

ORIGINAL ARTICLE

Zika Virus Disease in Colombia — Preliminary Report

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ABSTRACT

BACKGROUND

Colombia began official surveillance for Zika virus disease (ZVD) in August 2015. In October 2015, an outbreak of ZVD was declared after laboratory-confirmed disease was identified in nine patients.

METHODS

Using the national population-based surveillance system, we assessed patients with clinical symptoms of ZVD from August 9, 2015, to April 2, 2016. Laboratory test results and pregnancy outcomes were evaluated for a subgroup of pregnant women. Concurrently, we investigated reports of microcephaly for evidence of congenital ZVD.

RESULTS

By April 2, 2016, there were 65,726 cases of ZVD reported in Colombia, of which 2485 (4%) were confirmed by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. The overall reported incidence of ZVD among female patients was twice that in male patients. A total of 11,944 pregnant women with ZVD were reported in Colombia, with 1484 (12%) of these cases confirmed on RT-PCR assay. In a subgroup of 1850 pregnant women, more than 90% of women who were reportedly infected during the third trimester had given birth, and no infants with apparent abnormalities, including microcephaly, have been identified. A majority of the women who contracted ZVD in the first or second trimester were still pregnant at the time of this report. Among the cases of microcephaly investigated from January 2016 through April 2016, four patients had laboratory evidence of congenital ZVD; all were born to asymptomatic mothers who were not included in the ZVD surveillance system.

CONCLUSIONS

Preliminary surveillance data in Colombia suggest that maternal infection with the Zika virus during the third trimester of pregnancy is not linked to structural abnormalities in the fetus. However, the monitoring of the effect of ZVD on pregnant women in Colombia is ongoing. (Funded by Colombian Instituto Nacional de Salud and the Centers for Disease Control and Prevention.)

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ZIKA VIRUS IS A FLAVIVIRUS TRANSMITTED primarily by the bite of an infected aedes mosquito. In Colombia, a country with a population of 48 million, *Aedes aegypti* and *Aedes albopictus* mosquitoes are the species that are most commonly found at elevations below 2000 m above sea level. Transmission of Zika virus from mother to fetus and sexual transmission have both been reported.^{1,3} Zika virus infection during pregnancy can cause microcephaly and other severe brain defects in the fetus or infant and has been associated with other adverse pregnancy and birth outcomes.

The first outbreak of Zika virus disease (ZVD) in continental South America occurred in Brazil, where autochthonous transmission was confirmed in May 2015.⁴ Although preliminary monitoring began in Colombia after the recognition of the outbreak in Brazil, the Colombian Instituto Nacional de Salud (INS) began official surveillance for ZVD in August 2015. In early October 2015, a ZVD outbreak was declared after the first cluster of laboratory-confirmed cases was identified in nine patients from northern Colombia. After that report, the INS retrospectively identified Zika virus in an archived serum sample from July 2015.

To characterize the epidemiology of ZVD in Colombia, we describe the incidence of ZVD according to sex and age, the distribution of ZVD geographically, and the pregnancy and birth outcomes for a subgroup of women who contracted ZVD during pregnancy. Since limited data are available on the persistence of Zika virus RNA in serum obtained from pregnant women,⁵ we examined the distribution of the days from symptom onset to serum collection among pregnant women who tested positive for the Zika virus on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. Finally, we summarized all case reports of microcephaly from January 2016 through April 2016 without regard to known Zika virus infection.

METHODS

PUBLIC HEALTH SURVEILLANCE SYSTEM

In Colombia, the INS maintains a national public health surveillance system for notifiable conditions, including dengue, chikungunya, and Zika virus infections, acute flaccid paralysis (in children ≤15 years of age), and congenital defects, including microcephaly. Information that is collected by health care centers is compiled and transmit-

ted to the national public health surveillance system, which aggregates and publishes the results weekly. The typical reporting time by health care centers to preliminary national reporting is approximately 1.5 weeks. For this report, the study period was August 9, 2015, to April 2, 2016⁶; cases that were retrospectively identified before epidemiologic week 32 (beginning on August 9, 2015) are not included because ZVD was not consistently monitored by the nationwide surveillance system before then.

For this analysis, ZVD cases include all the patients who were reported to the INS with symptoms of ZVD, with and without laboratory confirmation. Laboratory-confirmed ZVD is defined as the presence of clinical symptoms of ZVD and a positive serum result for Zika virus RNA on RT-PCR assay.

MOLECULAR DETECTION OF ZIKA VIRUS

During the study period, molecular detection of Zika virus was performed with the use of the SuperScript III Platinum One-Step RT-PCR System (Invitrogen). We used oligonucleotides ZIKV 1087/ZIKV 1163 and the ZIKV 1108-FAM probe in a final volume of reaction of 25 μ l, according to the Lanciotti protocol.⁷ The sensitivity for the test is 25 genomic copies per reaction. The thermal profile consisted of a step of reverse transcription at 50°C for 30 minutes, activation of the enzyme at 95°C for 15 minutes, and 45 cycles at 95°C for 15 seconds and 60°C for 1 minute for hybridization and extension with the use of ABI7500 equipment (ThermoFisher Scientific).

REPORTING OF ZVD CASES

Starting in October 2015, the INS mandated immediate reporting of all symptomatic ZVD cases.⁸ The initial case definition for ZVD was fever and at least one of the following symptoms: nonpurulent conjunctivitis, headache, rash, pruritus, or arthralgia, with no known alternative cause. On December 24, 2015, the symptom criteria were revised to include fever and rash, plus at least one of the following symptoms: nonpurulent conjunctivitis, headache, pruritus, arthralgia, myalgia, or malaise. Health care providers documented whether a patient met the symptom criteria, but these data were not reported to the INS and are not included in this report. On the basis of an investigation of a Zika outbreak in the department (i.e., state) of Bolivar in October 2015, the distri-

bution of symptoms that were reported were rash (in 93% of patients), fever (in 80%), pruritus (in 76%), myalgia (in 65%), arthralgia (in 64%), headache (in 62%), conjunctivitis (in 55%), and malaise (in 34%).

TESTING IN SUBGROUPS OF SYMPTOMATIC PATIENTS

The INS arboviral reference laboratory conducted RT-PCR testing for Zika virus RNA on samples obtained from a subgroup of patients with symptomatic ZVD from four subpopulations of interest: infants (<12 months), pregnant women, adults 65 years of age or older, and persons with coexisting illnesses (e.g., chronic conditions, cancers, and autoimmune disorders).⁸ Samples with negative Zika RT-PCR results were tested for dengue and chikungunya virus RNA by means of RT-PCR assay. Patients with negative Zika RT-PCR results are included in the case count because a blood sample may have been collected when Zika RNA was not detectable because of low viremia or because of the mild nature of symptoms, a factor that complicates the accurate report of a date of symptom onset. To explore detection of Zika virus RNA in serum, we analyzed the available data on RT-PCR results in samples obtained from pregnant women according to the number of days from the reported onset of symptoms to sample collection. Serologic testing for Zika virus immunoglobulin M antibodies was not available in Colombia during this study period.

GEOGRAPHIC DISTRIBUTION OF OUTBREAK

Case reports of ZVD include basic demographic information, such as age, sex, and date of symptom onset. To assess the geographic distribution of the outbreak, we mapped the incidence of reported ZVD for both the total population and pregnant women, according to the reporting area (32 states and 5 districts). We used the number of ZVD cases and population estimates to calculate the cumulative incidence of ZVD in the total population, according to age and sex, per 100,000 population and in pregnant women per 100,000 women of childbearing age.^{9,10} The total population was included for each reporting area, regardless of elevation above sea level.

PREGNANCY OUTCOMES AND MICROCEPHALY

We report pregnancy and birth outcomes through the cutoff date for follow-up (May 2, 2016) in a

subgroup of 1850 women who had delivered and had complete information on the gestational week at the time of symptom onset. The INS is monitoring pregnant women with reported ZVD and investigating case reports of adverse fetal and infant outcomes that might be related to Zika virus infection, including all case reports of microcephaly, defined as 3 SD below the mean for gestational age and sex, with confirmation 24 hours after delivery. We summarize case investigations for microcephaly from January through April 2016 that were collected without respect to Zika symptoms or the results of laboratory studies.¹¹

STATISTICAL ANALYSIS

We used Poisson regression to estimate incidence ratios comparing female patients with male patients, along with 95% confidence intervals, using Proc Genmod software (SAS). Analyses with laboratory-confirmed cases only were also conducted. The analyses summarize data from ongoing surveillance and were conducted as part of public health practice.

RESULTS

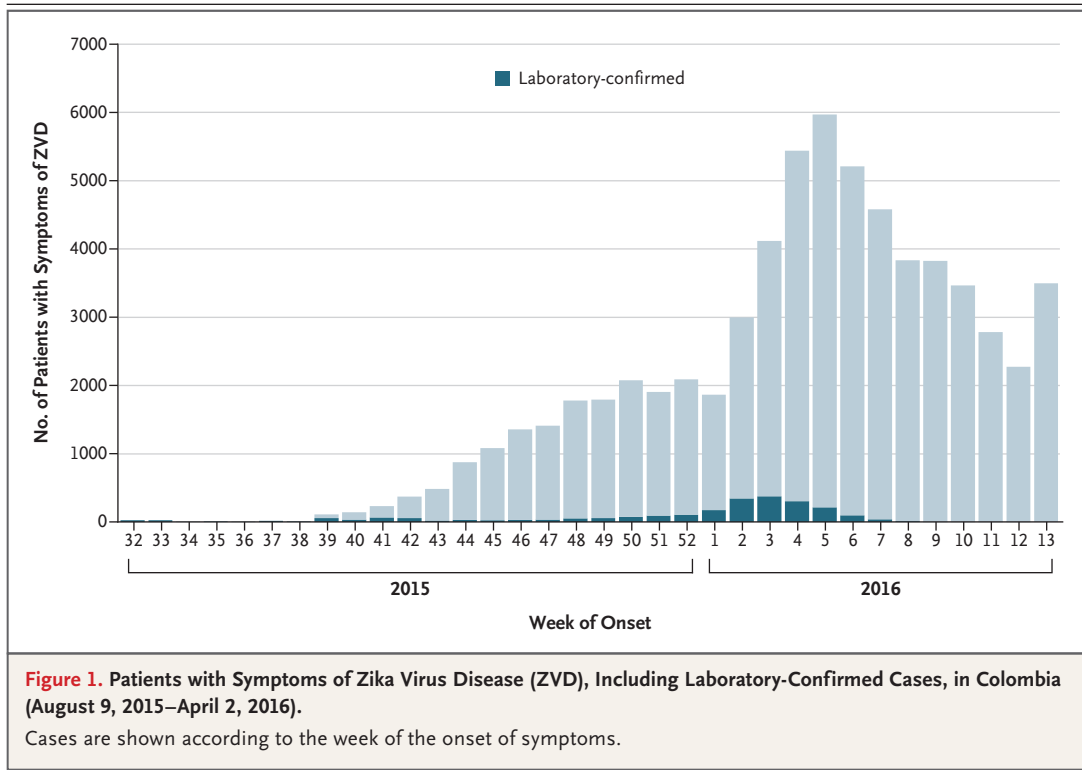
PATIENTS WITH ZVD

From August 9, 2015, through April 2, 2016, a total of 65,726 cases of ZVD were reported in Colombia, with 2485 (4%) that were positive on RT-PCR assay. During this period, 11,944 pregnant women with ZVD were reported in Colombia, with positive results on RT-PCR in 1484 cases (12%). There is currently complete information on gestational age at the time of symptom onset for a subgroup of 1850 pregnant women with ZVD.

Among the 65,726 patients who were reported to have ZVD, 2336 (4%) were hospitalized at the time that the case was reported, including 938 of the 11,944 pregnant women (8%). The number of reported ZVD cases steadily increased from October 2015 through January 2016, with the largest number of cases reported during the week of January 31 to February 6 (epidemiologic week 5) (Fig. 1). From February 7 to April 2 (weeks 6 to 13), the number of reported cases decreased overall, although a few areas were reporting an increased number of cases at week 13.

EXTENT OF ZVD OUTBREAK

Zika virus has spread rapidly throughout Colombia since the first locally acquired case was confirmed.



The ZVD cases are widely distributed across Colombia, with at least one laboratory-confirmed case in 35 of the 37 reporting areas. Seventeen reporting areas had more than 1000 cases; 59,585 cases (91%) were reported from these 17 areas (Fig. 2). The highest incidence of ZVD (1342 per 100,000 population) was reported on San Andres and Providencia, islands in the Caribbean Sea, which was followed by an incidence of 655 per 100,000 in Norte de Santander, a state in the northeast region of the country adjacent to the Venezuelan border, and an incidence of 517 per 100,000 in the state of Huila. For pregnant women, the highest incidence of ZVD was reported in Norte de Santander (621 per 100,000 women of childbearing age), the city of Barranquilla (342 per 100,000), and the state of Huila (333 per 100,000) (Fig. 3). Similar geographic patterns were seen for laboratory-confirmed cases.

Of the 3384 Zika RT-PCR assays that were performed in Colombia during this time period, 2037 (60%) were conducted on samples obtained from pregnant women; 73% of the samples obtained both from the total population and from pregnant women had positive results. Among a subgroup of 1850 pregnant women with complete

data, 582 had serum samples tested on RT-PCR assay; of these samples, 326 (56%) were positive for Zika virus (Fig. 4). Among samples that tested positive on RT-PCR assay, the mean number of days from the reported onset of symptoms to sample collection was 2.6 (median, 2.0; range, 0 to 21). For samples that were RT-PCR–negative, the mean number of days from the reported onset of symptoms to sample collection was 4.0 (median, 2.0; range, 0 to 76). Among the RT-PCR–positive samples, 10 of 326 (3%) were collected more than 7 days after symptom onset; among RT-PCR–negative samples, 17 of 256 (7%) were collected more than 7 days after symptom onset. Among all 555 samples that were collected up to 7 days after reported symptom onset, 316 (57%) were positive on RT-PCR assay. Among the RT-PCR–negative samples, 8 had positive results for dengue and 23 had positive results for chikungunya.

FEMALE-TO-MALE INCIDENCE RATIO

Two thirds of the reported ZVD cases were diagnosed in female patients, although these results were probably affected by referral and testing bias because of the concern about ZVD during preg-

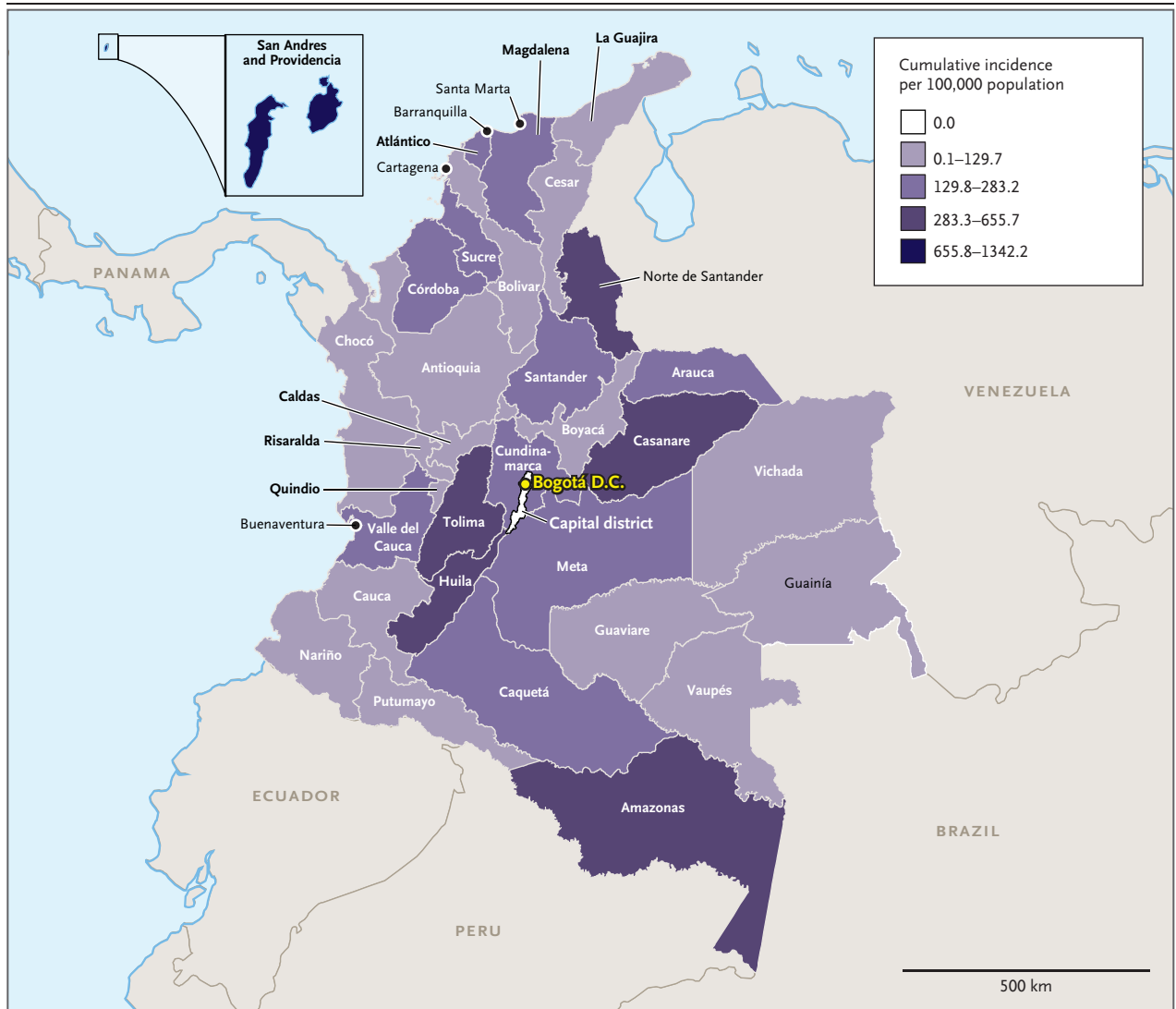


Figure 2. Cumulative Incidence of Zika Virus Disease with Clinical Symptoms in Colombia, According to Reporting Area (August 9, 2015–April 2, 2016).

Shown are the reporting areas, which include 32 departments (i.e., states) and 5 districts (the major cities of Barranquilla, Bogotá, Buenaventura, Cartagena, and Santa Marta). The total incidence of Zika virus disease was reported separately for Barranquilla (which had 348 cases per 100,000 population), Cartagena (88 cases per 100,000), and Santa Marta (376 cases per 100,000). The Instituto Nacional de Salud did not report the incidence in Bogotá, since the cases originated in other reporting areas. The incidence in Buenaventura was included in the total number for the state of Valle del Cauca.

nancy. There was significant variation in estimated incidence according to sex and age (Table 1). Although the incidence of ZVD was similar in girls and boys who were 4 years of age or younger, the incidence was significantly higher among female patients than among male patients in all other age groups. The incidence of ZVD was approximately three times as high among girls and women between the ages of 15

and 29 years as among boys and men in the same age group. The highest incidence ratio comparing female patients to male patients was 3.42 (95% confidence interval [CI], 3.25 to 3.59) among those between the ages of 20 and 24 years. The incidence ratios between female patients and male patients were larger when the analyses were limited to laboratory-confirmed cases.

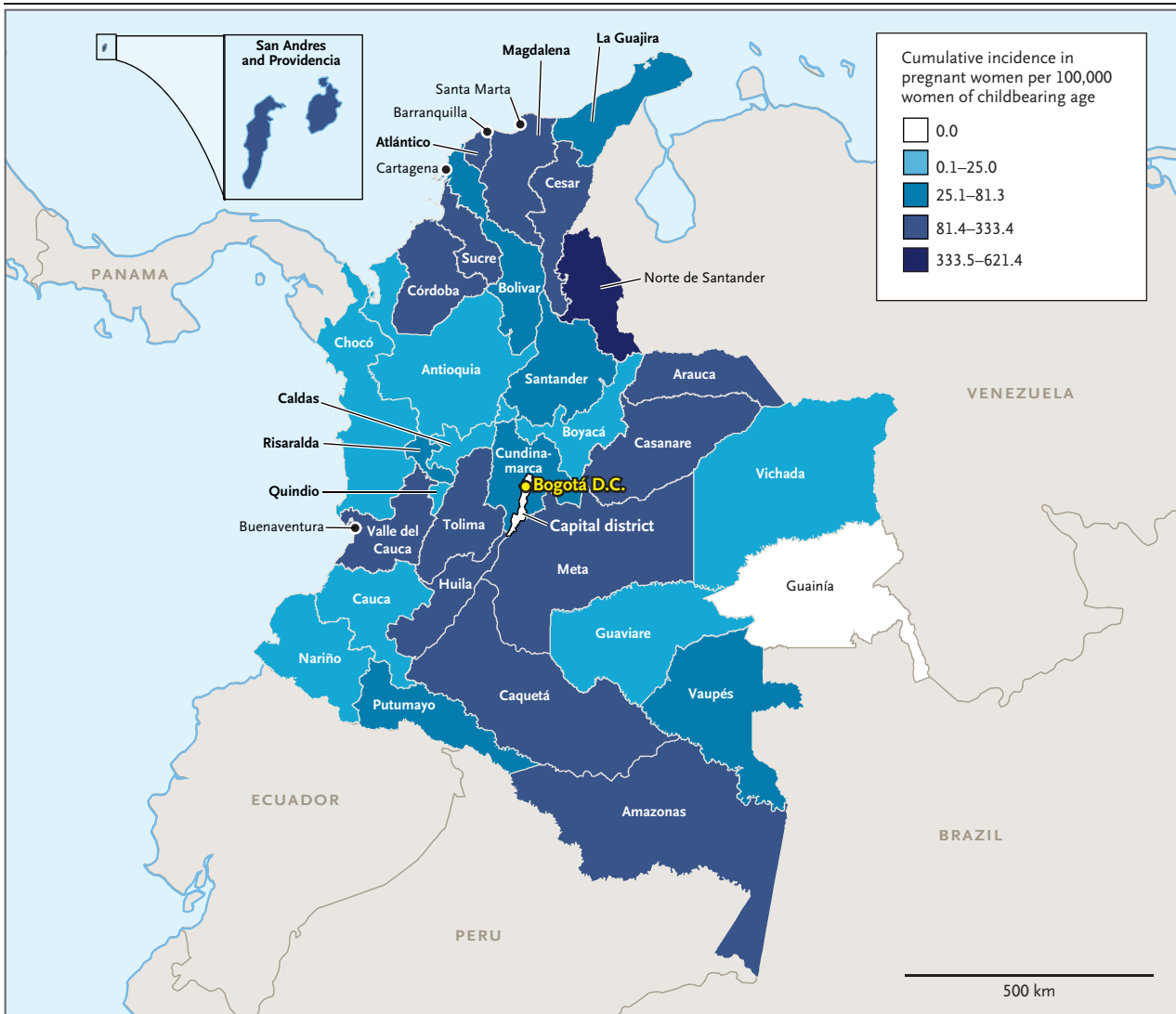


Figure 3. Cumulative Incidence of Zika Virus Disease with Clinical Symptoms among Pregnant Women in Colombia, According to Reporting Area (August 9, 2015–April 2, 2016).

Shown is the incidence of Zika virus disease among pregnant women per 100,000 women of childbearing age in the reporting areas described in Figure 2. The incidence in these women was reported separately for Barranquilla (which had 342 cases per 100,000), Cartagena (27 cases per 100,000), and Santa Marta (306 cases per 100,000).

DATA ON TRIMESTER OF INFECTION

At the time of this report, most pregnancies with ZVD were still ongoing, and key data, including the trimester in which ZVD was diagnosed, are still being collected. Among a subgroup of 1850 pregnant women with ZVD for whom complete data on the trimester of infection were available, 532 reportedly contracted the infection in the first trimester, 702 in the second trimester, and 616 in the third trimester. At the time of data cutoff, among the women in whom ZVD had been diag-

nosed, pregnancies were ongoing in 84% of those with a diagnosis in the first trimester and in 71% of those with a diagnosis in the second trimester. For the 616 women in whom ZVD was diagnosed in the third trimester, 82% of their infants were born at term with a normal birth weight, 2% were born at term with a low birth weight, 8% were preterm, and 1% died during the perinatal period; 7% are still being followed. No cases of microcephaly or brain abnormalities have been reported in this group to date.

NATIONAL SURVEILLANCE FOR MICROCEPHALY

From January 1, 2016, to April 28, 2016, a total of 50 infants with possible microcephaly were reported to the national surveillance system for birth defects. Of these cases, 26 are still under investigation, and 20 were deemed to have resulted from causes other than Zika virus infection, including STORCH (syphilis, toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes) infections, genetic causes, neural-tube defects, and other causes among infants with negative results on Zika RT-PCR whose mothers had no symptoms of ZVD during pregnancy. Four infants with microcephaly had laboratory evidence of congenital Zika virus infection on RT-PCR assay, a negative STORCH evaluation, and normal karyotypes. Of the 4 infants, who were born between 37 and 39 weeks of gestation, 1 had abnormal brain findings on ultrasonography and 3 had abnormal findings on hearing evaluations. Other clinical findings for the cases included decreased muscle tone, problems sucking or swallowing, and amyoplasia of the lower limbs. None of the four mothers had symp-

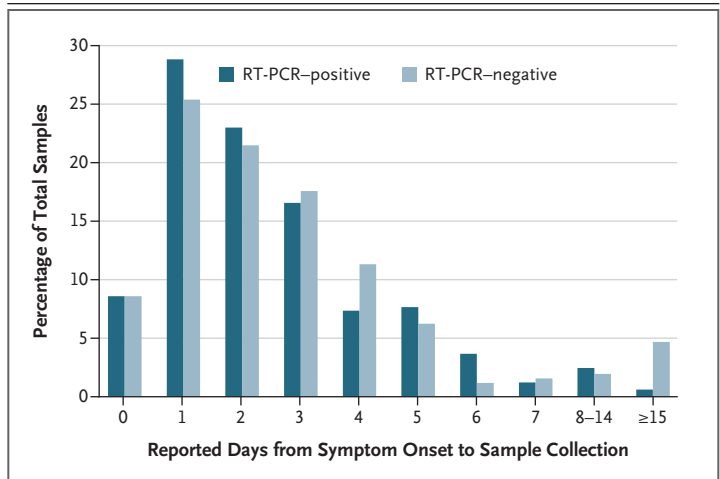


Figure 4. Distribution of Days from the Onset of Symptoms of Zika Virus Disease to Sample Collection.

Shown are data for 582 pregnant women with symptoms of Zika virus disease for whom Zika virus RNA was detectable on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. Of the 582 samples, 326 (56%) were positive for Zika virus. The mean number of days from the reported onset of symptoms to sample collection was 2.6 days for RT-PCR–positive samples and 4.0 days for RT-PCR–negative samples.

Table 1. Incidence of Zika Virus Disease with Clinical Symptoms in Colombia, According to Age and Sex (August 9, 2015–April 2, 2016).

Age	Male Sex			Female Sex			Female-to-Male Incidence Ratio (95% CI)
	Population	ZVD Cases	Incidence per 100,000	Population	ZVD Cases	Incidence per 100,000	
	<i>number</i>			<i>number</i>			
All ages	23,799,679	21,592	90.7	24,403,726	44,133	180.8	1.99 (1.96–2.03)
Age group — yr							
0–4	2,211,071	2,366	107.0	2,110,566	2,222	105.3	0.98 (0.93–1.04)
5–9	2,177,132	1,294	59.4	2,081,546	1,454	69.9	1.18 (1.09–1.27)
10–14	2,187,619	1,447	66.1	2,095,089	1,655	79.0	1.19 (1.11–1.28)
15–19	2,218,821	1,314	59.2	2,126,291	3,935	185.1	3.12 (2.94–3.33)
20–24	2,196,610	2,034	92.6	2,095,681	6,631	316.4	3.42 (3.25–3.59)
25–29	2,005,736	2,415	120.4	1,952,203	6,736	345.0	2.87 (2.74–3.00)
30–34	1,736,122	2,508	144.5	1,803,602	5,534	306.8	2.12 (2.03–2.23)
35–39	1,557,606	1,975	126.8	1,648,373	4,080	247.5	1.95 (1.85–2.06)
40–44	1,385,333	1,579	114.0	1,494,077	2,807	187.9	1.65 (1.55–1.75)
45–49	1,375,401	1,345	97.8	1,508,394	2,528	167.6	1.71 (1.60–1.83)
50–54	1,275,603	1,150	90.2	1,404,887	2,301	163.8	1.82 (1.69–1.95)
55–59	1,046,914	768	73.4	1,171,877	1,731	147.7	2.01 (1.85–2.19)
60–64	813,311	556	68.4	915,085	1,073	117.3	1.72 (1.55–1.90)
≥65	1,612,400	841	52.2	1,996,055	1,446	72.4	1.39 (1.28–1.51)

toms of ZVD during pregnancy and therefore were not reported as part of ZVD monitoring.

DISCUSSION

The outbreak of ZVD has spread rapidly throughout Colombia since the first cluster of laboratory-confirmed cases was identified in October 2015, with 65,726 cases reported, including in 11,944 pregnant women as of April 2, 2016. However, these numbers underestimate the total effect of the ZVD outbreak, since they do not account for asymptomatic infection or unreported clinical illness. High ZVD incidence was reported among girls and women between the ages of 15 and 29 years, which was three times the incidence among male patients in the same age group. Notably, it is unclear to what extent reporting and testing biases may be inflating the number of women who have been identified with ZVD because of the concern about Zika infection during pregnancy. Projections that are based on the timing of the outbreak in Colombia would suggest that women with first-trimester exposures are likely to deliver at term beginning soon after the cutoff date for this report.¹²

Case reports of microcephaly are starting to emerge and be investigated.¹¹ Laboratory evidence of congenital Zika virus infection has been found in four infants born with microcephaly so far, all among women with asymptomatic Zika virus infection. In our analysis of a subgroup of 1850 pregnant women, more than 90% who were reportedly infected during the third trimester have delivered with no cases of microcephaly.

The higher incidence of ZVD among girls and women between the ages of 15 and 29 years than among boys and men in the same age group might be the result of a true increase in risk, reporting or testing bias, or increased health care-seeking behavior among female patients. However, among persons between the ages of 45 and 64 years, the higher ZVD incidence among women than among men suggests that women may actually have an increased susceptibility to symptomatic Zika virus infection, since in this age group a reporting bias that was based on concern with respect to pregnancy would have a lesser role. It is unknown whether sexual transmission from men to women has also played a role in the increased incidence in women. During the Zika outbreak on Yap Island in 2007, the reported rate of infec-

tion among female patients (17.9 per 1000) was also higher than that among male patients (11.4 per 1000); however, seroprevalence was similar in both sexes.¹³ In the current Zika outbreak in Puerto Rico, 64% of patients are female.¹⁴ Because 73% of all births in Colombia occur among girls and women between the ages of 15 and 29 years,¹⁰ the high incidence of ZVD in this age group is a major concern and highlights the urgency of prevention efforts targeting this group, who might have intended or unintended pregnancies. In addition, the association between Zika virus infection during pregnancy and adverse pregnancy and birth outcomes emphasizes the need to closely monitor the large cohort of pregnant women with ZVD and their infants.^{15,16}

The number of days from the reported date of the onset of symptoms to sample collection for pregnant women with positive results on Zika RT-PCR ranged from 0 to 21 days, a range indicating that viremia with ZVD may last longer than a week. However, the longer intervals reported (i.e., >15 days) should be interpreted with caution, since they may represent aberrations in symptom recognition and reporting rather than a true extension of the period of positivity. The mild presentation of many cases of ZVD might make it difficult to accurately pinpoint the date of symptom onset, a factor that contributes to inaccuracies in estimating the time from symptom onset to sample collection, which may in turn affect the interpretation of laboratory test results. In a published case report, Zika RNA was detected in the serum of a pregnant woman at 4 weeks and 10 weeks after the clinical onset of infection but not after delivery.⁵ Further research is needed to better understand the persistence of viremia in pregnant women with ZVD.

Additional challenges with ongoing population-based surveillance of ZVD include remote locations, porous borders with neighboring countries, and underreporting by health care providers, all of which limit the ability to ascertain all cases of ZVD. Cases might be underreported if they occur in areas that are not considered to be at risk for ZVD, such as those at elevations of more than 2000 m above sea level. Geographic variation in ZVD cases corresponds to areas in which *A. aegypti* mosquitoes are prevalent in Colombia. In addition, changes in ZVD case definitions during our study period may have affected reporting, and some patients with afebrile ZVD

might be missed, since fever is a required symptom in the case definition but is not always present during symptomatic Zika virus infection.^{2,13} However, it is unclear whether reporting areas strictly adhered to mandated symptom criteria when reporting ZVD cases, since these data are not available for analysis. Differential reporting of clinically compatible cases might occur, since the symptoms that were included in the case definition overlap with other conditions. Although a small percentage of symptomatic ZVD cases, mainly from the four priority groups, were laboratory-confirmed on RT-PCR assay, stratified analyses of laboratory-confirmed cases were consistent with the main findings. Health care providers have been advised to consider dengue and chikungunya virus infections when evaluating patients, since both viruses remain endemic and patients can have similar symptoms.

Providers are in a unique position to educate patients about the importance of mosquito-bite prevention to reduce the risk of all mosquito-borne illnesses. This counseling is particularly important for women, especially those at risk for unintended pregnancy in the context of a ZVD outbreak. In 2010, a total of 52% of pregnancies were unintended in Colombia, 61% of women of reproductive age used contraception, and less than half of sexually active women between the ages of 15 and 24 years reported the use of a condom during the last episode of sexual intercourse.¹⁷ Since ZVD can be transmitted sexually,^{3,18} providers should counsel pregnant women whose male

sexual partners are at risk for Zika virus infection about the importance of condom use or abstinence to prevent Zika virus transmission.

The ongoing outbreak of ZVD in the Americas poses a major public health threat, particularly for fetuses of infected pregnant women.¹⁹ Nationwide population-based surveillance in Colombia has been critical for monitoring the status of the outbreak by focusing prevention efforts and rapidly assessing adverse outcomes. The INS continues to update its ZVD case counts and has started reporting the number of cases of microcephaly and the Guillain-Barré syndrome; links between Zika virus infection and these outcomes are being investigated further.¹¹ The INS is implementing intensified surveillance of pregnant women with ZVD in selected sites to better understand the spectrum of adverse pregnancy and infant outcomes associated with Zika virus infection and to identify the effect of factors such as the timing of infection during pregnancy.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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