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The Cost And Burden Of Chikungunya In The Americas

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Abstract

Background: Chikungunya virus (CHIKV) is a mosquito-transmitted virus that emerged in the Caribbean in late 2013 and proceeded to spread throughout the Americas. Acute CHIKV disease is characterized by high fever and potentially debilitating arthralgia. In a proportion of cases, serious long-term sequelae following acute disease have been reported. These conditions primarily include chronic inflammatory rheumatisms, but can also involve depression, sensorineural effects, headaches and cognitive delays following neonatal infection.

Methods: We developed data-driven computational simulation models for acute and long-term health conditions associated with CHIKV infection to estimate the economic cost and health burden of the 2013–2015 CHIKV epidemic in the Americas, accounting for underreporting of cases. We parameterized our models using clinical, epidemiological, and cost data which were collected through extensive literature review.

Findings: Accounting for underreporting, we estimated a total of over 39.9 million cases in the Americas, imposing a burden of over 23.8 million disability adjusted life years (DALYs) lost and about US$185 billion from a societal perspective. Burden and cost varied substantially by region, with the Caribbean accounting for nearly half of the entire disease burden and costs. Over 90% of DALYs and 95% of costs were attributable to chronic inflammatory rheumatism.

Interpretation: Given that there are no effective prevention methods or treatments for chikungunya, the emergence of CHIKV in the Americas creates a considerable strain on individuals and health systems, both currently and in the future. These results highlight the need for increased efforts in vector control to prevent new cases and in investigation into best practices for managing the growing burden of CHIKV-related long-term sequelae.

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Introduction

In late 2013, chikungunya virus (CHIKV) was reported in the Western Hemisphere for the first time, on the Caribbean island of St. Martin.[1] Transmitted predominantly by the *Aedes aegypti* and *Aedes albopictus* mosquitoes, the virus quickly spread throughout the Caribbean and the Americas. By the end of 2015, more than 1.8 million clinically suspected chikungunya cases in 45 countries and territories had been reported to the Pan American Health Organization (PAHO).[2]

Symptoms of acute infection with CHIKV frequently include fever, potentially debilitating arthralgia, and skin rash.[3] In rare instances, complications of acute disease may include myocarditis, Guillain-Barré Syndrome, mild hemorrhage, and encephalitis.[4] Death in association with CHIKV infection is very rare (<0.1% of hospitalized cases), and is more likely to be associated with exacerbation of pre-existing chronic medical conditions.[5] However, long-term morbidity associated with CHIKV infection can be substantial, as 12.7–63.8% of those with symptomatic chikungunya report experiencing chronic inflammatory rheumatism, including chronic arthritis and arthralgia, beyond the scope of acute infection.[5–15] These symptoms can last months to years post-acute infection, in rare cases lasting as long as six years.[16] Though less established, CHIKV patients have reported increased rates of depression (7–19%),[7,9,13,15] hearing loss and blurry vision (5–24%),[7–9,16] and headaches, dizziness, memory and concentration problems (6–22%) beyond the scope of acute infection.[7–9]

Mother-to-child transmission of CHIKV has been observed among pregnant women having symptom onset during the intrapartum period, ±2 days from delivery; the vertical transmission rate for these women has been reported to be 49%.[17] While infection early in pregnancy does not appear to impact fetal development, neonatal infection with CHIKV is associated with both severe acute symptoms and the possibility of long-term developmental delays. Severe acute symptoms include encephalopathy (36–47%),[17,18] thrombocytopenia (89%),[17] febrile seizures,[19] and blistering hyperpigmented rash.[20] Neonatal CHIKV infection is associated with delays in cognitive development in areas such as coordination, language, movement, and sociability.[18] Particularly poor outcomes are noted for neonates who develop encephalopathy during acute infection, with a proportion of these neonates developing conditions such as microcephaly (42%) or symptoms matching cerebral palsy (33%).[18]

These acute and long-term symptoms create a significant economic and disease burden for individuals, health systems and societies. There is currently no vaccine for CHIKV or any specific treatment; rather, at all stages of disease, guidelines direct physicians to treat symptomatically.[21] Acetaminophen or similar analgesics are typically used during acute infection. Treatments for chronic inflammatory rheumatisms can become costlier due to medications and duration and treatment: NSAIDs and first-line disease-modifying antirheumatic drug (DMARD) methotrexate are most commonly available in Latin America due to relatively low costs, but biologics, which are second-line DMARDs are more expensive and less widely accessible.[22–24] Beyond the direct costs of medication, several indirect costs are accrued by acute and chronic chikungunya: days of missed work due to illness, decreased productivity while at work due to disability, transportation to health providers, among others.

Here, we estimate both the burden of disease and the cost of the introduction of CHIKV to the Americas. Similar studies have projected the cost of disease in previous outbreaks in La Réunion Island,[25] in Andhra Pradesh, India,[26] and in Colombia during the epidemic in the Americas.[27] The 2014 burden of disease due to chronic inflammatory rheumatism in Latin America has been estimated to 151,031–167,950 disability adjusted life years (DALYs),[28] but this estimate did not account for underreporting, did not include the Caribbean, and did not take into consideration varying durations of sequelae. To our awareness, this is the first study to estimate both the burden and cost of the chikungunya epidemic in the Americas and the first to consider additional sequelae beyond chronic inflammatory rheumatism in calculating the burden of disease.

Methods

We developed data-driven computational simulation models to evaluate the economic cost and disease burden for chikungunya in the Americas based on cases reported from 2013–2015, accounting for underreporting of disease. For our estimates, we used case counts per country as reported by the Pan American Health Organization (PAHO), which are derived from member state publications or websites, or from reports from International Health Regulation (IHR) National Focal Points (NFP). Confirmed, suspected and imported cases for each country were included in our analysis. Confirmed cases tested positive by viral isolation, RT-PCR, anti-CHIKV IgM detection, or a four-fold increase of anti-CHIKV IgG titers. Suspected cases included patients with acute onset fever >38°C and severe arthritis or arthralgia not explained by other conditions, and who reside or had visited an area with CHIKV circulation within two weeks of symptom onset.[2,29]

Accounting for Underreporting

Due to the novelty of chikungunya in the Americas, many jurisdictions did not previously have a surveillance system for chikungunya. Because of CHIKV's similar transmission patterns to dengue virus (DENV), in many instances, chikungunya surveillance was integrated into existing systems for dengue.[30–32] Due to absence of widespread data on the underreporting of chikungunya, we accounted for underreporting for chikungunya cases using previously recorded underreporting rates for dengue, which have varied from by region and time of analysis from 1–59.[33,34] We used an average expansion factor (EF) of 21.65 for our estimates, varying it between minimum and maximum reported EFs in our sensitivity analysis.

Estimation of Burden of Disease

For each estimated case that sought care in a country, an individual entered independent models where they encountered distributions of probabilities for being an ambulatory or hospitalized acute chikungunya case, and for developing chronic inflammatory rheumatism, depression, sensorineural problems, or persistent headaches. DALYs, which take into consideration the years of life lost (YLL) due to premature mortality and years lived with disability (YLD) from a health condition, were used as a measure of burden of disease. Due to the rarity of death from chikungunya, we focused our DALY estimates on YLD, which is calculated from a given disability weight (DW), years lived with condition, and incidence. We assigned a specific DW from the Global Burden of Disease (GBD) Study 2013 to calculate DALYs for acute illness, chronic inflammatory rheumatism, cognitive delays from neonatal CHIKV infection, depression, sensorineural effects and headaches (Table 1).[35] Duration of acute disease was sampled from a truncated exponential distribution with a median of 6.3 days and maximum of 21 days. To model the distribution of durations for all long-term sequelae aside from neonatal CHIKV, we fit regression models using data from published literature between the prevalence of the symptom and the study time-point post-acute disease.[36] The number of neonatal CHIKV infections were estimated using the country-specific birth rates, population sizes, and previously published prevalence of vertical transmission and lasting cognitive disabilities.[17,18] Country-specific average life spans were used for calculating duration of lasting cognitive disabilities.[37] DALYs were calculated for each condition using health state-specific DWs multiplied by duration of the condition.

Estimation of Costs

We calculated total societal costs for acute illness, chronic inflammatory rheumatism and cognitive delays from neonatal infection. We estimated both direct costs from medical treatment and indirect costs from either missed work or decreased productivity at work due to disability. We did not calculate costs associated with depression, sensorineural problems, and persistent headaches, as insufficient data is available in terms of care-seeking behaviors and treatment options for these conditions in relation to CHIKV. Each individual in our models encountered distributions of probabilities for all treatment events, and all distributions of durations were estimated using the same methods as used for DALY calculations. For ambulatory acute chikungunya cases, we assumed individuals incurred costs from an outpatient doctor visit, and acetaminophen (4g/day) for each day of illness.[21] Hospitalized acute chikungunya cases incurred costs of hospitalization per day for their length of stay,[13,30,38] as well as cost of acetaminophen (4g/day) for their duration of illness.[21]

The treatment for chronic inflammatory rheumatism was dependent on the duration of pain. All chronic inflammatory rheumatisms lasting less than three months accrued costs of NSAIDs (celecoxib 200mg/day or ibuprofen 1200 mg/day).[22] Although methotrexate, a first-line DMARD, is recommended for CHIKV-related arthritis lasting beyond three months,[22] we took into consideration structural delays in accessing treatment from a rheumatologist in Latin America, as described for other joint-related symptoms, such as rheumatoid arthritis.[16,39,40] Additionally, we attempted to take into consideration lack of availability to biologics as a second-line treatment, as previously reported in Latin America.[40] If individuals had chronic inflammatory rheumatism that persisted past when they were able to seek rheumatic care and that was beyond three months, they entered one of three pathways: continuing daily NSAID use, switching to methotrexate (15mg/week) with a supplement of folic acid (1mg/day),[16,22] or beginning using methotrexate for at least three months but switching to biologics due to failed methotrexate treatment (Figure 1).[16,22] All cases with chronic inflammatory rheumatism lasting three months or longer who also accessed rheumatic care received a diagnostic x-ray and incurred costs of rheumatologist visits.[22]

Country-specific costs were used in estimating distribution of costs for medical services. Using available data, regression models were fit between country GDP per capita and cost of medical service,[41] and these models were used to predict cost for countries for which cost data was not available. Due to the lack of correlation between cost of medications and GDP per capita, an average cost of each medication was taken and used for all countries (Table 1). Costs associated with neonatal infection were estimated using previously reported costs for cerebral palsy in the United States, and converted into respective country costs by region using comparative purchasing power parities.[42,43] We used average country monthly wage to estimate indirect costs,[44] and used estimates for rheumatoid arthritis to predict decreases in productivity and missed work for chronic inflammatory rheumatism.[45–48]

Each input parameter distribution was randomly sampled and events executed for the total number of estimated cases in each country. The simulation was run 1,000 times for each country. Simulations were performed in R version 3.2.2 and package rworldmap was used for mapping.[49,50] All costs are reported in March 2016 US dollars.

Results

We estimate approximately 39.9 million (range: 1.8–108.9 million) CHIKV cases in the Americas from 2013–2015, based on PAHO case reports and EF=21.65 (range: 1–59). Our simulations projected that the emergence of chikungunya in the Americas has caused 23,824,464 DALYs and has created a total cost of $185 billion from a societal perspective, including $83.6 billion in direct costs and $101.4 billion in indirect costs. On average, chronic inflammatory rheumatism was the source of 91.0% of DALYs, 96.5% of direct costs, and 94.4% of indirect costs. Indirect costs accounted for 54.9% of total costs. The region with with highest burden of both cost and disease was the Caribbean, which accounted for 46.4% of total DALYs lost, and 49.0% of total costs (Figure 2).

Estimation of Direct and Indirect Costs

The total societal cost in the Caribbean was $90.7 billion (range: $87.5–$94.0 billion), in the Andean region was $55.4 billion (range: $54.2–$56.8 billion), in Central America was $33.8 billion (range: $32.4–$35.1 billion), in the Southern Cone was $2.7 billion (range: $1.6–$2.9 billion) and in North America was $2.4 billion (range: $2.1–$2.7 billion) (Table 2). The countries with the highest total cost were Colombia ($45 billion, range: $44.3–$45.7 billion), the Dominican Republic ($43.9 billion, range: $43.3–$44.6 billion), and El Salvador ($15.2 billion, range: $14.8–$15.6 billion). The Caribbean accounted for 49.0% of all costs, the Andean region accounted for 30.0%, Central America accounted for 18.3%, the Southern Cone for 1.4% and North America for 1.3%.

The per-capita cost for chikungunya in Central America was $737 (range: $709–$762), in the Caribbean was $2,042 (range: $1,981–$2,105), in the Southern Cone was $10 (range: $9–$11), in the Andean region was $404 (range: $395–412) and in North America was $5 (range: $4.50–$5.40). Countries and territories with the highest per-capita costs were Saint Barthelemy, Martinique, and Guadeloupe (Supplementary Table 1).

Estimation of Disease Burden in DALYs

The average burden of disease was 0.60 (95% Confidence Interval [CI]: 0.41–0.83) DALYs per case. The average societal burden of disease was 2,432 (95% CI: 1,656–3,390) DALYs per 100,000 population, but this varied greatly by region: 24,882 (95% CI: 16,938–34,678) DALYS per 100,000 population in the Caribbean, 11,440 (95% CI: 7,788–15,943) DALYs per 100,000 population in Central America, 5,094 (95% CI: 3,468–7,100) per 100,000 population in the Andean region, 122 (95% CI: 83–170) per 100,000 population in the Southern Cone, and 41 (95% CI: 28–57) per 100,000 population in North America (Figure 2). The countries with the highest disease burden per population were Saint Barthelemy, Martinique, and Guadeloupe—all in the less Antilles of the Caribbean. Chronic inflammatory rheumatism was the overwhelming source of DALYs from chikungunya, as 91.0% of all DALYs were associated with this condition

Total DALYs lost also varied by region: we projected 11,050,521 (95% CI: 7,522,687−15,400,992) DALYs in the Caribbean, 6,998,121 (95% CI: 4,763,998−9,753,169) DALYs in the Andean region, 5,247,959 (95% CI: 3,572,569−7,313,995) DALYs in Central America, 331413 (225,610−461,884) DALYs in the Southern Cone, and 196,451 (95% CI: 133,822−273,632) DALYs in North America (Table 3).

Burden and Cost of Neonatal Infection

We estimate approximately 801 cases of neonatal CHIKV through vertical transmission, of which 291–379 will develop neonatal encephalopathy in the Americas. Among those with neonatal encephalopathy, 97–126 will experience lasting disability similar to cerebral palsy, with impacts on their movement, motor skills, and possibly intellectual capabilities. The total lifetime cost from a societal perspective for these sequelae is estimated to be $63.3 million (range: $59.4–$77.3 million). The total burden of disease associated with long-term sequelae from neonatal infection is 3,707 (95% CI: 2,511–5,013) DALYs.

Sensitivity Analysis

Varying the cost of drugs from the minimum to maximum drug prices resulted in a 18.7% decrease and 11.9% increase in overall costs, respectively. Varying the expansion factor to EF=1 led to a decrease in cost and DALYs lost by 95.4%, and EF=59 led to an increase in cost and DALYs by 172.5%.

Discussion

Our computational simulation model uses data collected from an extensive literature review to reveal the substantial economic and disease burden of the introduction and continued spread of CHIKV in the Americas: we estimate a societal cost of $185 billion and a burden of 23.8 million DALYs through the end of 2015. Chronic inflammatory rheumatism was the source of the vast majority of cost and DALYs lost. Geographically, we project that the Caribbean region bears nearly half of all cost and burden associated with the epidemic, followed by the Andean region and Central America. Not only has the chikungunya epidemic in the Americas created a strain on health systems, but our per-case estimates indicate that chronic chikungunya conditions may continue to place substantial strains on individuals, even in lower levels of CHIKV transmission.

The association between acute CHIKV infection and chronic inflammatory rheumatism and neonatal encephalopathy has been well-established in the literature. While we estimated that only 97–126 children throughout the Americas will develop lasting disabilities from neonatal infection, these sequelae accounted for a societal cost of $63.3 million (range: $59.4–$77.3 million), which is over $610,000 per case. While disability from neonatal CHIKV is a rare outcome among vertically transmitted CHIKV cases, it is severe, costly, and warrants increased attention. The links between depression, sensorineural problems and cerebral effects have been reported multiple times, but are less thoroughly established. We included them in our analysis in order to provide as comprehensive of an investigation into the burden of CHIKV as possible, but further investigation is needed to better understand the relationship between these conditions and CHIKV. We estimated that depression associated with chikungunya infection accounts for about 8% of total DALYs, but we do not know if this may arise independently of or synergistically with chronic inflammatory rheumatism. While no specific links have been drawn between CHIKV-associated chronic inflammatory rheumatism and depression, past research has reported positive correlations between depression and rheumatic disorders.[51,52]

Our estimates for both cost and DALYs lost due to chikungunya are higher than previous cost-of-illness studies in previous outbreaks. We believe this is due to our accounting for underreporting, our inclusion of other sequelae beyond chronic inflammatory rheumatism, and our use of distributions for the durations and prevalence for chronic sequelae, all of which have not been performed in prior estimates. In an outbreak in Andhra Pradesh, India, burden of disease was estimated to be 0.03 DALYs per case, but the study reported that chronic joint pain affected only 4% of individuals lasting for a mean duration of 19 days.[26] Few economic and disease burdens have been estimated for the epidemic in the Americas, and those that have only capture the first year of virus transmission. For Latin America in 2014, one study suggested that 45.1–50.1% of 855,890 acute CHIKV cases developed chronic inflammatory rheumatism, creating 151,031–167,950 DALYs lost, or 0.39 DALYs per case.[28] Our per-case estimate of 0.60 DALYs is slightly higher, potentially due to our use of distributions of chronic rheumatism durations instead of a point estimate. Another study in Colombia in 2014 found that chronic rheumatic symptoms were responsible for at least 95% of total estimated costs, similar to our estimate of 91%.[27] However, because this study was conducted before the majority of cases in the country occurred, we find higher overall estimates for burden and costs.

The cost and burden of chikungunya proves to be substantial even in comparison to other major diseases in the Americas. The annual cost of dengue in the Americas has been estimated to be $2 billion per year, causing about 72,277 DALYs annually.[33] In just over two years of epidemic chikungunya transmission, the cost has been over 46 times that predicted cost of dengue in the same period, and over 150 times the number of DALYs, even though dengue's case fatality rate is higher than that of chikungunya. Chagas, a disease with a multi-year chronic phase, is estimated to account for approximately 806,170 DALYs and $627.5 million annually.[53] In countries eligible for the GAVI, the Vaccine Alliance, (Bolivia, Cuba, Guyana, Haiti, Honduras, and Nicaragua), it has been estimated that the impact of introducing a vaccine for human papilloma virus (HPV), vaccination would save 31,384 DALYS,[54] and for rotavirus vaccine would save 50,063 DALYs.[55] In these same countries, the burden of disease from chikungunya during this epidemic was projected to be 3.1 million (2.1–4.3 million) DALYs and cost to be $18.6 billion ($17.7–$19.5 billion). Given a sufficient susceptible population, future epidemics of chikungunya in the Americas or elsewhere may be possible, and ample efforts should be made for prevention measures for this costly disease.

It is likely that we underestimate the true cost and burden of chikungunya in the Americas. First, our model only included individuals who sought care for acute infection, omitting a potentially significant portion of infected individuals who chose not or were unable to seek medical care. Care-seeking behaviors have yet not been well documented for chikungunya: early investigations in Puerto Rico and Suriname recorded that 63% of CHIKV-positive and 79.5% of CHIKV-suspected participants sought care, respectively.[30,56] Care-seeking behavior can vary largely by region, environment, and economic status,[57] which interferes with the ability to accurately account for these variations across such a diverse region. Next, we may have underestimated total costs for medical services: we used values from the WHO-CHOICE project, which reports costs from the public sector per country,[38] excluding often higher costs from services used in the private sector, and we did not include costs that might be introduced from physical therapy, patient education, surgery or other related medical needs. Finally, we did not include costs of vector control, increased surveillance, or loses of tourism revenue, which are all potentially important arenas of cost from a society perspective.[58]

A major strength of our study was the consideration of sequelae beyond chronic inflammatory, such as cognitive delays from CHIKV-associated neonatal encephalitis. Furthermore, our use of distributions for prevalence and durations of sequelae allows us to model outcomes that reflect the uncertainty and variety of real-world disease progression scenarios. Our study also had several limitations. First, we did not differentiate between chronic arthralgia and arthritis in accounting for treatments for chronic inflammatory rheumatisms. While past studies assessing long-term effects of CHIKV infection did not differentiate between these two sequelae, the conditions do differ in prevalence and duration; arthritis is rarer than arthralgia, but often requires costlier treatments.[59] Therefore, by assessing the two in the same manner, we likely overestimate the true cost and burden of disease. There are also several limitations in using an average expansion factor for dengue in order to account for underreporting of chikungunya. The two diseases may have different reporting patterns for a variety of reasons: for instance, as a new disease to the region, chikungunya may be more likely to be under-recognized or misdiagnosed, doctors may not reliably report cases due to high patients loads, and there may be a lag or deficit in reporting chikungunya due to the novel nature of the surveillance system. Surveillance system structure varies substantially between and within countries, and using an average underreporting factors ignores that heterogeneity. Additionally, we did not account for over-reporting in our analysis, which may contribute to an overestimate of cost and burden of disease: as almost all countries report all suspected cases without laboratory confirmation, there are likely to be cases reported that are misdiagnosed as CHIKV. We assumed that the progression of treatment and medication choices and doses were the same for each country, which may not accurately reflect variations in treatment and prescription practices. Finally, estimates on a region or country scale overlook heterogeneity of burden or costs within countries.

As demonstrated by CHIKV, when novel viruses transmitted by the *Aedes aegypti* mosquito are introduced to the Americas, they have the potential to rapidly spread through immunologically naïve populations and create considerable economic costs and health burdens. Increased efforts to implement and design more effective vector control methods would curb the burdens created not only by CHIKV, but by DENV, zika virus, and other mosquito-borne pathogens yet to emerge or reemerge. Additional efforts to find alternative and less costly methods for treating or managing long-term pain caused by CHIKV infection remain important, given the high proportion of the population of the Americas experiencing sequelae currently or in the future.

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Tables and Figures

Table 1. Input parameters values and definitions.

Definition	Values	Distribution	References
Probabilities and Duration Distributions			
Length of Acute Illness	2–21 days	Truncated exponential, λ=0.143	[6,30,60]
Length of Hospitalization	3–15 days	Uniform	[13,30]
Probability of Hospitalization	0.13–0.15	Uniform	[14,30]
Probability of Chronic Inflammatory Rheumatism	0.1270–0.6383	Uniform	[5–15]
Probability of missing work during acute illness	0.52–1.00	Uniform	[61,62]
Decrease in productivity from chronic inflammatory rheumatism	0.07–0.25	Uniform	[45,46]
Time absent from work due to chronic inflammatory rheumatism (days lost per month)	0.2–0.344	Uniform	[47,48]
Probability of methotrexate failure and commencement of biologics	0.13	--	[16]
Probability of depression	0.07–0.19	Uniform	[7,13,63]
Probability of sensorineural problems	0.05–0.24	Uniform	[7–9,16]
Probability of headache	0.06–0.22	Uniform	[7–9]
Length of time to seeing rheumatologist post-acute disease	3–24 months	Uniform	[16,39]
Probability of access to biologics	0.6–1	Uniform	[40]
Probability of vertical transmission in a pregnancy	0.0025	--	[17]
Probability of developing severe neonatal encephalitis given infection	0.364–0.474	Uniform	[17,18]
DALY Calculations: Disability Weights (DW)			
Acute Illness (DW: Moderate Infectious Disease)	0.051 (95% CI: 0.032, 0.074)		[35]
Severe Acute Illness (DW: Severe Infection Disease	0.133 (95% CI: 0.088, 0.190)		[35]
Chronic Inflammatory Rheumatism (DW: Generalized moderate musculoskeletal disorder)	0.317 (95% CI: 0.216, 0.440)		[35]
Depression (DW: Major Depressive Disorder, Mild Episode)	0.145 (95% CI: 0.099, 0.209)		[35]
Sensorineural (DW: Moderate Hearing Loss)	0.027 (95%CI: 0.015, 0.042)		[35]
Persistent Headache (DW: Tension Type Headache)	0.037 (95% CI: 0.022, 0.057)		[35]
Neonatal infection-associated severe cognitive disability (DW: Motor and Cognitive Impairments Severe)	0.542 (95% CI: 0.374, 0.702)		[35]
Neonatal infection-associated moderate cognitive disability (DW: Motor and Cognitive Impairments Moderate):	0.203 (95%CI: 0.134, 0.290)		[35]
Medication Costs			
Acetaminophen cost per day (mean, range)	\$0.41 (\$0.04–\$1.32)		[64–69]

NSAIDs cost per day (mean, range)	$0.33 ($0.06–$0.60)		[64–67]
Methotrexate cost per week (mean, range)	$1.66 ($0.23–$4.26)		[64,65,67,68]
Folic Acid cost per day, (mean, range)	$0.07 ($0.02–$0.21)		[64,65,68]
Biologics cost per week (mean, range)	$491.51 ($283.58–$611.00)		[65]
Hospitalization Cost, per day	Country-specific		[38]
Cost per outpatient visit	Country-specific		[38]
Cost of x-ray	Country-specific		[70,71]
Cost of rheumatologist per year	Country-specific		[72,73]

Table 2. Region estimates for economic burden of chikungunya in the Americas (means and ranges).

Region	Direct Acute Costs	Direct Chronic Costs	Indirect Acute Cost	Indirect Chronic Costs	Perinatal Sequelae Costs	Total	Percent of Total Cost
Caribbean	$1,454,831,470 ($1,405,877,033–$1,505,423,710)	$37,879,718,000 ($35,596,085,500–$40,326,243,000)	$2,874,113,190 ($2,850,432,720–$2,900,830,410)	$48,459,792,000 ($47,614,675,000–$49,315,110,000)	$28,384,667 ($24,658,756–$32,110,578)	$90,696,839,327 ($87,491,729,009–$94,079,717,698)	49.0%
Central America	$315,068,079 ($308,361,490–$321,798,634)	$17,481,331,900 ($16,284,525,041–$18,569,874,000)	$896,405,120 ($890,258,460–$901,931,830)	$15,111,738,400 ($14,887,560,282–$15,291,774,100)	$17,707,949 ($15,383,516–$20,032,381)	$33,822,251,448 ($32,386,088,789–$35,105,410,945)	18.3%
Andean Region	$1,029,396,500 ($1,011,935,000–$1,045,309,900)	$23,405,410,000 ($22,399,965,000–$24,471,520,000)	$1,735,253,500 ($1,727,698,500–$1,743,667,000)	$29,257,400,000 ($28,980,390,000–$29,510,960,000)	$20,355,411 ($17,683,460–$23,027,363)	$55,447,815,411 ($54,137,671,960–$56,794,484,263)	30.0%
Southern Cone	$15,433,260 ($14,102,568–$16,623,200)	$1,124,117,000 ($131,279,638–$1,328,121,000)	$85,136,700 ($83,494,190–$86,596,900)	$1,434,858,000 ($1,386,642,900–$1,484,908,000)	$842,295 ($731,731–$952,859)	$2,660,387,255 ($1,616,251,027–$2,917,201,959)	1.4%
North America	$105,400,240 ($93,100,432–$118,170,280)	$745,272,000 ($599,815,890–$907,642,000)	$85,377,900 ($82,647,800–$88,084,800)	$1,439,025,000 ($1,346,193,600–$1,535,370,000)	$1,046,361 ($909,011–$1,183,712)	$2,376,121,501 ($2,122,666,733–$2,650,450,792)	1.3%
Total	$2,920,129,549 ($2,833,376,523–$3,007,325,724)	$80,635,848,900 ($75,011,671,069–$85,603,400,000)	$5,676,286,410 ($5,634,531,670–$5,721,110,940)	$95,702,813,400 ($94,215,461,782–$97,138,122,100)	$68,336,683 ($59,366,474–$77,306,892)	$185,003,414,942 ($177,754,407,518–$191,547,265,656)	
Percent of Total Cost	1.58%	43.59%	3.07%	51.73%	0.04%		

Table 3. DALYs by region and chikungunya-related condition for the Americas (means and 95% CI).

Region	Acute Illness	Chronic Joint Pain	Depression	Sensorineural	Cerebral	Perinatal Sequelae	Total	Percent of Total DALYs
Caribbean	26188 (16723–37807)	10056099 (6852106–13957993)	910216 (621458–1311966)	11080 (4431–21047)	46220 (27484–71208)	718 (486–971)	11050521 (7522687–15400992)	46.4%
Central America	12434 (7940–17951)	4774795 (3253488–6627476)	432338 (295183–623163)	5259 (2104–9993)	21930 (13040–33786)	1203 (815–1627)	5247959 (3572569–7313995)	22.0%
Andean Region	16579 (10587–23935)	6367138 (4338491–8837668)	576464 (393586–830903)	7012 (2805–13323)	29270 (17406–45098)	1658 (1123–2242)	6998121 (4763998–9753169)	29.4%
Southern Cone	785 (501–1133)	301527 (205457–418524)	27309 (18645–39362)	332 (133–631)	1384 (823–2132)	76 (51–102)	331413 (225610–461884)	1.4%
North America	473 (302–683)	181743 (123837–252262)	13147 (8976–18949)	201 (174–381)	835 (496–1286)	53 (36–71)	196451 (133822–273632)	0.8%
Total	56459 (36053–81510)	21681302 (14773380–30093922)	1959473 (1337847–2824344)	23884 (9646–45375)	99639 (59249–153510)	3707 (2511–5013)	23824464 (16218686–33203674)	
Percent of Total DALYs	0.24%	91.00%	8.22%	0.10%	0.42%	0.02%		

Figure 1. Model Diagram for the Progression of Treatment for Post-CHIKV Chronic Inflammatory Rheumatism.

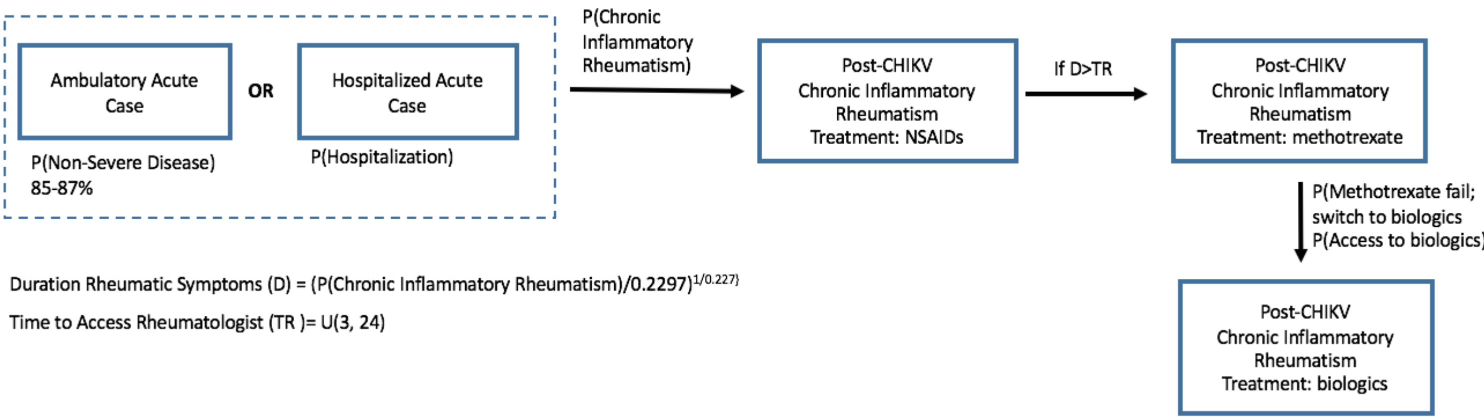
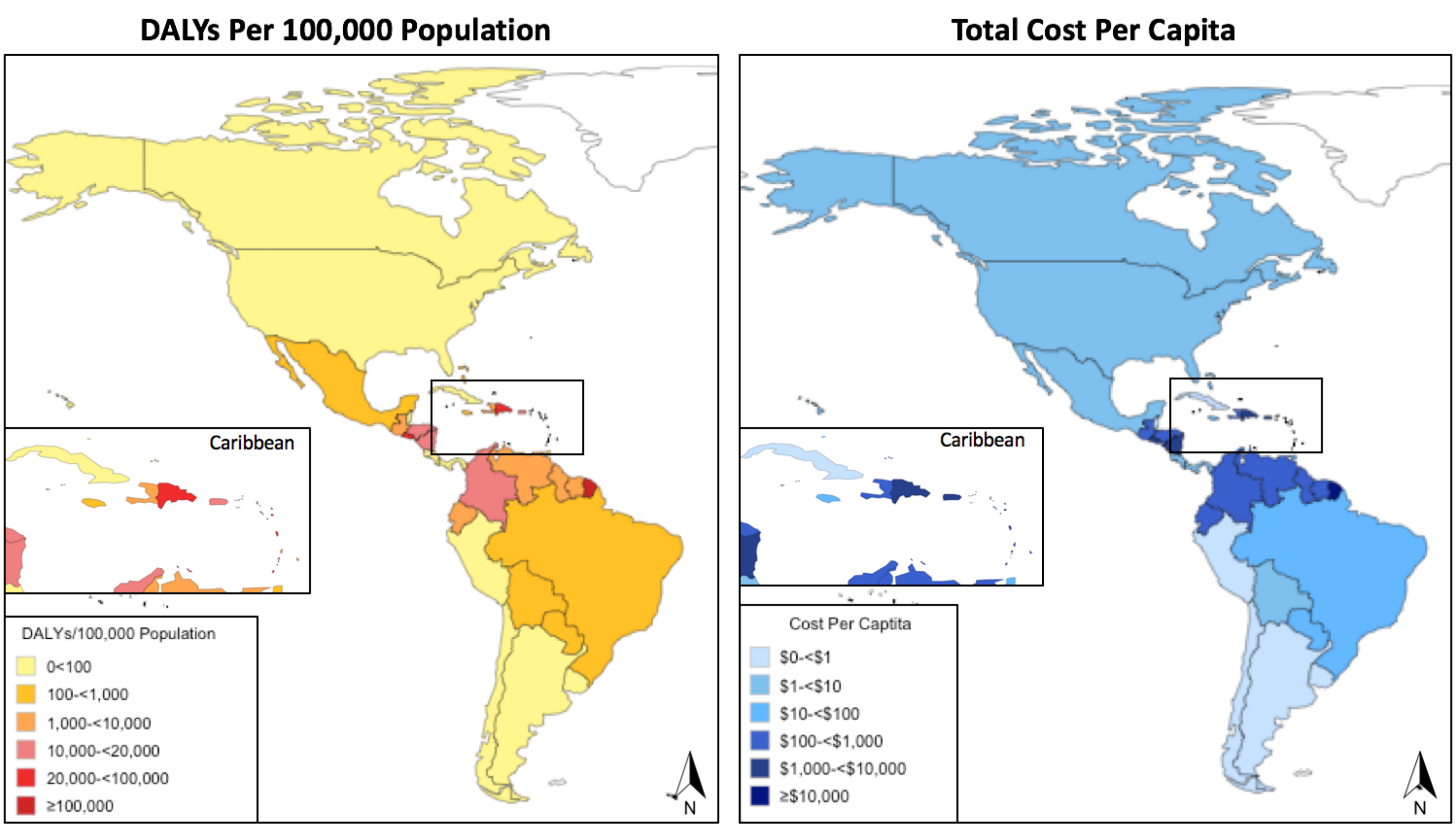


Figure 2. Maps of DALYs per population and cost per capita by country in the Americas from 2013–2015.



Supplementary Table 1. Country-specific estimates for economic cost and burden of disease in the Americas, 2013–2015.

Country	Total Cost	Total Costs Per Capita	Total Cost per Case	Total DALYs	Total DALYs per 100,000
Total Americas	**$184,945,005,700**	**$189**	**$4,628**	**23,824,464**	**2,432**
North America	**$2,375,166,000**	**$5**	**$7,091**	**196,451**	**41**
Bermuda	$5,816,000	$84	$20,662	164	236
Canada	$62,350,000	$2	$13,519	2,704	8
Mexico	$1,123,000,000	$9	$4,408	149,417	123
USA	$1,184,000,000	$4	$15,722	44,165	14
Central American Isthmus	**$33,802,188,700**	**$737**	**$3,841**	**5,247,959**	**11,440**
Belize	$258,700	$1	$3,983	38	11
Costa Rica	$32,290,000	$7	$5,232	3,681	75
El Salvador	$15,230,000,000	$2,386	$4,017	2,260,945	35,421
Guatemala	$5,119,000,000	$323	$3,922	778,595	4,909
Honduras	$7,222,000,000	$874	$3,676	1,171,706	14,184
Nicaragua	$6,171,000,000	$1,000	$3,574	1,029,819	16,696
Panama	$27,640,000	$7	$5,189	3,174	81
Andean Area	**$55,437,110,000**	**$404**	**$4,724**	**6,998,121**	**5,094**
Bolivia	$87,470,000	$8	$3,797	13,742	127
Colombia	$45,000,000,000	$920	$4,614	5,816,880	11,889
Ecuador	$3,246,000,000	$203	$4,448	435,244	2,723
Peru	$27,640,000	$1	$3,422	3,318	11
Venezuela	$7,076,000,000	$229	$5,788	728,937	2,363
Southern Cone	**$2,659,517,000**	**$10**	**$4,787**	**331,413**	**122**
Argentina	$11,220,000	$0	$6,243	1,072	3
Brazil	$2,261,000,000	$11	$4,915	274,371	136
Chile	$3,597,000	$0	$5,933	362	2
Uruguay	$0	$0	$0	-	-
Paraguay	$383,700,000	$55	$4,116	55,607	804
Caribbean	**$90,671,024,000**	**$2,042**	**$4,893**	**11,050,521**	**24,882**
Anguilla	$20,480,000	$1,280	$7,220	1,689	10,556
Antigua and Barbuda	$188,900,000	$2,076	$5,975	18,851	20,716
Aruba	$263,100,000	$2,381	$8,311	18,875	17,082
Bahamas	$18,190,000	$48	$7,778	1,395	365

Barbados	$257,800,000	$891	$6,370	24,136	8,337
British Virgin Islands	$89,030,000	$2,739	$10,436	5,088	15,657
Cayman Islands	$91,810,000	$1,669	$15,363	3,564	6,479
Curacao	$409,900,000	$2,779	$7,064	34,597	23,456
Dominica	$379,100,000	$5,193	$4,653	48,583	66,552
Grenada	$328,900,000	$2,990	$4,906	39,982	36,348
Guyana	$465,600,000	$579	$3,971	69,923	8,702
Jamaica	$244,200,000	$87	$6,231	23,384	836
Montserrat	$14,950,000	$2,990	$5,480	1,627	32,541
Saint Kitts and Nevis	$89,500,000	$1,755	$6,310	8,456	16,581
Saint Lucia	$89,950,000	$552	$4,705	11,401	6,994
Saint Vincent and the Grenadines	$136,900,000	$1,336	$4,539	17,988	17,549
Sint Maarten	$63,080,000	$1,577	$6,198	6,068	15,171
Suriname	$135,700,000	$250	$5,120	15,803	2,908
Trinidad and Tobago	$56,930,000	$42	$7,621	4,455	332
Turks and Caicos Islands	$5,201,000	$106	$9,238	335	684
US Virgin Islands	$414,500,000	$3,986	$10,415	23,732	22,819
Cuba	$1,903,000	$0	$4,394	258	2
Dominican Republic	$43,920,000,000	$4,172	$3,761	6,962,392	66,132
French Guiana	$3,423,000,000	$13,424	$6,937	294,238	115,387
Guadeloupe	$13,590,000,000	$29,038	$7,674	1,055,808	225,600
Haiti	$4,704,000,000	$450	$3,357	835,591	7,988
Martinique	$12,900,000,000	$31,891	$8,045	956,243	236,401
Puerto Rico	$6,957,000,000	$1,888	$8,984	461,774	12,535
Saint Barthelemy	$453,500,000	$50,389	$11,309	23,908	265,647
Saint Martin	$957,900,000	$26,608	$7,107	80,376	223,267