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Evaluation of Patients for Zika Virus Infection in a Travel Clinic in the United States, 2016

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Doctor of Medicine

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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

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Abstract

Evaluation of Patients for Zika Virus Infection in a Travel Clinic in the United States, 2016

By Javier Valle

Zika is an emerging infection that has challenged the U.S. public health system. Characterization of patients with possible and confirmed infection is urgently needed to better understand risks for infection in U.S. travelers and to inform evolving evaluation guidelines. To address these needs, we performed a retrospective electronic health record (EHR) review of patients evaluated for Zika virus (ZIKV) infection at an academic-affiliated travel clinic in Atlanta, Georgia from January 1 through August 31, 2016. We evaluated 46 patients who presented to the clinic during this period for evaluation of possible ZIKV infection, including patients with ZIKV infection symptoms, asymptomatic patients with possible exposure to ZIKV, and referral visits for ZIKV testing.

Among the 46 patients evaluated, 30 (65.2%) were tested for ZIKV, of which 8 patients (17.4%) had laboratory evidence of infection (7 confirmed, 1 probable). Among those who were tested for ZIKV, the three most frequent symptoms reported were headache (86.7%), Rash (76.7%), and fever (66.7%). Among patients who were tested for ZIKV, rash and headache were the most sensitive predictors of having laboratory evidence of infection (100% each). Having ≥3 positive ZIKV-related symptoms had a sensitivity of 88% (95% CI: 47%-100%) and a specificity of 50% (95% CI: 28%-72%) for having laboratory evidence of Zika (+LR: 1.75). Our findings may assist clinicians and public health agencies in addressing timely clinical decision making for ZIKV testing.

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By Javier Valle

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Introduction

Zika virus (ZIKV) infection – a flavivirus arboviral infection -- is an emerging infectious disease [1, 2]. The typical incubation period between exposure from an *Aedes* mosquito bite and onset of symptoms is approximately 3-12 days [3]. In most cases, however, ZIKV infection is asymptomatic [4]. Symptomatic patients commonly present with fever, rash, arthralgia, headache, conjunctivitis, and myalgia [2]. Less common manifestations of ZIKV infection include oral ulcers, abdominal pain, diarrhea, and neurologic syndromes such as Guillain-Barré [5]. Although the illness is typically mild, infection in pregnant women has been linked to congenital microcephaly and other complications of pregnancy [6]. The recent epidemic of ZIKV infection has catalyzed efforts to elucidate the association between congenital ZIKV transmission and neural tube defects, ocular abnormalities, neuromuscular deformities, and hearing loss [7]. Sexual transmission of ZIKV is also of public health concern, especially in non-endemic areas where non-travelers may be exposed through their traveling partners [8].

Since its emergence in Brazil in 2015, there has been increased concern regarding travel-related Zika cases diagnosed in non-epidemic countries [9]. During the height of the epidemic, the majority of U.S. travelers who sought pre-travel consultations prior to travel to Zika-affected areas in the western hemisphere were of reproductive age and planned to travel for vacation [10]. As of September 2016, travel-related cases accounted for nearly all of the 2,382 probable and confirmed cases that had been reported to ArboNET, the CDC's national surveillance system for arboviral infections [11].

The CDC recommends that healthcare providers consult with their state health departments for guidance on ordering and interpreting ZIKV tests [12]. In Georgia, guidance for ZIKV testing is provided by the Georgia Department of Public Health (GDPH) which considers

ZIKV testing for symptomatic males or for females and pregnant women (either asymptomatic or symptomatic) who have a history of ZIKV exposure defined as recent travel to a Zika-affected area; individuals with suspected sexual transmission; or cases of suspected local mosquito transmission [13]. The Council of State and Territorial Epidemiologists (CSTE) established clinical criteria for ZIKV disease case definitions as having at least one of the following symptoms: maculopapular rash, fever, conjunctivitis, or arthralgia [14].

Because Zika is an emerging infection that has challenged the U.S. public health system, improved characterization of patients with possible and confirmed infection is urgently needed to better understand risks for infection in U.S. travelers and to inform evolving evaluation guidelines. We conducted a retrospective chart review of patients who were evaluated by a U.S.-based travel medicine clinic for ZIKV infection. We examined the performance of clinical symptoms for identifying ZIKV cases. Our findings may assist clinicians and public health agencies in addressing timely clinical decision making for ZIKV testing.

Methods

A retrospective electronic health record (EHR) review of patients evaluated for ZIKV at an academic-affiliated travel clinic in Atlanta, Georgia from January 1 through August 31, 2016 was performed. Inclusion criteria were patients of any age who presented to the clinic during this period for evaluation for possible ZIKV infection, including patients with ZIKV infection symptoms, asymptomatic patients with possible exposure to ZIKV, and referral visits for ZIKV testing. Patient charts were abstracted using a case report form that captured the following patient information: age, sex, pregnancy status, travel destinations, reason for travel, travel accommodations, use of mosquito bite prevention methods, symptoms, vaccination history (e.g., yellow fever vaccine), history of arboviral infection, duration from first possible exposure

to symptom onset, duration from symptom onset to presentation to healthcare providers and testing, history of unprotected sex following exposure, ZIKV testing performed, and final test results. Purpose of travel were classified using travel purpose categories used in the GeoSentinel Surveillance System [15]. Mosquito bite prevention included any of the following methods: using insect repellant or Permethrin-treated clothing, wearing long sleeved shirts and long trousers, use of mosquito bed nets, sleeping in screened and or air-conditioned rooms. The date of first entering a Zika-affected area to the first date of symptom onset was used to calculate the number of days from first possible ZIKV exposure to symptom onset.

Epidemiologic linkage was defined as travel to an area with active ZIKV transmission as reported by CDC [16], or a history of engaging in unprotected sexual intercourse (vaginal, oral, or anal) with an exposed partner (symptomatic or asymptomatic). Zika-related symptoms were defined as having the most commonly reported symptoms -- fever, rash, arthralgia, or conjunctivitis – and less common symptoms reported in previous Zika outbreaks, including cough, sore throat, oral ulcers, abdominal pain, vomiting, diarrhea, fatigue, chills, and headache [1]. Testing of suspected cases were generally performed using GDPH testing criteria, which during the study period required at least two Zika-related symptoms out of the four primary symptoms-- fever, rash, arthralgia, conjunctivitis, or pregnant women (symptomatic or asymptomatic) with possible exposure to ZIKV via travel or sexual contact [13]. Testing was primarily performed at either the Emory Medical Laboratories or the Georgia Public Health Laboratory (with confirmation PRNT testing done at CDC Ft. Collins for positive IgM testing at GADPH, etc.).

Probable and confirmed Zika cases were defined using the CSTE definition for noncongenital ZIKV disease [14]. A “probable” case was defined as having clinical criteria for non-congenital disease, and epidemiologic linkage, and laboratory evidence of recent ZIKV or

flavivirus infection by the following: either a positive ZIKV IgM antibody test of serum or CSF with either positive neutralizing antibody titers against ZIKV and dengue or other flaviviruses endemic to the area where exposure occurred; or, a negative dengue virus IgM antibody test and no neutralizing antibody testing performed. A "confirmed" case was defined as having clinical criteria for non-congenital disease and laboratory evidence of recent ZIKV infection by the following: either detection of ZIKV by culture, viral RNA, or viral antigen in serum, CSF, tissue, or other specimen; or, a positive ZIKV IgM antibody test of serum or CSF with positive ZIKV neutralizing antibody titers and negative neutralizing antibody titers against dengue or other flaviviruses endemic to the area where exposure occurred [14].

The diagnostic performance of individual Zika-related symptoms (individually and in combination) to identify patients with positive ZIKV test results (including ZIKV testing results under the "probable" case definition) was determined. Descriptive and statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The chi-square test was used to assess differences in categorical variables between case groups and the Kruskal-Wallis test was used to examine differences in median values between the 3 case groups. Individuals in the "not tested" category were included in the descriptive analysis, but were excluded from the performance testing analyses. We assessed statistical significance at the $\alpha = 0.05$ level.

Results

Forty-seven patients met inclusion criteria for this case series. One patient, for whom EHR data was not available, was excluded [Figure 1]. Forty-six patients were included in our descriptive analysis, of which 30 were tested (65.2%). Among those who met GADPH testing criteria and were tested, 8 patients (17.4%) met CSTE criteria for confirmed or probable ZIKV disease (7 confirmed, 1 probable). Five pregnant patients were tested for Zika; however, none

tested positive. Among those not tested for ZIKV, 15 had epidemiologic linkages and exhibited possible Zika-related symptoms, but otherwise did not meet testing criteria. Others who were not tested included 1 that had no exposure risk but possible ZIKV symptoms and was not pregnant. The median age for those who were tested was 34 (IQR: 8.5) and 33.5 years (IQR: 7.0), respectively [Table 1]. Confirmed and probable ZIKV cases were majority male (62.5%) and those who tested negative were majority female (77.3%). Five who tested negative were pregnant. All confirmed and probable cases lived in Georgia. The most frequented countries by all patients were Dominican Republic, Guatemala, Jamaica, and Mexico [data not shown]. Two individuals that were tested had not traveled to an active Zika transmission area, one of which had suspected sexual transmission. Almost all of those not tested had traveled to a Zika-affected area. Most patients traveled for tourism and all confirmed or probable cases stayed between 1 and 4 weeks compared to those who tested negative, who mostly stayed between less than 1 week to 2 weeks. The majority of patients denied practicing any form mosquito bite avoidance measure (87%). Among confirmed or probable cases, the median days from first possible exposure to symptom onset was 9 days (IQR: 8.5); among symptomatic non-cases, 7.5 days (IQR: 8.0); and among those who reported Zika-related symptoms who were not tested, 6.5 days (IQR: 12.0). Patients exhibited similar median days from symptom onset to seeking medical evaluation between confirmed or probable cases (7 days, IQR: 11.5), non-cases (6.5 days, IQR: 8.0), and those not tested (6 days, IQR: 6.0).

Among those who were tested for ZIKV, the three most frequent symptoms reported were headache (86.7%), Rash (76.7%), and fever (66.7%). Rash was not reported by any of those not tested for ZIKV. Many patients had multiple specimens sent to different laboratories for ZIKV testing. GDPH, Emory, and commercial laboratories were the centers with the highest frequencies of ZIKV testing samples [Table 1]. The presence of rash was significantly different

between the case groups, with all 8 cases reporting rash and all 16 of those not tested denying having a rash, reflective of the clinical criteria used for testing [Table 2]. Significant trends among case groups were observed for symptoms including conjunctivitis (p=0.02), headache (p=0.01), nausea or vomiting (p=0.01), diarrhea (p=0.01), chills or sweats (p=0.01), cough or sore throat (p=0.01), and rhinorrhea or sinusitis (p=0.02). Rash (100%), headache (100%), fever (87.5%), myalgia (66.7%), and conjunctivitis (62.5%) were the most frequently reported symptoms among confirmed or probable cases. Among non-cases, headache (81.8%), rash (68.2%), fever (59.1%), and myalgia (59.1%) were most frequently reported. Fever (87.5%), cough or sore throat (68.8%), headache (62.5%), myalgia (56.3%), and chills or sweats (56.3%) were the most common symptoms among those not tested. The presence of arthralgia was seldom reported by patients (only 12.5% of cases, 4.6% of non-cases, and 6.3% of those not tested). The median maximum temperature reported was highest among those not tested (101.8 °F, IQR: 3.0); however, there was no significant difference between the case groups.

Among those tested for ZIKV, fever was predictive of confirmed or probable ZIKV disease with a sensitivity of 88% (95% CI: 47%-100%), a specificity of 41% (95% CI: 21%-64%), a negative predictive value of 90% (56%-100%), and a positive likelihood ratio of 1.48 for diagnosing ZIKV infection [Table 3]. Rash performed with a sensitivity of 100% (95% CI: 63%-100%), a specificity of 32% (95% CI: 14%-55%), a negative predictive value of 100% (95% CI: 59%-100%), and a positive likelihood ratio of 1.47. Conjunctivitis had a sensitivity of 63% (95% CI: 24%-91%), a specificity of 55% (95% CI: 32%-76%), a negative predictive value of 80% (95% CI: 52%-96%), and a positive likelihood ratio of disease diagnosis of 1.38. Headache performed with a sensitivity of 100% (95% CI: 63%-100%), a specificity of 18% (95% CI: 5%-40%), a negative predictive value of 100% (95% CI: 40%-100%), and a positive likelihood ratio of 1.22 for diagnosing ZIKV infection. Arthralgia had a sensitivity of 13% (95% CI: 0%-53%), a specificity of

95% (95% CI: 77%-100%), a negative predictive value of 75% (95% CI: 55%-89%), and a positive likelihood ratio of 2.50. Nausea and vomiting exhibited a specificity of 82% (95% CI: 60%-95%), and a negative predictive value of 69% (95% CI: 48%-86%). Diarrhea had a sensitivity of 25% (95% CI: 3%-65%), a specificity of 91% (95% CI: 71%-99%), and a positive likelihood of 2.75. The negative predictive value for diarrhea was 77% (95% CI: 56%-91%). Edema had a specificity of 95% (95% CI: 76%-100%), and a negative predictive value of 74% (95% CI: 54%-89%). Abdominal pain performed with a specificity of 82% (95% CI: 60%-95%), and a negative predictive value of 69% (95% CI: 48%-86%). Oral ulcer had a specificity of 95% (95% CI: 77%-100%), and a negative predictive value of 75% (95% CI: 55%-89%).

There were no significant differences between confirmed or probable cases and non-cases for those patients in which serum blood testing was ordered as part of the diagnostic workup [Table 4]. The median platelet count was lower in confirmed or probable cases compared to non-cases (187 billion/L, IQR: 109 billion/L vs 251 billion/L , IQR: 92 billion/L, respectively) [Table 4]. However, all documented values were within normal limits.

Among patients tested for ZIKV, not reporting any Zika-related symptoms had a specificity of 86% (95% CI: 65%-97%) and a negative likelihood ratio of 1.16 for being diagnosed with ZIKV infection [Table 6]. Reporting ≥ 1 Zika-related symptom was associated with a 100% sensitivity (95% CI: 63%-100%), a specificity of 14% (95% CI: 3%-35%), and a negative predictive value of 100% (95% CI: 29%-100%). For those who reported ≥ 2 Zika-related symptoms, the diagnostic accuracy was 100% sensitive (95% CI: 63%-100%), 18% specific (95% CI: 5%-40%), with a positive likelihood ratio of 1.22. Having ≥ 3 Zika-related symptoms performed with 88% sensitivity (95% CI: 47%-100%), 50% specificity (95% CI: 28%-72%), and a positive likelihood ratio of 1.75. Reporting all 4 Zika-related symptoms had the highest likelihood ratio (+LR: 2.75), a sensitivity of 38% (95% CI: 9-76%), and a specificity of 86% (95% CI: 65%-97%).

Discussion

This study describes the experience of a U.S. clinic evaluating patients with possible ZIKV infection during the height of the Zika epidemic in 2016. A significant proportion of patients evaluated were not tested, largely due to stringent testing criteria from GDPH that focused testing resources on those symptoms that were most suggestive of disease (i.e., two or more of the symptoms of fever, rash, arthralgia, and conjunctivitis) or potentially exposed pregnant women. ZIKV infection is reportedly asymptomatic in as many as 80% of infected individuals [4]; therefore, asymptomatic cases may have been present among those not tested, since the majority had risk factors for ZIKV exposure.

Among those tested, having ≥ 3 Zika-related symptoms had a high sensitivity (88%) and a high likelihood of disease (+LR: 1.75) compared to other sums of symptoms. The increasing trend of positive likelihood ratios observed with increasing minimum number of positive Zika-related symptoms was expected, since having a patient with more of the common Zika-related symptoms increases the clinical suspicion for ZIKV infection. Also expected were the lower likelihoods of disease associated with having 0 symptoms or ≥ 1 symptom. These reflect earlier GDPH ZIKV testing criteria that required a minimum of 2 Zika-related symptoms for a patient to be considered for testing. As of March 2017, the total number of confirmed travel-related Zika cases in Georgia was 116 [17]. Our low positive predictive values are indicative of the low Zika prevalence at the state level and within our own study population. One other study has also assessed the performance of ZIKV clinical criteria for clinical decision making on potential Zika cases and found CSTE clinical criteria as a whole to have a sensitivity of 100% and a specificity of 2% [18].

The most prevalent symptoms in our study population were rash, fever, headache, conjunctivitis, and myalgia, which is similar to earlier descriptions of Zika symptoms [4].

However, our overall study population exhibited lower presence of arthralgia than recent studies of travel-associated Zika in US travelers [19] and in European travelers [20]. In assessing individual symptom performance in screening for ZIKV infection diagnosis, rash, headache, and fever exhibited the highest sensitivities. This result was expected since almost all confirmed or probable cases exhibited these symptoms. Fever and rash had a higher likelihoods of disease diagnosis compared to headache. We also evaluated the performance of less typical Zika-related symptoms for diagnosing ZIKV infection in our study population. Oral ulcer, edema, arthralgia, abdominal pain, nausea or vomiting, and diarrhea exhibited high specificities since few to none of the confirmed or probable cases reported these symptoms.

Sixteen subjects were not tested for ZIKV. Many of these patients presented to the clinic during the subacute phase of disease or were diagnosed with an alternative diagnosis such as viral upper respiratory tract infection. Given that the majority of these patients had an epidemiologic linkage to ZIKV due to travel to an active Zika transmission area, we could have missed an opportunity to diagnose additional cases. This reflects Zika testing criteria during this period.

There were two exceptions in our inclusion criteria: one patient who traveled to Indonesia and one who traveled to India. The patient who traveled to Indonesia presented with Zika-associated symptoms. The clinical suspicion for Zika infection was high and GDPH was contacted for testing guidance. This patient tested negative for ZIKV through both state laboratory and Emory laboratory testing. As a result, he was included in the analysis. The patient who traveled to India also reported Zika-related symptoms. However, this patient was diagnosed with Group A streptococcus infection; therefore, GDPH was not contacted and ZIKV testing was not offered. This patient was included in our descriptive analyses but not for further analysis. Both Indonesia and India are currently listed by the CDC as being areas with Zika risk

but not included in the list of Zika travel notice areas [21]. The changing landscape of Zika-transmission areas listed for consideration of ZIKV exposure was also a challenge experienced by our clinic in identifying potential Zika cases.

We tested five pregnant patients. Two of these suspected cases had Zika-related symptoms and an epidemiologic linkage to ZIKV. Three of the patients were asymptomatic but had exposure risk. Of these, two had traveled to a Zika-affected area and one had engaged in unprotected sex with an exposed partner. There were no fetal abnormalities reported for any of the five pregnant patients. These five suspected cases reflect the priority placed on pregnant women and sexually-transmitted cases by our local and national public health agencies.

One of the strengths of our study is that our clinic is a specialized travel clinic which received a large number of patients for evaluation for a U.S.-based clinic. Providers had a heightened level suspicion for evaluating potential Zika cases, were aware of existing clinical criteria for ZIKV infection, the evolving Zika public health response, and were familiar with existing surveillance systems such as GeoSentinel. This may have allowed them to most accurately document details of individual patient travel history, exposures, and the presence and timing of symptoms. Another strength is our adherence to existing criteria and guidance that makes our analysis an accurate assessment of our performance that may be generalizable to clinics in a similar practice environment.

Testing criteria limited our ability to test asymptomatic patients. Probable cases had not been retested to confirm their status, presenting a potential misclassification bias. We may have missed diagnosing subjects who were not offered testing although they demonstrated an epidemiologic linkage and reported Zika-related symptoms. The presence of alternative diagnoses minimizes this bias in this group. We do not believe misclassification was an issue

with our “cases” categorization since both confirmed and probable cases were combined into one category. Another limitation of this study is a small sample size which limited our analytic capacity to assess the predictive value of symptoms. However, our sample size is still a large case series for a U.S. clinic. As such, our findings may not be generalizable to clinics in endemic areas. Our study also included mostly adult patients, although we diagnosed a 17 year-old patient.

Our findings may assist clinicians and public health agencies in addressing timely clinical decision making for ZIKV testing which has proven to be a common challenge. In one case report, the authors described a major challenge to diagnosing imported ZIKV cases as accurately diagnosing cases outside the viremic period [22]. Even in Brazil, the epicenter of the current outbreak, the authors of a case series concluded that a major challenge in both Zika-affected areas and non-endemic areas is initiating a timely evaluation of suspected cases [1].

We found that among 30 patients meeting clinical testing criteria, 8 tested positive, suggesting that the epidemiologic and symptom criteria have a relatively high predictive value. However, given that a high percentage of asymptomatic patients are presumed, the testing criteria presumably misses a significant, if not majority, of ZIKV infections. This creates a significant limitation in ZIKV surveillance in the U.S. Furthermore, since asymptomatic ZIKV infected individuals have been documented to transmit the disease sexually [8], and their role in mosquito borne transmission is presumed, limited testing criteria presumably misses a large percentage of cases that may contribute to local transmission. As testing capacity increases and test performance in asymptomatic individuals is better described, revised testing guidance might improve ZIKV surveillance in the U.S. Future research could further streamline clinical decision-making models and increase the index of suspicion for testing potential Zika cases in the outpatient setting. Wider access to accurate screening modalities (and validation of these

tests in symptomatic and asymptomatic persons) will help providers evaluate and advise patients.

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Figures and Tables

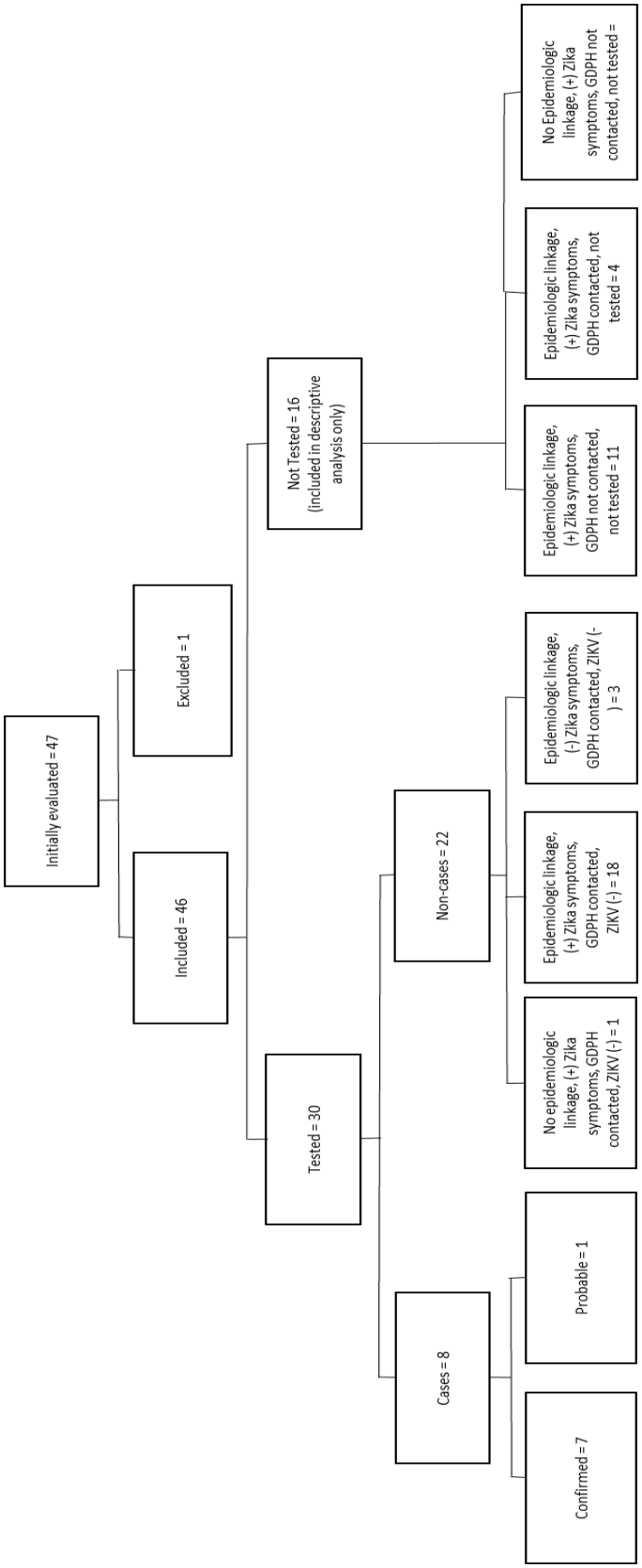

Figure 1. Selection and categorization of the TravelWell Zika Study subjects, Atlanta, GA 2016.

Table 1. Description of the TravelWell Zika Study population, Atlanta, GA 2016.

	Case		Non-case		Not tested	
	N	**%**	**N**	**%**	**N**	**%**
Total	8	100.0	22	100.0	16	100.0
Age median(IQR)	34	8.5	33.5	7.0	40.5	16.5
Sex						
Male	5	62.5	5	22.7	8	50.0
Female	3	37.5	17	77.3	8	50.0
Race/Ethnicity						
Non-Hispanic White	2	25.0	9	40.9	5	31.3
Non-Hispanic Black	0	0.0	4	18.2	5	31.3
Hispanic	1	12.5	0	0.0	2	12.5
Other	0	0.0	0	0.0	1	6.3
Missing	5	62.5	9	40.9	3	18.8
State of residence						
California	0	0.0	0	0.0	1	6.3
Florida	0	0.0	0	0.0	1	6.3
Georgia	8	100.0	21	95.5	13	81.3
Illinois	0	0.0	0	0.0	1	6.3
Virginia	0	0.0	1	4.6	0	0.0
Pregnant						
Yes	0	0.0	5	13.5	0	0.0
No	8	100.0	16	72.7	14	87.5
Unknown	0	0.0	1	4.6	2	12.5
History of travel to a Zika-affected country**						
Yes	8	100.0	20	90.9	15	93.8
No	0	0.0	2	9.1	1	6.3
Reason for travel						
Business	1	12.5	6	27.3	1	6.3
Tourism	3	37.5	10	45.5	10	62.5
Other	4	50.0	5	22.7	5	31.3
Missing	0	0.0	1	4.6	0	0.0
Length of travel						
< 1 week	0	0.0	9	40.9	6	37.5
1-2 weeks	6	75.0	10	45.5	4	25.0
2-4 weeks	2	25.0	1	4.6	4	25.0
> 4 weeks	0	0.0	1	4.6	2	12.5
Missing	0	0.0	1	4.6	0	0.0
Travel accommodation						
Hotel	2	25.0	4	18.2	4	25.0
Other*	1	12.5	4	18.2	6	37.5
Unknown	5	62.5	14	63.6	6	37.5
Mosquito bite prevention						
Yes	2	25.0	2	9.1	2	12.5
No	6	75.0	20	90.9	14	87.5

Number of days from last suspected ZIV exposure to symptom onset						
Median (IQR)	9	8.5	7.5	8.0	6.5	12.0
Number of days from symptom onset to seeking medical care						
Median (IQR)	7	11.5	6.5	9.0	6	6.0
Location of ZIKV lab tests ordered*						
Georgia Department of Public Health lab	6	15.0	16	14.6		
Emory University lab	4	10.0	10	9.1		
Commercial lab	4	10.0	7	6.4		
CDC lab	3	7.5	7	6.4		
Blood bank	0	0.0	0	0.0		
Other lab***	0	0.0	1	0.9		

Patients tested vs not tested utilizing published GDPH Zika-related symptoms	**Had a Zika Test**	**Did Not Have a Zika Test**
N(%)	30	16
Symptoms		
Fever	20 (66.7)	14 (87.5)
Rash	23 (76.7)	0 (0.0)
Conjunctivitis	15 (50.0)	4(25.0)
Arthralgia	19 (63.3)	5 (31.3)
Myalgia	17 (56.7)	9 (56.3)
Headache	26 (86.7)	10 (62.5)
Nausea/Vomiting	4 (13.3)	7 (43.8)
Travel to Zika-affected area		
Yes	28 (93.3)	15 (93.8)
No	2 (6.7)	1 (6.3)

*Some patients had up to 8 specimens submitted for laboratory testing.
** 1 patient traveled to Indonesia and tested negative for Zika, 1 patient was a suspected sexually-transmitted case who tested negative, and 1 patient traveled to India and was not tested.

***The location of ZIKV laboratory testing for 1 patient could not be verified.

Table 2. Symptoms reported by TravelWell Zika Study subjects, Atlanta, GA, 2016.

*Symptom		Case		Non-Case		Not tested		‡p-value
		N	%	N	%	N	%	
Fever								
	Yes	7	87.5	13	59.1	14	87.5	0.10
	No	1	12.5	9	40.9	2	12.5	
Max Temperature (°F), median (IQR)								
		99.0	0.0	100.8	1.7	101.8	3.0	**0.24
Rash								
	Yes	8	100	15	68.2	0	0.0	**<.0001**
	No	0	0.0	7	31.8	16	100.0	
Conjunctivitis								
	Yes	5	62.5	10	45.5	4	26.7	**0.02**
	No	3	37.5	12	54.6	11	73.3	
Headache								
	Yes	8	100	18	81.8	10	62.5	**0.01**
	No	0	0.0	4	18.2	6	37.5	
Arthralgia								
	Yes	1	12.5	1	4.6	1	6.3	0.19
	No	7	87.5	21	95.5	15	93.8	
Myalgia								
	Yes	4	66.7	13	59.1	9	56.3	0.08
	No	2	33.3	9	40.9	7	43.8	
Nausea/Vomiting								
	Yes	0	0.0	4	18.2	7	43.8	**0.01**
	No	8	100	18	81.8	9	56.3	
Diarrhea								
	Yes	2	25.0	2	9.1	7	43.8	**0.01**
	No	6	75.0	20	90.9	9	56.3	
Edema								
	Yes	0	0.0	1	4.8	0	0.0	0.51
	No	7	100	20	95.2	13	100.0	
Chills/Sweats								
	Yes	1	16.7	5	22.7	9	56.3	**0.01**
	No	5	83.3	17	77.3	7	43.8	
Cough/Sore throat								
	Yes	3	37.5	8	36.4	11	68.8	**0.01**
	No	5	62.5	14	63.6	5	31.3	
Rhinorrhea/Sinusitis								
	Yes	2	25.0	5	23.8	8	50.0	**0.02**
	No	6	75.0	16	76.2	8	50.0	
Abdominal pain								
	Yes	0	0.0	4	18.2	4	25.0	0.05
	No	8	100	18	81.8	12	75.0	
Fatigue								
	Yes	3	50.0	5	25.0	5	38.5	0.05
	No	3	50.0	15	75.0	8	61.5	
Oral ulcer								
	Yes	0	0.0	1	4.6	0	0.0	0.49
	No	7	100	21	95.5	16	100.0	

‡Fisher's Exact Test used

**Kruskal-Wallis test used

*There were missing/"unknown" responses for some variables.

Table 3. Performance of individual reported symptoms for diagnosing ZIKV infection in TravelWell Zika study subjects , Atlanta, GA, 2016.

*Symptom		Case		Non-Case		‡p-value	Sens	(95% CI)	Spec	(95% CI)	PPV	(95% CI)	NPV	(95% CI)	+LR	-LR
		N	%	N	%											
Fever																
	Yes	7	87.5	13	59.1	0.21	0.88	(0.47, 1.00)	0.41	(0.21, 0.64)	0.35	(0.15, 0.59)	0.90	(0.56, 1.00)	1.48	0.31
	No	1	12.5	9	40.9											
Max Temperature (°F), median (IQR)																
		99.0	0.0	100.8	1.7	0.09										
Rash																
	Yes	8	100	15	68.2	0.14	1.00	(0.63, 1.00)	0.32	(0.14, 0.55)	0.35	(0.16, 0.57)	1.00	(0.59, 1.00)	1.47	0.00
	No	0	0.0	7	31.8											
Conjunctivitis																
	Yes	5	62.5	10	45.5	0.68	0.63	(0.24, 0.91)	0.55	(0.32, 0.76)	0.33	(0.12, 0.62)	0.80	(0.52, 0.96)	1.38	0.69
	No	3	37.5	12	54.6											
Headache																
	Yes	8	100	18	81.8	0.55	1.00	(0.63, 1.00)	0.18	(0.05, 0.40)	0.31	(0.14, 0.52)	1.00	(0.40, 1.00)	1.22	0.00
	No	0	0.0	4	18.2											
Arthralgia																
	Yes	1	12.5	1	4.6	0.47	0.13	(0.00, 0.53)	0.95	(0.77, 1.00)	0.50	(0.01, 0.99)	0.75	(0.55, 0.89)	2.50	0.92
	No	7	87.5	21	95.5											
Myalgia																
	Yes	4	66.7	13	59.1	1.00	0.67	(0.22, 0.96)	0.41	(0.21, 0.64)	0.24	(0.07, 0.50)	0.82	(0.48, 0.98)	1.13	0.81
	No	2	33.3	9	40.9											
Nausea/Vomiting																
	Yes	0	0.0	4	18.2	0.55	0.00	(0.00, 0.00)	0.82	(0.60, 0.95)	0.00	(0.00, 0.00)	0.69	(0.48, 0.86)	0.00	1.22
	No	8	100	18	81.8											
Diarrhea																
	Yes	2	25.0	2	9.1	0.28	0.25	(0.03. 0.65)	0.91	(0.71, 0.99)	0.50	(0.07, 0.93)	0.77	(0.56, 0.91)	2.75	0.82
	No	6	75.0	20	90.9											
Edema																
	Yes	0	0.0	1	4.8	1.00	0.00	(0.00, 0.00)	0.95	(0.76, 1.00)	0.00	(0.00, 0.00)	0.74	(0.54, 0.89)	0.00	1.05
	No	7	100	20	95.2											
Chills/Sweats																
	Yes	1	16.7	5	22.7	1.00	0.17	(0.00, 0.64)	0.77	(0.55, 0.92)	0.17	(0.00, 0.64)	0.77	(0.55, 0.92)	0.73	1.08
	No	5	83.3	17	77.3											
Cough/Sore throat																
	Yes	3	37.5	8	36.4	1.00	0.38	(0.09, 0.76)	0.64	(0.41, 0.83)	0.27	(0.06, 0.61)	0.74	(0.49, 0.91)	1.03	0.98
	No	5	62.5	14	63.6											
Rhinorrhea/Sinusitis																

	Yes	2	25.0	5	23.8	1.00	0.25	(0.03, 0.65)	0.76	(0.53, 0.92)	0.29	(0.04, 0.71)	0.73	(0.50, 0.89)	1.05	0.98
	No	6	75.0	16	76.2											
Abdominal pain																
	Yes	0	0.0	4	18.2	0.55	0.00	(0.00, 0.00)	0.82	(0.60, 0.95)	0.00	(0.00, 0.00)	0.69	(0.48, 0.86)	0.00	1.22
	No	8	100	18	81.8											
Fatigue																
	Yes	3	50.0	5	25.0	0.33	0.50	(0.12, 0.88)	0.75	(0.51, 0.91)	0.38	(0.09, 0.76)	0.83	(0.59, 0.96)	2.00	0.67
	No	3	50.0	15	75.0											
Oral ulcer																
	Yes	0	0.0	1	4.6	1.00	0.00	(0.00, 0.00)	0.95	(0.77, 1.00)	0.00	(0.00, 0.00)	0.75	(0.55, 0.89)	0.00	1.05
	No	7	100	21	95.5											

*There were missing/"unknown" responses for some variables.

‡Fisher's Exact Test used

Table 4. Comparison of laboratory results between cases and non-cases, Atlanta, GA, 2016.

	Case		**Non-case**		**p-value**
Laboratory test	Median	IQR	Median	IQR	
WBC (billion cells/L)	3.9	2.3	6.3	4.1	0.14
HCT (%)	42.6	5.05	41.55	4.9	0.27
Hgb (g/dL)	15.5	1.8	14.35	1.8	0.17
PLT (billion/L)	187	109	251	92	0.31
AST (U/L)	24	2	41	31	0.31
ALT (U/L)	20.5	4.5	43	66	0.24
ALP (U/L)	61	11	65	66	0.37
Total Bilirubin (mg/dL)	0.6	0.2	0.6	0.2	0.67

Table 5. Performance of CSTE case definition symptom combinations for diagnosing ZIKV infections in TravelWell Zika Study subjects, Atlanta, GA, 2016.

Number of positive symptoms*	Case	%	Non-case	%	‡p-value	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	(95% CI)	NPV	(95% CI)	LR+	LR-
N	8	26.7	22	73.3											
0	0	0.0	3	13.6	0.54	0.00	(0.00, 0.00)	0.86	(0.65, 0.97)	NA	NA	0.70	(0.50, 0.86)	0.00	1.16
≥1	8	100.0	19	86.4	0.54	1.00	(0.63, 1.00)	0.14	(0.03, 0.35)	0.30	(0.14, 0.50)	1.00	(0.29, 1.00)	1.16	0.00
≥2	8	100.0	18	81.8	0.55	1.00	(0.63, 1.00)	0.18	(0.05, 0.40)	0.31	(0.14, 0.52)	1.00	(0.40, 1.00)	1.22	0.00
≥3	7	87.5	11	50.0	0.10	0.88	(0.47, 1.00)	0.50	(0.28, 0.72)	0.39	(0.17, 0.64)	0.92	(0.62, 1.00)	1.75	0.25
≥4	3	37.5	3	13.6	0.30	0.38	(0.09, 0.76)	0.86	(0.65, 0.97)	0.50	(0.12, 0.88)	0.79	(0.58, 0.93)	2.75	0.72

*Symptoms included fever, rash, arthralgia, or conjunctivitis

‡Fisher's Exact Test used