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Evaluation of Zika Virus Testing Through the Washington State Department of
Health

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Abstract

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Objectives

We used Washington State Department of Health (DOH) Zika surveillance data from January 1 to October 31, 2016 to (1) describe the population of individuals for whom Zika testing was requested, (2) determine whether health care provider (HCP) disciplines differ in appropriate referral practices for Zika testing, and (3) determine whether HCP disciplines differ in referral of positive Zika patients for testing.

Methods

Descriptive analysis with t-test and Chi-squared test was used to evaluate whether patient characteristics and HCP discipline differed by public health test approval status and laboratory

results. Logistic regression was used to calculate odds ratios of approved test referral and referral of positive Zika patients by HCP discipline.

Results

Obstetrician/Gynecologist (OBGYN) and General Practice disciplines bore the greatest burden of Zika testing requests. Patient age, sex, pregnancy and symptom status, and discipline of HCP that made the request differed significantly by public health test approval status and laboratory results. Compared with OBGYNs, General Practice and “Other” disciplines had elevated odds of referring patients for whom testing was not approved by public health, whereas Emergency and Internal Medicine disciplines had elevated odds of requesting testing for laboratory positive patients.

Conclusions

Given the potentially severe consequences of Zika infection to pregnant women, testing guidance in place during this study appropriately fostered disproportionate testing of asymptomatic pregnant females. However, asymptomatic pregnant women rarely test positive. This supports the recent Center for Disease Control and Prevention recommendation to limit routine testing of asymptomatic pregnant females.

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INTRODUCTION

Since the initial detection of an outbreak in Brazil in April 2015, Zika virus has become a global concern.(1) Zika virus is a flavivirus transmitted through the bite of infected *Aedes* species mosquitos, mainly *Ae. aegypti* and *Ae. albopictus*, similar to dengue and Yellow Fever.(2) Unique to Zika, however, is that it can also be transmitted person-to-person sexually through semen and vaginal fluids, and from mother to fetus.(3-5) While 80% of Zika infections are asymptomatic and 20% result in minor flu-like symptoms, infection has been associated with severe complications such as Guillain-Barre Syndrome in adults, and causally linked to microcephaly in fetuses and infants.(5-7) During 2016, active virus transmission was reported in parts of the US, Central and South America, the Caribbean, the Pacific Islands, Africa, and several countries in Southeast Asia.(8)

Aedes mosquitos capable of vectoring Zika virus are not currently present in Washington State, making local transmission of Zika by mosquito improbable.(9) Zika infection and transmission are still possible for Washington residents through travel, sexual contact, or other rare transmission pathways such as laboratory exposure. Real-time reverse transcription-polymerase chain reaction (rRT-PCR) and enzyme-linked immunosorbent assay (ELISA) testing for Zika became available for Washington State residents through a public health reference laboratory in January 2016. However, guidance for testing from the Centers for Disease Control and Prevention (CDC) have changed multiple times as new information on Zika and test performance is gathered.(10) With these changes comes the necessity of informing healthcare providers (HCP) and laboratories of what testing is available and for whom testing is recommended. This challenge is innate to emerging disease surveillance and test development.

Misunderstanding of testing recommendations may result in the unnecessary use of public health and healthcare resources or unreliable results for patients for whom testing is not indicated.

The purpose of this study was to approximate the distribution of the burden of Zika test requests across HCP by discipline and the characteristics of patients for whom test requests were submitted. This study also sought to evaluate if some HCP disciplines are more likely to request testing for patients for whom testing is not recommended, indicating a need for more public health outreach to those disciplines, and if some HCP disciplines are more likely to request testing for patients who will ultimately test positive for Zika, indicating another important area for outreach and collaboration.

METHODS

STUDY POPULATION AND DATA COLLECTION

We analyzed Zika surveillance data and test request data collected by local health jurisdictions (LHJs) and submitted to the Washington State Department of Health (DOH) between January 1 and October 31, 2016. Health care providers submit requests to LHJs, which screen to determine if testing is indicated (based on DOH-defined criteria) and then submit requests to DOH. For requests submitted by LHJs and a small number of requests submitted directly to DOH from HCP, DOH then approves or denies testing. DOH criteria have largely followed CDC guidance and have changed multiple times during January to October 2016 as more was learned about Zika endemic areas and the duration of viral detection in the body. General testing criteria during the study period required travel to an area with active Zika virus transmission or sexual contact with a person who traveled to such an area. For pregnant females,

the exposure must occur during the periconceptional period or during pregnancy. For females who are not pregnant and for males, the criteria also require symptoms consistent with Zika virus disease. Testing was recommended for infants that exhibited microcephaly after maternal travel in an endemic area, or infants born to mothers with positive or inconclusive infection. Data collected from test requests included patient age, sex, pregnancy status, if and which symptoms were present, as well as data on the HCP requesting testing, if specimens were sent for testing, and test results. HCP discipline was determined either from surveillance data or by searching public records of the provider's name and clinic. LHJs generally performed an initial review to approve or deny testing based on DOH testing criteria, and reported all LHJ-approved requests to DOH. DOH then performed a final review to approve or deny testing. As LHJs did not routinely report denied requests to DOH, the denied requests available at DOH included those for which DOH disagreed with the approval granted by the LHJ, and specimens submitted directly to DOH, for which testing eligibility was determined retrospectively. The sample included in this study is therefore a subset of the total denied requests made during the study period, and it was not possible to differentiate between screened and directly submitted requests in this dataset. As determining Zika infection status can be a lengthy process that often requires multiple rounds of testing, the period of January 1 to October 31, 2016, was selected to minimize the inclusion of individuals who had yet to complete testing at the time of analysis. Only Washington State residents were included in this analysis. As DOH does not routinely collect disease surveillance data from individuals who test negative for Zika at commercial labs, all commercial testing data was excluded from this analysis.

OUTCOMES

The two outcomes of interest for this study were DOH approval status of test requests and laboratory results of approved requests. Among DOH-approved requests, data on laboratory results were used to identify patients who were laboratory positive for Zika per Council of State and Territorial Epidemiologists (CSTE) Zika guidelines.(11) Individuals were included as positive cases of Zika if they met the CSTE classification for confirmed or probable Zika virus disease or infection. Rejected requests were not tested for Zika, and were therefore excluded from evaluation of laboratory results.

INDEPENDENT VARIABLES

The exposure of interest in this study was the discipline of the HCP who requested Zika testing. HCP discipline was aggregated into five categories based on similarities in the types of medical services provided and characteristics of patients likely to be seen by those disciplines. The Emergency category included Emergency Medicine and Urgent Care providers. General Practice included General Practice, Pediatrics, Naturopathy, Family Medicine, and Community Health providers. Internal Medicine included Internal Medicine and Infectious Disease providers. The OBGYN category included obstetricians, fertility specialists, Maternal Fetal Medicine specialists, and midwives. The Other category aggregated non-primary care specialties that made the fewest number of requests, including Dermatology, Gastroenterology, Gerontology, Neurology, Oncology, and Surgery. Other independent variables used in this analysis included patient age in years, and binary variables for sex, pregnancy status, and experience of symptoms consistent with Zika virus disease.

DATA ANALYSIS

We used t-test, Pearson's Chi-squared test, and Fisher Exact test to evaluate if proportions and means of patient characteristics and discipline of HCP that requested testing differed between requests that were and were not approved for testing, and results that did or did not show laboratory evidence of Zika infection.

Multivariable logistic regression was used to calculate odds ratios (OR) of test requests made by HCPs of each discipline being approved or rejected. As the OBGYN category represented the greatest number of test requests, this category was selected as the reference category. Pregnancy status and symptomology were identified *a priori* as potential confounders in the relationship between HCP discipline and request rejection due to testing criteria. However, this relationship is unclear. Therefore, to explore the role of confounders, one model was fit adjusting for pregnancy status, and a second model was fit adjusting for both pregnancy status and experience of symptoms. Among requests that were accepted for testing, multivariable logistic regression was also used to calculate OR of test requests made by HCPs of each discipline resulting in positive test results. Again, OBGYN was used as the reference category for two models, one adjusting for pregnancy status alone, and the other adjusting for both pregnancy status and experience of symptoms.

All analyses were conducted using the statistical computing software R (R Foundation for Statistical Computing, Vienna, Austria) with the packages "xlsx" and "dplyr."(12-14) This project was determined to be exempt from human research subjects review by the Washington State Institutional Review Board (Project E-020317-H).

RESULTS

Between January 1 and October 31, 2016, HCPs made 1,060 requests for Zika testing through public health on behalf of Washington State residents. Of those requests, the discipline of the HCP could be identified for 1,022 requests, which were included in the descriptive and logistic analyses. Of those 1,022 requests, 126 did not meet DOH testing criteria and were rejected for testing at DOH. The majority of requests were made on behalf of patients who were female, pregnant, and asymptomatic, and by OBGYN and General Practice disciplines. (Table 1) Requests for testing were more likely to be accepted for younger patients, for females (especially pregnant females), and for persons with symptoms. OBGYNs had the highest rate of acceptance for testing at DOH.

Of the 896 approved requests that were tested for Zika virus, 50 were positive. The majority of positive cases were female, not pregnant, and symptomatic, while the majority of negative patients were female, pregnant, and asymptomatic. While OBGYN disciplines requested testing for most of the negative patients, the majority of positive cases were referred by General Practice disciplines. Patient age, sex, pregnancy status, symptomology, and discipline of HCP that made the request differed significantly by laboratory results (Table 1).

Among patients of the same pregnancy status, General Practice and “Other” disciplines had significantly greater odds than OBGYN disciplines of referring a patient for whom testing was not recommended (Table 2). Among patients of the same pregnancy and symptom status, General Practice, Internal Medicine, and “Other” disciplines had significantly greater odds than OBGYN disciplines of the same outcome. Among patients of the same pregnancy status, all disciplines had significantly greater odds than OBGYN disciplines of having positive test results.

Table 1. Characteristics of Washington Public Health Zika testing requests made between January 1 and October 31, 2016 by request acceptance status and laboratory results.

	Request Rejected	Request Accepted	Total	p-value	Laboratory Positive	Laboratory Negative	Total	p-value
	N (%)	N (%)	N		N (%)	N (%)	N	
N	126 (14%)	896 (86%)	1,022		50 (6%)	846 (94%)	896	
Mean Age (Age Range)	35 (0-73)	32 (0-76)	--	0.0220	37 (15-76)	31 (0-73)	--	0.0268
Sex:				<0.0001				0.0002
Male	37 (24%)	120 (76%)	157		16 (13%)	104 (87%)	120	
Female	89 (10%)	776 (90%)	865		34 (4%)	742 (96%)	776	
Pregnancy Status (among females only)				<0.0001				<0.0001
Pregnant	36 (6%)	617 (94%)	653		7 (1%)	610 (99%)	617	
Not Pregnant	26 (15%)	146 (85%)	172		27 (18%)	119 (82%)	146	
Unknown	27 (68%)	13 (32%)	40		0	13 (100%)	13	
Symptomology:				<0.0001				<0.0001
Symptomatic	9 (3%)	308 (97%)	317		47 (15%)	261 (85%)	308	
Asymptomatic	105 (15%)	583 (85%)	688		3 (1%)	580 (99%)	583	
Unknown	12 (71%)	5 (29%)	17		0	5 (100%)	5	
HCP type:				0.0001				<0.0001
Emergency Medicine	7 (14%)	44 (86%)	51		8 (18%)	36 (82%)	44	
General Practice	47 (14%)	279 (86%)	326		28 (10%)	251 (90%)	279	
Internal Medicine	12 (18%)	53 (82%)	65		9 (17%)	44 (83%)	53	
OBGYN	54 (9%)	516 (91%)	570		4 (1%)	512 (99%)	516	
Other	6 (60%)	4 (40%)	10		1 (25%)	3 (75%)	4	

Table 2. Odds ratios of a request for public health Zika testing made between January 1 and October 31, 2016 being rejected or identifying a laboratory positive Zika virus case given HCP discipline, adjusting for patient pregnancy status or pregnancy and symptom status.

	Odds ratio of request rejection given HCP discipline						Odds ratio of a positive test result given HCP discipline					
	OR	(95% CI)	aOR*	(95% CI)	aOR**	(95% CI)	OR	(95% CI)	aOR*	(95% CI)	aOR**	(95% CI)
OBGYN	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Emergency Medicine	1.52	(0.65-3.54)	1.39	(0.56-3.48)	2.82	(0.70-11.27)	28.45	(8.18-98.97)	6.35	(1.40-28.76)	4.05	(0.87-18.89)
General Practice	1.61	(1.06-2.44)	1.62	(1.04-2.52)	3.01	(1.83-4.94)	14.28	(4.95-41.15)	4.18	(1.13-15.47)	2.92	(0.77-11.10)
Internal Medicine	2.16	(1.09-4.30)	2.08	(0.99-4.35)	5.96	(2.46-14.46)	26.18	(7.75-88.45)	6.02	(1.37-26.50)	4.10	(0.90-18.64)
Other	14.33	(3.92-52.37)	15.29	(4.01-58.31)	20.44	(4.02-104.03)	42.67	(3.62-503.28)	18.99	(1.14-316.75)	66.61	(1.60-2771.41)
* Adjusted for patient pregnancy status												
** Adjusted for patient pregnancy and symptom status												

DISCUSSION

Between January 1 and October 31, 2016 in Washington State, OBGYN and General Practice disciplines made the most Zika virus testing requests through public health. The majority of testing was done on asymptomatic pregnant females. However, most positive cases were symptomatic and not pregnant. General Practice, Internal Medicine, and “Other” disciplines had the greatest odds of referring a patient for whom testing was not recommended, while Emergency and Internal Medicine disciplines had the greatest odds of requesting testing for patients who tested positive.

HCP ability to appropriately apply testing guidance is necessary for the efficient identification of patients infected with Zika. HCP disciplines that bear a large burden of requests or exhibit greater odds of having a request rejected or referring positive patients indicate areas for increased public health outreach and collaboration. OBGYN and General Practice disciplines bore the greatest burden of Zika test requests. This is likely due to testing guidance, which, due to concerns of congenital infection and resulting adverse outcomes, promoted testing of asymptomatic pregnant females with possible exposure to Zika starting in February 2016. Differences in patient age, sex, pregnancy status, and symptom status by request rejection status and laboratory results largely reflect DOH testing criteria, as well. “Other” disciplines had the greatest odds of requesting testing for a patient for whom testing was not recommended. These disciplines requested Zika testing much less frequently than other disciplines, and therefore may be less familiar with DOH testing criteria. General Practice and Internal Medicine disciplines also had elevated odds of request rejection between the two models. The increase in odds of

rejection when symptom status was controlled for likely reflects that OBGYN disciplines refer predominantly asymptomatic females while other disciplines refer more symptomatic patients. “Other” disciplines also had the greatest odds of requesting testing for a positive case. However, as only four patients referred by “Other” disciplines were tested, this result is likely biased due to small sample size. Emergency and Internal Medicine disciplines also had significantly elevated odds of identifying positive cases. Most positive cases were symptomatic, therefore this likely reflects symptomatic patient care-seeking behavior. Given the relatively large volume of requests made by General Practice disciplines and the elevated odds of both request rejection and identifying a positive case, these disciplines represent a population for increased public health outreach to clarify testing criteria and facilitate identification of infected patients.

Zika testing represents a considerable cost to public health, both financially and in terms of personnel labor. However, testing guidance has intentionally fostered extensive testing among asymptomatic pregnant females, a population that resulted in relatively few positive cases in this sample. Zika infection is frequently unaccompanied by symptoms and knowledge of infection can be used to inform decisions about terminating a pregnancy.(5-7) However, there is no cure for Zika or microcephaly, it is unknown how often pregnancies are terminated due to Zika infection, and testing may cause unnecessary anxiety among some patients. The recent decision by CDC to no longer routinely recommend Zika testing for asymptomatic pregnant females may be effective in decreasing costs to public health while still maintaining testing among high risk pregnant females.(15) Further research is required to assess the impact of changes to testing recommendations on patient care, surveillance quality, and costs to public health.

LIMITATIONS

This study has several limitations. Selection bias is innate to surveillance data. The patients included in this study reflect a select group in Washington State that had access to healthcare and sought testing for Zika virus. However, as the subsidized testing offered by public health mitigates some of the costs associated with Zika testing, the study population may represent a more diverse sample of the population than if testing had only been conducted commercially. Varying levels of request screening by LHJs prior to reporting requests to DOH likely led to selection bias by jurisdiction. However, this selection bias is likely to be consistent across HCP disciplines within each jurisdiction. Additionally, HCPs that directly submitted specimens to DOH without first contacting LHJ were included. This practice may be associated with provider discipline, but could not be assessed as direct submission was not recorded. We assumed that the distribution of HCP disciplines in the rejected population included in this study is generalizable to the greater population of rejected requests screened by LHJs. However, if this population is not generalizable to requests screened by LHJs, then the relative odds of request rejection across HCP disciplines found by this study may be biased. Availability of patient characteristic data differed by request acceptance status as data was not consistently reported on rejected requests, which may have biased results of the descriptive analysis. It was necessary to aggregate HCP disciplines to increase sample sizes for analysis, which may have resulted in some loss of information. However, we aggregated disciplines based on similarities in expected patient populations to maximize clinical significance of findings.

It is impossible to assess from this dataset alone the quantity and quality of patient and test request screening done by HCPs, as commercial testing became available in mid-2016. Therefore, the findings of this study can only indicate recommended disciplines for public health

outreach. Incomplete surveillance of this disease also means that this study may not reflect the true prevalence of Zika in Washington.

CONCLUSION

Given the potentially severe consequences of Zika infection to pregnant females, testing guidance during the study period appropriately fostered disproportionate testing of asymptomatic pregnant females. The burden of this testing fell largely on OBGYN and General Practice HCP disciplines, who represent an important population for public health outreach and collaboration for Zika testing and surveillance in Washington State. However, asymptomatic pregnant females rarely tested positive, and the volume of testing is costly for public health. The CDC has since updated their guidance to no longer routinely recommend testing among asymptomatic pregnant females. It is yet unclear how this guidance will affect testing and surveillance.

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