)	0.917
Cough (n = 121; n = 35)	22	(18.2)	2	(5.7)	0.25 (0.05–1.15)	0.075
Haemorrhagic tendencies (n = 121; n = 35)	4	(3.3)	0	(0.0)	–	0.575*
Icterus (n = 120; n = 35)	1	(0.8)	1	(2.9)	1.14 (0.06–21.87)	0.929

*Fisher's exact test.
[a]p-value and OR corresponds to the comparison of 'preceding dengue infection and chikungunya' vs. 'chikungunya infection', adjusted for comorbid diabetes mellitus.
[b]Number of subjects in the 'chikungunya' infection group and the 'preceding dengue infection and chikungunya' group, respectively.

Table A2
Analysis of possible confounders on acute and chronic clinical disease presentation.

	Sample with clinical data on acute disease presentation					Total sample				
	Chikungunya infection (n = 123)		Preceding dengue infection and chikungunya (n = 36)		p-value[a]	Chikungunya infection (n = 242)		Preceding dengue infection and chikungunya (n = 57)		p-value[a]
	n	(%)	n	(%)		n	(%)	n	(%)	
Age										
18–40	28	(22.8)	6	(16.7)		57	(23.6)	9	(15.8)	
41–60	71	(57.7)	24	(66.7)		117	(48.3)	37	(64.9)	
> 61	24	(19.5)	6	(16.7)	0.614	68	(28.1)	11	(19.3)	0.079
Sex										
Male	29	(23.6)	9	(25.0)		67	(27.7)	12	(21.1)	
Female	94	(76.4)	27	(75.0)	0.860	175	(72.3)	45	(78.9)	0.307
Co-morbidity										
Joint disease	16	(13.0)	6	(16.7)	0.588*	31	(12.8)	10	(17.5)	0.350
Cardiovascular disease[c]	26	(21.1)	10	(27.8)	0.402	58	(24.0)	13	(22.8)	0.853
Neurologic disease	1	(0.8)	1	(2.8)	0.403*	8	(3.3)	3	(5.2)	0.444*
Diabetes mellitus	9	(7.3)	8	(22.2)	**0.026***	27	(11.2)	11	(19.3)	0.097

*Fisher's exact test.
[a]p-value corresponds to the comparison between the groups 'chikungunya infection' and 'preceding dengue infection and chikungunya'.
[c]Cardiovascular disease group includes hypercholesterolemia and hypertension.

Table A3
Chronic chikungunya clinical presentation: preceding dengue infection and chikungunya vs. chikungunya infection.

	Chikungunya infection (n = 242)		Preceding dengue infection and chikungunya (n = 57)		Adjusted	Adjusted
	n	(%)	n	(%)	OR[a] (95% CI)	p-value[a]
Joint pain in the …						
upper extremities	106	(43.8)	24	(42.1)	0.78 (0.42–1.43)	0.418
lower extremities	98	(40.5)	31	(54.4)	1.86 (1.02–3.40)	**0.044**
Back/neck	66	(27.3)	17	(29.8)	1.12 (0.58–2.14)	0.741
Weakness in the …						
upper extremities	84	(34.7)	23	(40.4)	1.06 (0.57–1.96)	0.852
lower extremities	77	(31.8)	25	(43.9)	1.71 (0.93–3.12)	0.083

(*continued on next page*)

Table A3 (*continued*)

	Chikungunya infection (n = 242)		Preceding dengue infection and chikungunya (n = 57)		Adjusted	Adjusted
	n	(%)	n	(%)	OR[a] (95% CI)	p-value[a]
back/neck	53	(21.9)	15	(26.3)	1.18 (0.60–2.32)	0.643
Myalgia[b]	80	(33.2)	23	(40.4)	1.32 (0.71–2.44)	0.379
Fatigue	73	(30.2)	21	(36.8)	1.30 (0.71–2.41)	0.400
Sleeplessness	63	(26.0)	21	(36.8)	1.64 (0.88–3.05)	0.121
Sombreness[b]	40	(16.6)	10	(17.5)	0.99 (0.45–2.17)	0.974
Loss of vitality	57	(23.6)	18	(31.6)	1.36 (0.71–2.59)	0.354
Numbness	38	(15.7)	12	(21.1)	1.30 (0.62–2.72)	0.490
Paraesthesia	24	(9.9)	11	(19.3)	1.85 (0.83–4.11)	0.130
Nausea	27	(11.2)	6	(10.5)	0.86 (0.33–2.23)	0.752
Vomiting[b]	8	(3.3)	1	(1.8)	0.42 (0.05–3.63)	0.432
Abdominal pain[b]	20	(8.3)	7	(12.3)	1.45 (0.56–3.73)	0.447
Skin diseases	15	(6.2)	5	(8.8)	1.37 (0.47–3.99)	0.567
Hair loss	25	(10.3)	6	(10.5)	1.00 (0.38–2.58)	0.991

*Fisher's exact test.

[a]p-value and OR corresponds to the comparison of 'preceding dengue infection and chikungunya' vs. 'chikungunya infection', adjusted for age and concomitant diabetes mellitus.

[b]Total chikungunya infection group n = 241.

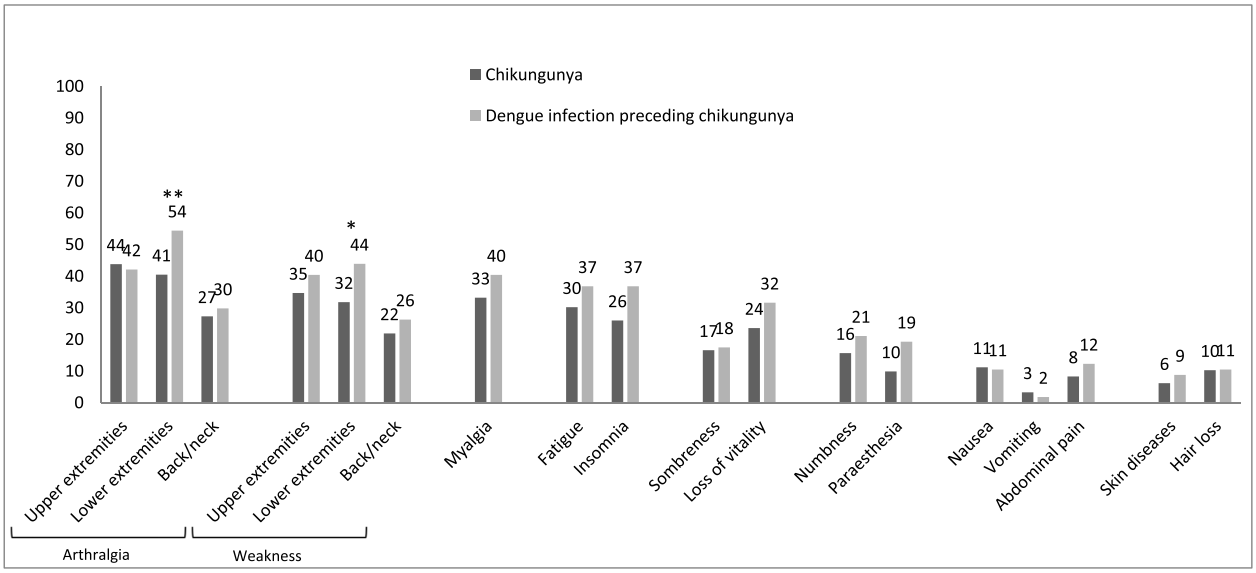

Fig. A1. Chronic chikungunya clinical presentation: Chikungunya infection vs. preceding dengue infection and chikungunya. **p < 0.050; *p= < 0.100.

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