CORRESPONDENCE

Zika Virus and the Guillain–Barré Syndrome — Case Series from Seven Countries

TO THE EDITOR: Zika virus (ZIKV) disease had been described as a mild, self-limiting illness associated with fever, rash, joint pain, and conjunctivitis.[1] However, during the outbreak in French Polynesia, 42 patients with ZIKV disease were found to have the Guillain–Barré syndrome, which represented a marked increase from the approximately 5 cases detected annually during the previous 4 years.[2] A connection with the Guillain–Barré syndrome had previously been described in association with other flavivirus illnesses[3,4] but not with ZIKV infection.

From April 1, 2015, to March 31, 2016, a total of 164,237 confirmed and suspected cases of ZIKV disease and 1474 cases of the Guillain–Barré syndrome were reported in Bahia, Brazil; Colombia; the Dominican Republic; El Salvador; Honduras; Suriname; and Venezuela. To examine the temporal association between ZIKV disease and the Guillain–Barré syndrome, graphical and time-series analyses were applied to these two independent data sets, which were collected through official International Health Regulations channels or from ministry of health websites (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). The data obtained from country reports contained no personally identifiable information and were collected as part of routine public health surveillance; therefore, the analysis was exempt from review by an ethics board. Differences between the observed and expected numbers of cases of the Guillain–Barré syndrome during the ZIKV transmission period, as well as differences in the incidence of the Guillain–Barré syndrome and ZIKV disease according to age and sex, were analyzed with the use of Poisson regression models (see the Supplementary Appendix).

The analysis suggests that changes in the reported incidence of ZIKV disease during 2015 and early 2016 were closely associated with changes in the incidence of the Guillain–Barré syndrome. During the weeks of ZIKV transmission, there were significant increases in the incidence of the Guillain–Barré syndrome, as compared with the pre-ZIKV baseline incidence, in Bahia State (an increase of 172%), Colombia (211%), the Dominican Republic (150%), El Salvador (100%), Honduras (144%), Suriname (400%), and Venezuela (877%) (Table 1). When the incidence of ZIKV disease increased, so did the incidence of the Guillain–Barré syndrome (Fig. 1A). In the six countries that also reported decreases in the incidence of ZIKV disease, the incidence of the Guillain–Barré syndrome also declined. When the seven epidemics of ZIKV disease are aligned according to week of peak incidence, the total number of cases of ZIKV disease and the Guillain–Barré syndrome are closely coincident (Fig. 1B), although the period from acquiring infection to reporting disease is approximately 2 weeks longer for ZIKV than for the Guillain–Barré syndrome, a pattern that is especially visible in data from Colombia and Venezuela. Whether the 2-week difference can be explained in terms of incubation periods or reporting delays is not yet known. We explored the potential effect of dengue virus circulation on the incidence of the Guillain–Barré syndrome and found no link (see the Supplementary Appendix). In any event, we infer from these two series of cases,

Table 1. Expected and Observed Numbers of Cases of the Guillain–Barré Syndrome.*

Region	Population	Pre-ZIKV Period			ZIKV Transmission Period						
		Mean Annual Cases of GBS (95% CI)	Annual Cumulative Incidence of GBS (95% CI)	Expected Cases of GBS per Week (95% CI)	Period of ZIKV Circulation	Reported Cases of ZIKV	Date Range	Expected Cases of GBS (95% CI)	Reported GBS Cases	Increase from Pre-ZIKV Mean (95% CI)	Rate Ratio (95% CI)†
	no.	*no.*	*cases/100,000*	*no.*	*wk*	*no.*		*no.*	*no.*	*%*	
Bahia, Brazil	15,203,934	57 (37 to 77)	0.37 (0.30 to 0.46)	1.1 (0.72 to 1.47)	52	30,266	1/1/2015 to 12/31/2015	57 (37 to 76)	155	171.9 (100.7 to 268.4)	2.7 (2.0 to 3.7)
Colombia	49,529,208	242 (48 to 436)	0.49 (0.44 to 0.54)	4.7 (0.93 to 8.39)	22	68,118	11/1/2015 to 3/31/2016	103 (20 to 185)	320	210.7 (148.8 to 287.9)	3.1 (2.5 to 3.9)
Dominican Republic	10,652,135	73 (47 to 114)‡	0.69 (0.56 to 0.83)‡	1.40 (0.91 to 2.20)‡	13	1,416	1/1/2016 to 3/31/2016	18 (12 to 29)	45	150.0 (44.7 to 331.8)	2.5 (1.5 to 4.3)
El Salvador	6,426,002	170 (99 to 241)	2.65 (2.27 to 3.06)	3.3 (1.90 to 4.64)	28	11,054	9/18/2015 to 3/31/2016	92 (53 to 130)	184	100.0 (55.7 to 156.9)	2.0 (1.6 to 2.6)
Honduras	8,423,917	110 (83 to 137)	1.31 (1.08 to 1.57)	2.1 (1.59 to 2.64)	13	17,485	1/1/2016 to 3/31/2016	27 (21 to 34)	71	144.4 (68.8 to 309.6)	2.6 (1.7 to 4.1)
Suriname	548,456	4 (−1 to 10)	0.73 (0.24 to 1.73)	0.1 (−0.03 to 0.20)	28	3,097	9/20/2015 to 3/31/2016	3 (0 to 6)	15	400.0 (44.8 to 1627.1)	5.0 (1.5 to 17.3)
Venezuela	31,292,702	214 (139 to 336)‡	0.69 (0.60 to 0.78)‡	4.12 (2.67 to 6.46)‡	17	32,801	12/6/2015 to 3/31/2016	70 (45 to 110)	684	877.1 (664.1 to 1149.6)	9.8 (7.6 to 12.5)

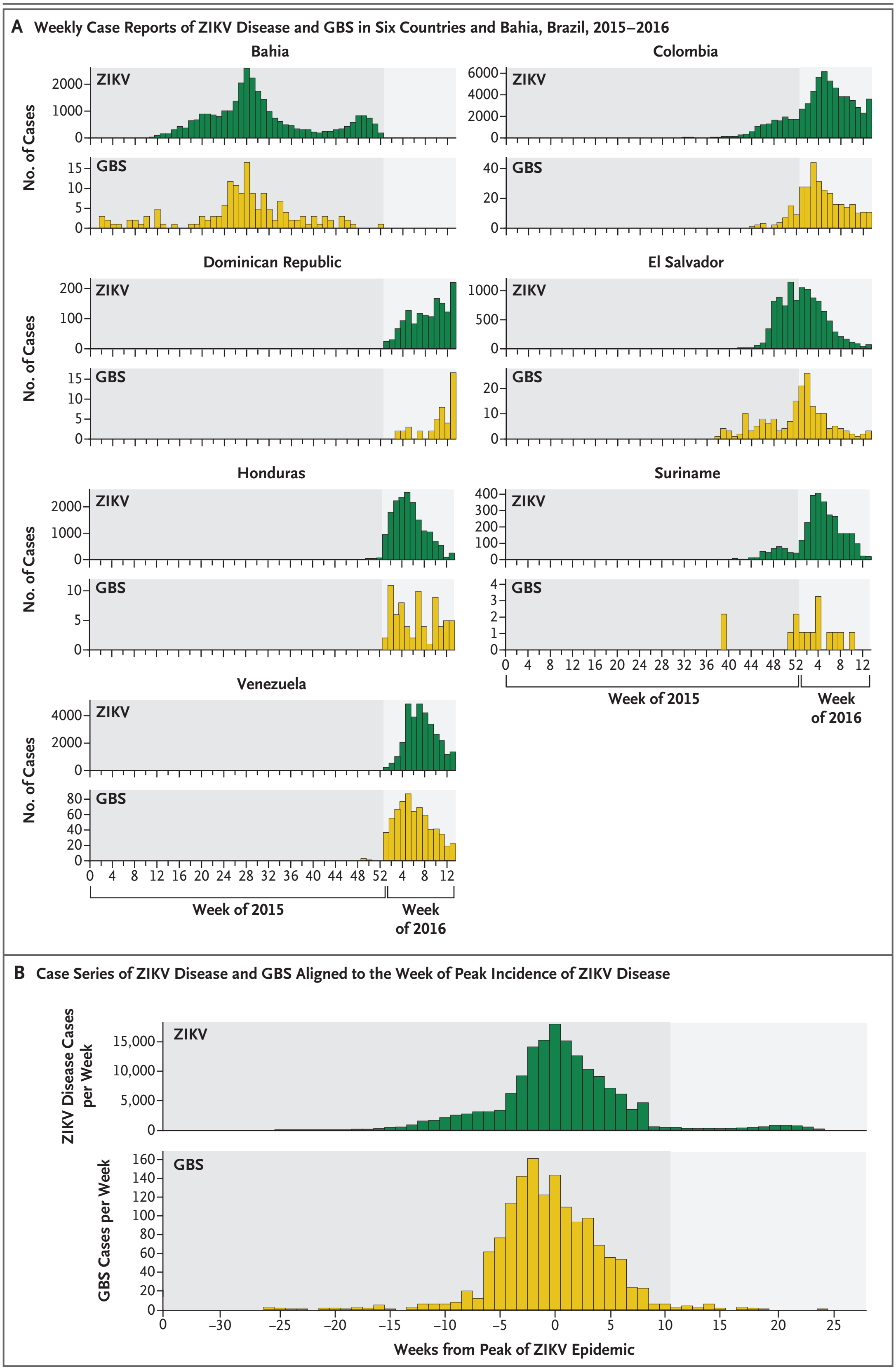
* CI denotes confidence interval, GBS the Guillain–Barré syndrome, and ZIKV Zika virus.
† Rate ratios are based on the incidence of GBS during the ZIKV transmission period as compared with that during the pre-ZIKV period.
‡ Values are estimates based on the median rates obtained from countries with information available.

Figure 1 (facing page). Cases of Zika Virus (ZIKV) Disease and the Guillain–Barré Syndrome (GBS).
Panel A shows weekly case reports of ZIKV disease and GBS in six countries and in Bahia, Brazil, 2015 to 2016. Panel B shows case series of ZIKV disease and GBS aligned to the week of peak incidence of ZIKV disease.

which were collected independently of each other, that ZIKV infection and the Guillain–Barré syndrome are strongly associated. Additional studies are needed to show that ZIKV infection is a cause of the Guillain–Barré syndrome.

Overall, females had a 75% higher reported incidence rate of ZIKV disease than did males (rate ratio, 1.75; 95% confidence interval [CI], 1.71 to 1.79); the rate was especially high among women 20 to 49 years of age (see the Supplementary Appendix). This difference was also observed in the Yap Island (Micronesia) epidemic[1] and could be due to greater exposure to the intradomiciliary mosquito vector, to more severe symptoms among women in this age group, to active health care–seeking behavior by females, or to enhanced reporting by health workers, given the risk of infection during pregnancy. However, the greater apparent risk of ZIKV disease among women 20 to 49 years of age was not matched by a similarly higher incidence of the Guillain–Barré syndrome, which may indicate an age and sex bias in the reporting of ZIKV disease. The reported incidence of the Guillain–Barré syndrome was 28% higher among males than among females (rate ratio, 1.28; 95% CI, 1.09 to 1.50) and consistently increased with age, findings that are in line with previous reports.[5]

Approximately 500 million people in Latin America and the Caribbean are at risk for ZIKV infection, because they live in areas that are less than 2000 m above sea level where competent aedes vectors also are found. It is clear that increases in the incidence of the Guillain–Barré syndrome to a level that is 2.0 and 9.8 times as high as baseline, as we have reported here, impose a substantial burden on populations and health services in this region. Reports of the Guillain–Barré syndrome could serve as a sentinel for ZIKV disease and other neurologic disorders linked to ZIKV, including microcephaly.


A Weekly Case Reports of ZIKV Disease and GBS in Six Countries and Bahia, Brazil, 2015–2016
Bahia
Colombia
Dominican Republic
El Salvador
Honduras
Suriname
Venezuela
No. of Cases
ZIKV
GBS
Week of 2015
Week of 2016
B Case Series of ZIKV Disease and GBS Aligned to the Week of Peak Incidence of ZIKV Disease
ZIKV Disease Cases per Week
GBS Cases per Week
Weeks from Peak of ZIKV Epidemic

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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2. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 2016;387:1531-9.
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4. Sejvar JJ, Bode AV, Marfin AA, et al. West Nile virus-associated flaccid paralysis. Emerg Infect Dis 2005;11:1021-7.
5. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barré syndrome worldwide: a systematic literature review. Neuroepidemiology 2009;32:150-63.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: dos Santos T, Rodriguez A, Almiron M, et al. Zika virus and the Guillain–Barré syndrome — case series from seven countries. N Engl J Med. DOI: 10.1056/NEJMc1609015

Zika virus and Guillain-Barré syndrome: case series from seven countries

Supplementary Appendix

Pan American Health Organization

Contents

1. Surveillance and Case Definitions

Zika virus disease

PAHO has been collecting data on confirmed and suspected cases of Zika virus disease from its Member States through official International Health Regulations (IHR) channels or from ministry of health websites, including the countries in this study. Zika virus disease was not a notifiable disease at the national level in Brazil until 17 February 2016, so there are no case counts for 2015. Since national data on cases of Zika virus disease were not systematically available, we restricted our analysis to the State of Bahia, which initiated mandatory notification of rash illness in April 2015.

Case definition for Zika virus disease. A suspected case is a patient with rash or elevated body temperature (> 37.2 °C) with at least one of the following symptoms not explained by other medical conditions: arthralgia or myalgia, non-purulent conjunctivitis or conjunctival hyperemia, headache or malaise. A confirmed case of Zika virus disease is a patient in whom the virus was identified by molecular or serologic methods.[1]

Guillain-Barré syndrome

Data for GBS are publically available for all states in Brazil via the Universal Health System online record of hospital discharges.[2] In the context of the ZIKV epidemic, Colombia, the Dominican Republic, El Salvador, Honduras, Suriname, and Venezuela have provided data on GBS through IHR channels. In the seven countries included in the study, GBS was not a notifiable condition for weekly reporting, therefore there is an unspecified delay involved in collecting data at the national level. Even though timeliness of reporting is affected by this delay, notifications are made by date of onset of symptoms, so they can be attributed retroactively to the epidemiological week when they occurred.

Case definitions for GBS used by countries in the Americas are based on the criteria outlined by the Brighton collaboration.[3] In the context of ZIKV transmission, however, reporting for GBS has been reviewed and revised in many countries. In the absence of established surveillance protocols specifically for Zika-associated GBS, data from the countries were slightly different, but all data sets included the total number of GBS cases detected. For all the countries included in this analysis, between 25% and 75% of GBS cases presented signs and symptoms compatible with Zika virus disease. In each country, at least one case of GBS was confirmed by laboratory means as having ZIKV infection since the introduction of the virus. The detection of cases of GBS per 1,000 cases of Zika virus disease detected by surveillance ranged from 4.1 (in Honduras) to 31.8 (in the Dominican Republic).

[1] Pan American Health Organization. Epidemiological Update: Zika virus infection, 16 October 2015 (http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32021&lang=en).
[2] Brazil Ministry of Health, Health indicators of hospital assistances. DATASUS (http://www2.datasus.gov.br/DATASUS/index.php).
[3] Kohl KS, Gidudu J, Bonhoeffer J, Braun MM, Buettcher M, Chen RT, et al. The development of standardized case definitions and guidelines for adverse events following immunization. Vaccine 2007;25:5671-4

2. Statistical Analysis

Cases of GBS and Zika virus disease per 100,000 population for the countries were calculated using the number of incident cases of GBS and Zika virus disease during the period of Zika virus circulation as the numerator and the annual mid-period population by age and sex (provided by the United Nations Population Division) as denominator.[4] We obtained baseline values for GBS incidence in each country by averaging observed rates of GBS in the years preceding the introduction of ZIKV. For countries (Dominican Republic and Venezuela) without historical GBS data available, we used the median rate reported for countries that did provide data. Using the baseline values, we also estimated how many cases would have been observed if the detection of GBS had remained constant for the period of ZIKV transmission and determined the percent increase in the detection of GBS based on the expected, baseline values. Statistical significance of this increase was conducted by testing the null hypothesis that there is no difference between the baseline values and the observed values of GBS during the period of Zika circulation at a level of $p<0.05$. A Poisson regression model was used to assess the ratio of cases of GBS per 100,000 population in the pre-Zika years compared with the number of cases of GBS for the period of known ZIKV circulation.

For the comparison of sex and age groups, a Poisson regression model was also used to fit the cases per 100,000 population of GBS and Zika virus disease as the response variable and sex and age groups as categorical covariates. The ratio of the rates of GBS per 100,000 population by sex and age group, including 95% confidence intervals (95% CI) and p-values, were also calculated, using the youngest age group as a reference.

3. Zika virus disease, Dengue fever, Chikungunya, and GBS

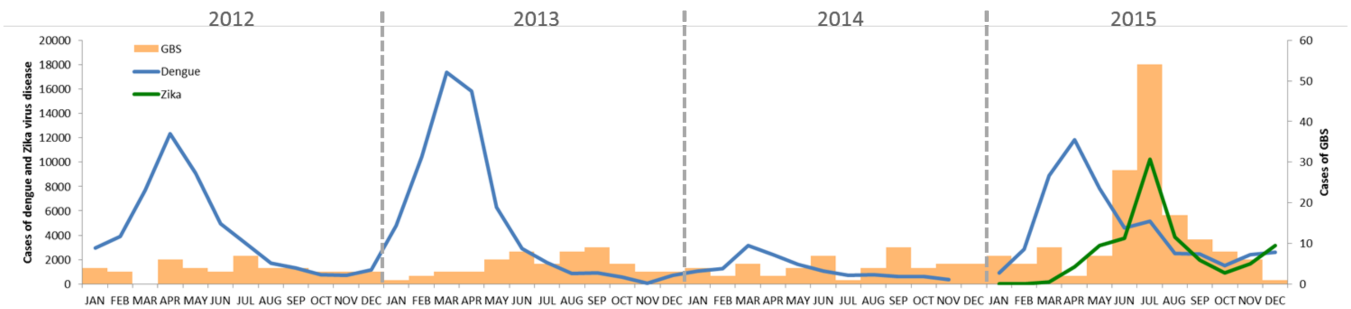
In the Brazilian State of Bahia no cases of GBS were identified during a second peak of Zika virus disease in December 2015 (Figure 1a, Research Letter). There are at least two possible explanations. First, there

[4] Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects: The 2012 Revision. (http://esa.un.org/unpd/wpp/index.htm).

were indeed cases of GBS, but they had not been reported by 31 March 2016. GBS is not a notifiable disease; and hospital discharges, including GBS cases, can be reported with delays of several months. A second possibility is that the increased incidence of illness in December 2015 was not due to ZIKV but rather to another arbovirus, such as dengue or chikungunya.

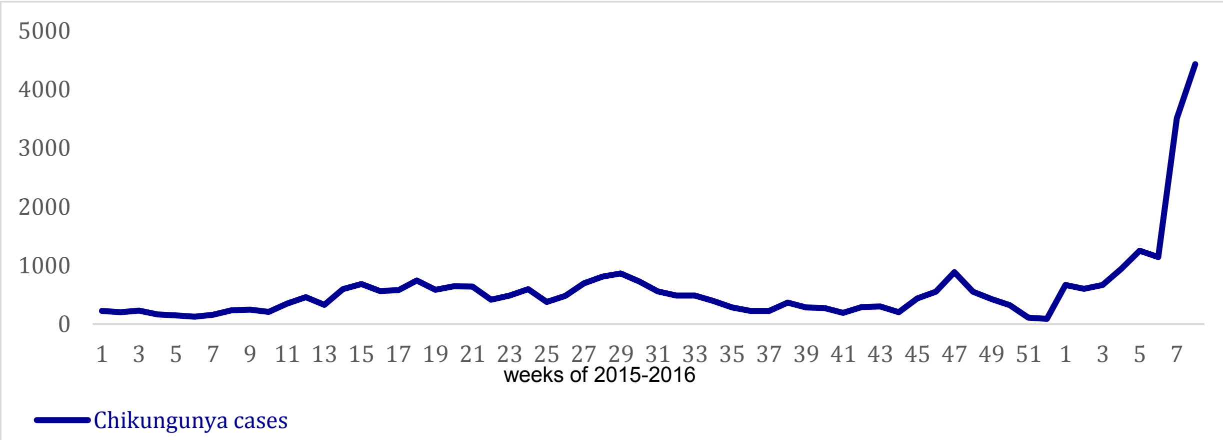
Figure S1 suggests that dengue fever is not the cause of the epidemics of GBS. The 2015 dengue epidemic in Bahia State, Brazil, preceded the Zika epidemic by approximately 17 weeks. It also shows that dengue started to increase in Bahia in December 2015.

Figure S1: Case series of dengue-like illness (blue line), Zika virus disease (green line), and Guillain-Barré syndrome (GBS, bars) in Bahia, Brazil, 2012-2015



Similarly Figure S2 shows that chikungunya started to increase in Bahia in December 2015. Both dengue and chikungunya coincided with the second peak of Zika virus disease, which suggest that cases of dengue and chikungunya may have been misclassified as Zika virus disease (no cases were confirmed as ZIKV) thereby the lack of concurrence between the observed second peak of Zika virus disease and GBS in Bahia in late 2015.

Figure S2 Cases of Chikungunya detected in the state of Bahia, Brazil, 2015.



In Honduras, a similar pattern was observed. Circulation of dengue fever in previous years (2010-2015), especially an epidemic year in 2010, did not appear to result in a corresponding increase in the cases of GBS detected (Figure S3). Furthermore, when dengue, zika, and GBS were plotted for the first 26 weeks of 2016, the peak of GBS coincided with the peak of Zika (Figure S4).

Figure S3: Case series of dengue-like illness (blue line) and Guillain-Barré syndrome (GBS, bars) in Honduras, 2010-2015

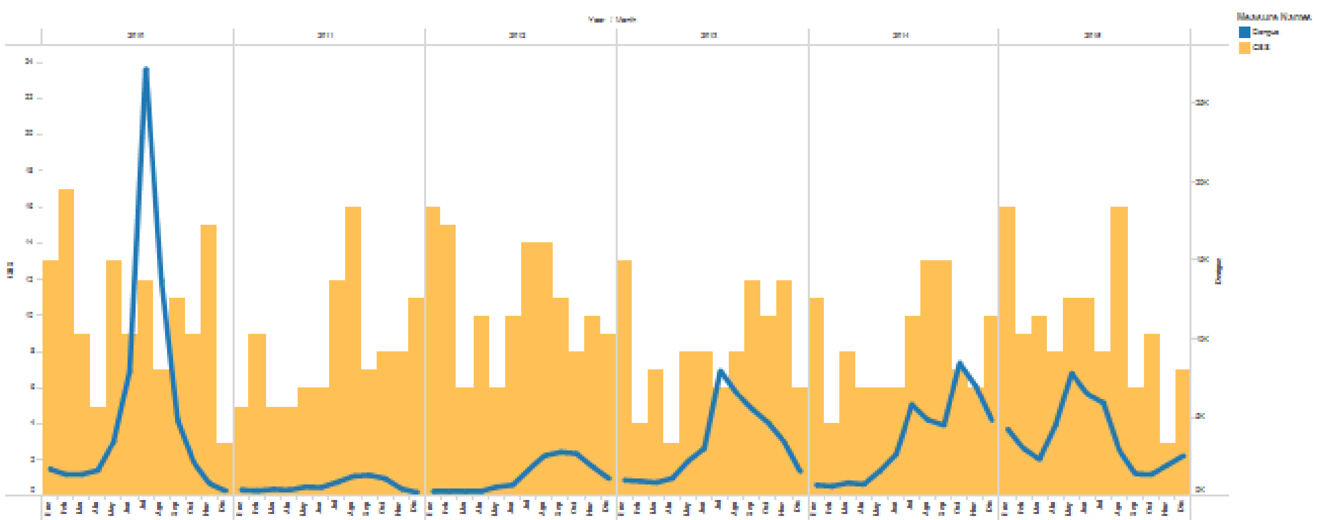
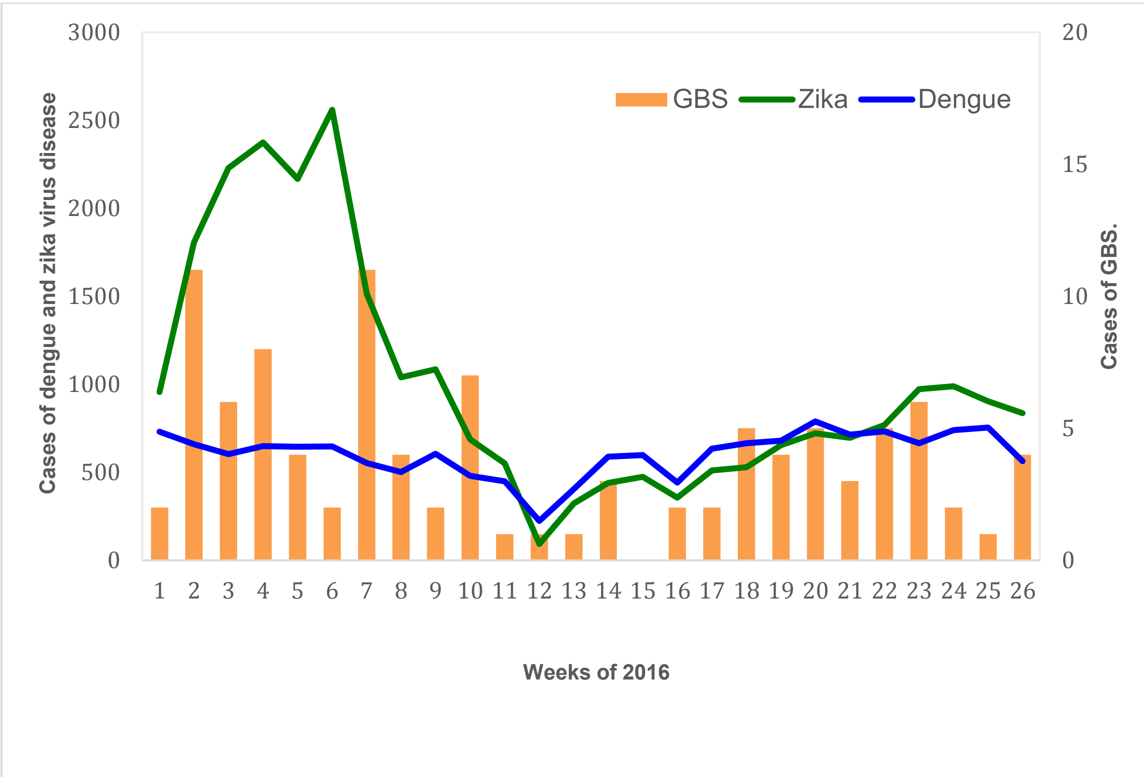


Figure S4: Case series of dengue-like illness (blue line), Zika virus disease (green line), and Guillain-Barré syndrome (GBS, bars) in Honduras, 2016



4. Patterns of Zika virus disease and Guillain-Barré syndrome by age and sex

Cases of Zika virus disease were reported by age and sex in Bahia State, Brazil, and in El Salvador. For GBS, age and sex data were available for Bahia State, Colombia, El Salvador, and Honduras. Sex was reported for 603 of the cases of GBS in these four settings, of which 55.2% were males. Table S1 shows the ratio of cumulative incidence of GBS and Zika virus disease, comparing the incidence among males and females.

Table S1. Rate Ration of Guillain-Barré Syndrome (GBS) and Zika incidence by gender.

		GBS		Zika		
Country or State	**Gender**	**Rate Ratio (95%CI)**	**P-value**	**Gender**	**Rate Ratio (95%CI)**	**P-value**
Bahia	Male	1.16 (0.85, 1.59)	0.3468	Male	-	-
	Female	-	-	Female	1.84 (1.80, 1.89)	<.0001
Colombia	Male	1.37 (1.11, 1.70)	0.0033	-	-	-
	Female	-	-	-		-
El Salvador	Male	1.29 (0.80, 2.09)	0.2937	Male		-
	Female		-	Female	1.41 (1.33, 1.49)	<.0001
Honduras	Male	0.99 (0.49, 2.01)	0.9808	-	-	-
	Female		-	-	-	-
All Countries	Male	1.28 (1.09, 1.50)	0.0025	Male	-	-
	Female		-	Female	1.75 (1.71, 1.79)	<.0001

Among females, those aged 20-29, 30-39, and 40-49 years were reported to have the highest cumulative incidence of Zika virus disease, with 241 (95% CI 234 to 248), 271 (95% CI 263 to 279), and 266 (95% CI 257 to 274) cases per 100,000 population, respectively (Figure S5a). The reported incidence of Zika virus disease per 100,000 population among males did not vary systematically among age groups. The cumulative incidence of GBS during the period of Zika virus circulation increased with age for males and females, with males over 60 years having the highest rates at 1.88 cases of GBS (95% CI 1.46 to 2.37) per 100,000 population (Figure S5b). The incidence was also greater for males than females in all but one age class (30-39 years), and overall.

Figure S4a. Reported total cases of Zika virus disease per 100,000 population (and CI 95%) by sex and age group in Bahia State (Brazil) and El Salvador.

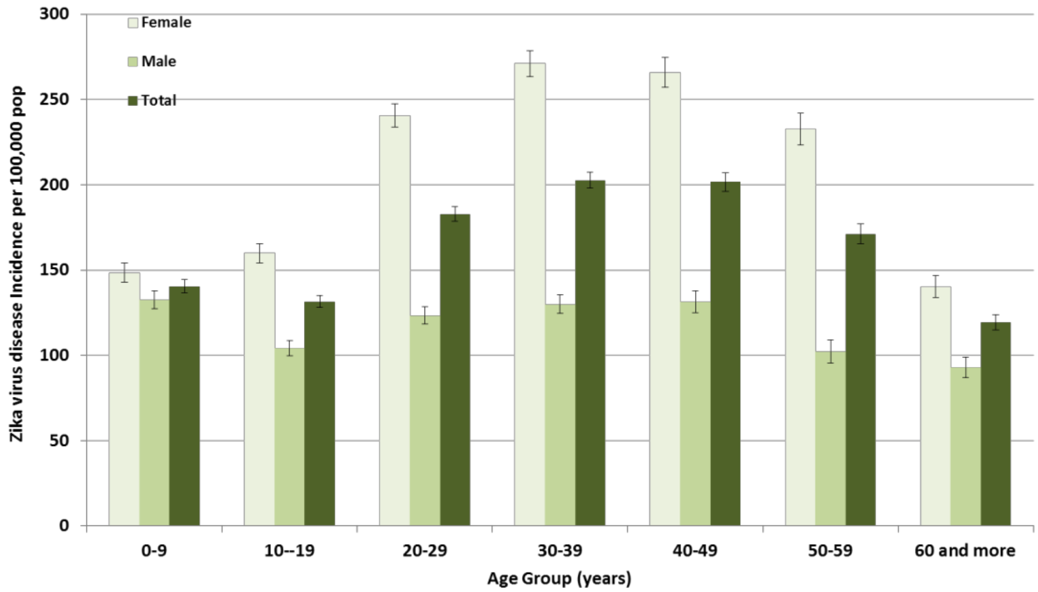


Figure S4b. Guillain Barré Syndrome (GBS) incidence per 100,000 population (and 95%CI) by gender and age group for the period of Zika virus circulation. Bahia state (Brazil), Colombia, El Salvador, and Honduras.