



# Rubella Surveillance and Diagnostic Testing among a Low-Prevalence Population, New York City, 2012–2013

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**ABSTRACT** The New York City Department of Health and Mental Hygiene (DOHMH) receives clinical and laboratory reports for rubella. Because rubella immunoglobulin M (IgM) assays may produce false-positive results and rubella infections may be asymptomatic, interpretation of positive IgM results can be challenging. Rubella reports received by DOHMH in 2012 to 2013 were reviewed. The rubella IgM testing purpose was determined through case investigation. Results of IgM testing by indirect enzyme-linked immunosorbent assay (ELISA) and capture enzyme immunoassay (EIA) were compared to determine positive predictive value (PPV) and specificity. DOHMH received 199 rubella reports; 2 were true cases. Of all reports, 77.9% were tested for rubella IgM erroneously, 19.6% were tested for diagnostic purposes, 2.0% had unknown test purpose, and 0.5% were not tested. PPV of indirect ELISA was 6% overall, 14% for diagnostic tests, and 0% for tests ordered erroneously. PPV of capture EIA was 29% overall, 50% for diagnostic tests, and 0% for tests ordered erroneously. Overall, specificity was 52% for indirect ELISA and 85% for capture EIA. Limiting rubella IgM testing to patients for whom rubella diagnosis is suspected and using a more specific IgM assay have the potential to reduce false-positive rubella IgM results.

**KEYWORDS** immunoglobulin M, immunoassays, rubella, serology, surveillance

Rubella was declared eliminated in the United States in 2004 and in all of the Americas in 2015; however, international importations from countries where rubella is endemic still occur (1–3). Rubella is a viral infection characterized by a generalized rash, lymphadenopathy, and arthralgia, though up to 50% of infections may be asymptomatic (4). Although rubella is usually a mild illness, infection with rubella virus during pregnancy can result in miscarriage, stillbirth, or congenital rubella syndrome, a serious condition characterized by birth defects, including hearing impairment, neurological abnormalities, and cardiac defects (4).

Given the grave consequences of rubella in pregnancy, prenatal rubella immunoglobulin G (IgG) testing for maternal immunity is the standard of care. IgG testing is recommended by the American College of Obstetricians and Gynecologists to identify women who are not immune to rubella for postpartum vaccination to prevent future rubella infection (5, 6).

Diagnostic testing for rubella should be performed when rubella infection is suspected based on clinical symptoms, particularly when international travel or known exposure has occurred. Diagnostic testing includes detection of rubella-specific immunoglobulin M (IgM) by enzyme immunoassay (EIA) or detection of rubella RNA by reverse transcriptase PCR (RT-PCR) to detect acute infection. Rubella-specific IgM is

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typically detectable between 4 and 30 days after rash onset; negative results for specimens collected before day 5 after rash onset should be repeated after day 5 (4). Rubella virus is best detected by PCR up to 4 days after rash onset but may be detectable from 1 week before to 2 weeks after rash onset (4). However, providers sometimes order rubella IgM tests inappropriately when testing for immunity or as a part of routine prenatal care for asymptomatic women (7). According to a national survey of state and local health departments, 6% to 11% of rubella investigations per year were conducted as a result of positive IgM results related to prenatal screening (8). Rubella IgM assays may produce false-positive results for several reasons, such as cross-reacting IgM resulting from infection with viruses other than rubella, the presence of rheumatoid factor, and persistent IgM after infection or vaccination (9–16). In countries with very low disease prevalence, such as the United States, the proportion of positive test results that are false positives increases (17). In addition, because the sensitivity and specificity of rubella IgM assay formats differ and up to 50% of rubella infections may be asymptomatic, interpretation of positive IgM results is challenging and often requires further investigation, particularly when testing pregnant women (18–22). This evaluation characterized rubella IgM testing in New York City (NYC) through the examination of clinical and laboratory reports received through the rubella surveillance system of the Department of Health and Mental Hygiene (DOHMH).

## RESULTS

**Reports to DOHMH.** DOHMH received a total of 199 rubella reports from 1 January 2012 through 31 December 2013, including 188 (95%) first reported by laboratories based on positive IgM results, 10 (5%) by health care providers, and 1 (1%) through DOHMH investigation of another suspected case of rubella (Table 1). Of the individuals reported to DOHMH, 88.9% (177) were female and 49.8% (99) were pregnant or postpartum (Table 1). Of all individuals reported, 77.9% (155) were tested for rubella IgM inappropriately, 19.6% (39) were tested for diagnostic purposes, 2.0% (4) had unknown test purpose, and 0.5% (1) was not tested. Overall, ages ranged from 0 to 64 years with a median and mean of 32 years. Among the 39 tested for diagnostic purposes, symptoms included fetal death or abnormality (59.0%,  $n = 23$ ), rash (30.8%,  $n = 12$ ), fever (25.6%,  $n = 10$ ), arthritis/arthralgia (7.7%,  $n = 3$ ), conjunctivitis (7.7%,  $n = 3$ ), and lymphadenopathy (7.7%,  $n = 3$ ) (Table 1).

**Laboratory testing.** Among the 199 reports received by the DOH, 99 (50%) were tested for rubella IgM by indirect enzyme-linked immunosorbent assay (ELISA) (Fig. 1). Of these 99 reports, 59 (60%) were discarded without need for further testing, due to either negative indirect ELISA IgM results, lack of symptoms and nonpregnant status, or lack of symptoms with records demonstrating prior immunity. Forty (40%) specimens were retested by capture EIA at CDC. Seven of the specimens tested by capture EIA were positive for rubella IgM, of which 5 were discarded as a result of high IgG avidity testing, lack of clinically compatible symptoms, and lack of international travel history, while 2 were confirmed as actual rubella cases (1% of all reports to DOHMH) (Fig. 1).

**Confirmed cases.** Both individuals with confirmed rubella were symptomatic, traveled internationally, and were not pregnant. One was a 27-year-old female from Italy who presented with rash, fever, conjunctivitis, and lymphadenopathy and was RT-PCR positive. She had been exposed in Italy to an individual with rubella. Control measures enacted by DOHMH included home isolation of the case while infectious as well as identification of 10 exposed persons (contacts) and ascertainment of their immunity to rubella. The second case was a 41-year-old male from Israel with rash, fever, arthritis/arthralgia, and lymphadenopathy. RT-PCR testing was not done. He was in China, Turkey, and Israel during his incubation period but denied having any known exposures to rubella. Control measures enacted by DOHMH included identification and communication with 21 contacts to determine their immunity to rubella. Among the 31 contacts of both cases, 16 (51.6%) had documented evidence of immunity (positive IgG titers,  $\geq 1$  dose of rubella-containing vaccine, or birth before 1957), 12 (38.7%) had unknown immunity status, and 3 (9.7%) were nonimmune. Two of the nonimmune

**TABLE 1** Characteristics of rubella reports to the New York City department of health and mental hygiene by testing purpose, 2012–2013

Characteristic	Total (n = 199)		Diagnostic (n = 39)		Inappropriate (n = 155)	
	n	% of total <sup>a</sup>	n	% of total <sup>a</sup>	n	% of total <sup>a</sup>
Source of first report						
Laboratory	188	95	32	82	153	99
Provider	10	5	7	18	2	1
DOHMH investigation	1	1	0	0	0	0
Sex						
Female	177	89	30	77	142	92
Male	22	11	9	23	13	8
Age (yr)						
Median	32	NA <sup>c</sup>	29	NA	33	NA
Range	0–64	NA	0–59	NA	2–64	NA
Pregnant or postpartum						
Yes	99	50	24	62	73	47
No	97	49	14	36	80	52
Unknown	3	2	1	3	2	1
IgM testing purpose						
Inappropriate	155	78	0	0	155	100
Diagnostic	39	20	39	100	0	0
Unknown	4	2	NA	NA	NA	NA
Not tested	1	1	0	0	0	0
Symptoms <sup>b</sup>						
Fetal abnormality or death	23	12	23	59	0	0
Rash	12	6	12	31	0	0
Fever	10	5	10	26	0	0
Arthritis/arthralgia	3	2	3	8	3	2
Conjunctivitis	3	2	3	8	0	0
Lymphadenopathy	3	2	3	8	2	1

<sup>a</sup>Rounded to the nearest percentage point.

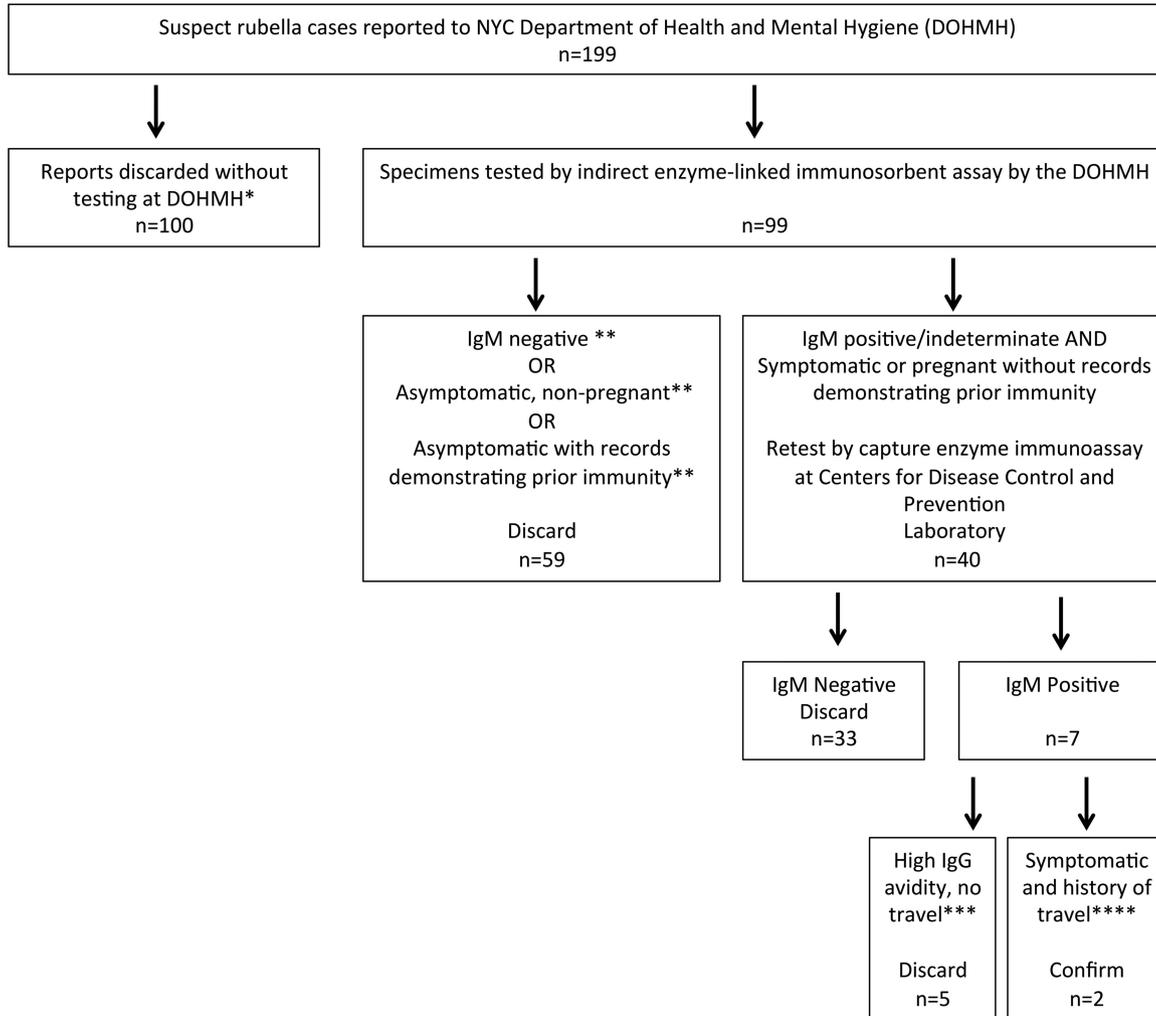
<sup>b</sup>Symptoms are not mutually exclusive.

<sup>c</sup>NA, not applicable.

contacts were placed on home isolation for the duration of the incubation period (through 23 days after the date of last exposure); one was identified after the incubation period and followed up by DOHMH to ensure they had not developed a rash. Of the 12 with unknown immune status, 7 (58%) were identified after the incubation period and denied symptoms and 5 (42%) were unable to be reached by phone, email, and/or mail. No secondary cases were identified.

**PPV and specificity of IgM assays.** The positive predictive value (PPV) of indirect ELISA was 6% (95% confidence interval [CI], 1 to 19%) overall, including a PPV of 14% (95% CI, 2 to 43%) for specimens tested for diagnostic purposes and 0% (95% CI, 0 to 16%) for specimens tested inappropriately. The PPV of capture EIA was 29% (95% CI, 4 to 71%) overall, with 50% (95% CI, 7 to 93%) for specimens tested for diagnostic purposes and 0% (95% CI, 0 to 71%) for specimens tested inappropriately (Table 2). PPVs were not significantly different between indirect ELISA and capture EIA ( $P = 0.12$ ) overall. PPVs were also not significantly different between diagnostic and inappropriate testing either for indirect ELISA ( $P = 0.15$ ) or for capture EIA ( $P = 0.43$ ).

The specificity of indirect ELISA was 50% (95% CI, 40 to 60%) overall, 49% (95% CI, 31 to 61%) for specimens tested inappropriately, and 52% (95% CI, 34 to 70%) for specimens with diagnostic testing. For capture EIA, the specificity was 85% (95% CI, 74 to 96%) overall, 86% (95% CI, 67 to 96%) for specimens tested inappropriately, and 83% (95% CI, 52 to 98%) for specimens with diagnostic testing (Table 3). Capture EIA had significantly greater specificity than indirect ELISA overall ( $P = 0.001$ ). Specificity was



**FIG 1** Classification status and rubella IgM testing by New York City Department of Health and Mental Hygiene’s Public Health Laboratory and Centers for Disease Control and Prevention Laboratory, 2012–2013. Abbreviations: CDC, Centers for Disease Control and Prevention Laboratory; DOHMH, Department of Health and Mental Hygiene; IgM, immunoglobulin M; NYC, New York City. \*, includes the following: no laboratory testing,  $n = 1$ ; tested by CDC without DOHMH testing,  $n = 2$ ; tested by labs other than DOHMH or CDC,  $n = 97$ ; \*\*, categories not mutually exclusive; \*\*\*, includes one individual who was unable to be reached to determine international travel history; \*\*\*\*, one of two was reverse transcriptase PCR positive.

not significantly different between diagnostic and inappropriate testing either for indirect ELISA ( $P = 0.82$ ) or for capture EIA ( $P = 0.76$ ).

**Timeliness.** The mean time from specimen collection to classification for all reports was 22 days among the 92 reports for which a classification date was available. Time to

**TABLE 2** Positive predictive value of rubella IgM assays by testing purpose, New York City, 2012–2013

IgM assay <sup>a</sup> type	Testing purpose	No. of samples:					PPV (%)	95% CI (exact)
		Tested	IgM negative	IgM indeterminate	IgM positive	Confirmed		
Indirect ELISA	All purposes	40	0	5	35	2	6	1–19
	Inappropriate	26	0	5	21	0	0	0–16
	Diagnostic	14	0	0	14	2	14	2–43
Capture EIA	All purposes	40	32	1	7	2	29	4–71
	Inappropriate	26	22	1	3	0	0	0–71
	Diagnostic	14	10	0	4	2	50	7–93

<sup>a</sup>Assays include only samples from individuals with IgM testing performed by both indirect ELISA by the NYC Department of Health and Mental Hygiene Public Health Laboratory and capture EIA by the Centers for Disease Control and Prevention Laboratory ( $n = 40$ ). EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay.

**TABLE 3** Specificity of IgM assays by test purpose, New York City, 2012–2013

IgM assay type	Testing purpose	No. of samples:			Specificity (%)	95% CI
		Tested	IgM negative	Discarded		
Indirect ELISA	All purposes <sup>a</sup>	96	47	94	50	40–60
	Inappropriate	65	32	65	49	37–61
	Diagnostic	31	15	29	52	34–70
Capture EIA	All purposes <sup>a</sup>	42	34	40	85	74–96
	Inappropriate	28	24	28	86	67–96 <sup>b</sup>
	Diagnostic	14	10	12	83	52–98 <sup>b</sup>

<sup>a</sup>Excludes results with unknown testing purpose (*n* = 3).

<sup>b</sup>Exact 95% CI.

classification was significantly greater for results that required follow-up testing at the CDC (mean, 34 days) than for those that did not (mean, 20 days) (*P* < 0.001).

**DISCUSSION**

This evaluation demonstrates that the surveillance system in NYC was successfully able to detect true cases of rubella, enabling the implementation of appropriate control measures. The detection of two cases in 2012 to 2013 is consistent with annual case counts of between 0 and 2 reported in NYC for the 10 years prior to the evaluation and 9 cases of rubella nationally in 2012 and 2013 (23–33).

Inappropriate rubella IgM testing constituted the majority of rubella reports to NYC DOHMH. This high burden of inappropriate testing contributed to the low PPV of reports identified by routine rubella surveillance in NYC. Providers frequently ordered rubella IgM tests inappropriately to test for immunity, often as a part of routine prenatal care. Even though the likelihood of rubella infection is low, DOHMH pursues additional testing due to the serious consequences of congenital rubella. False-positive results waste resources dedicated to unnecessary case investigation, repeat laboratory testing, and concern for patients and providers.

False-positive results from both IgM assays were common. The low PPV for IgM assays is not unexpected, as PPV decreases among populations with low disease prevalence (17). In fact, due to a high proportion of false-positive results, Mayo Medical Laboratories discontinued serologic testing for rubella IgM in 2008 (34). As expected, the PPV was higher for specimens tested for diagnostic purposes than for specimens tested inappropriately, although this difference was not statistically significant. Statistical significance was not achieved, likely due to the small sample size resulting from the low prevalence of rubella in NYC. The PPV for the capture EIA was greater than that of the indirect ELISA, although the difference was not significantly different.

In this evaluation, the specificity for the capture assay was significantly higher overall than that of the indirect assay. This result is consistent with previous studies reporting higher specificity of capture assays than of indirect assays (18, 22). However, two studies that tested serum samples collected in countries where rubella is endemic reported that specificities of capture assays and indirect assays were not significantly different (19, 20). These studies also reported higher specificities for indirect assays (87% to 98%, various manufacturers) and capture assays (93% to 99%, various manufacturers) than those of our evaluation (18–20). One contributing factor for this discrepancy may be that in NYC, laboratories are required to report only positive test results for rubella to DOHMH. Because the majority of rubella reporting to DOHMH originates from laboratories, the majority of the individuals tested by indirect ELISA at the DOHMH are being retested after prior positive rubella IgM results by commercial laboratories. These individuals may have medical reasons that would predispose them to have false-positive rubella results and may not be representative of the general population. A limitation of our evaluation is that indirect and capture assays were performed by different testing laboratories. Also, only tests that were positive by indirect ELISA were tested by capture EIA, so we could not compare the specificities of

the two assays using the same population. In our analysis, specificity was similar when calculated separately by testing purpose. This may be explained by the fact that specificity, unlike PPV, is not dependent on disease prevalence.

Rubella IgG avidity testing may provide additional information to help classify rubella reports in countries of nonendemicity, where the PPV for IgM assays may be low. However, IgG avidity testing has some limitations. Avidity testing cannot rule out rubella reinfection, which although rare, has been documented in the literature; therefore, consideration of clinical and epidemiological factors is necessary to assess the risk of possible exposure to rubella (35, 36). For pregnant women, avidity testing is most useful in early pregnancy, as it can help to rule out an infection in the first trimester, when risk to the fetus is greatest. It can take up to 4 months for antibodies to mature from low to high avidity. For a woman infected with rubella early in pregnancy, IgG avidity would remain low throughout the first trimester and would become high by the second or third trimester, so avidity testing later in pregnancy could provide a false sense of security (37). Thus, the timing of sample collection in relation to dates of international travel or exposure and trimester of pregnancy should be considered in case classification decisions.

The need for repeated laboratory testing also had an impact on timeliness. Prior to testing by capture EIA at the CDC, specimens had been tested by the DOHMH (indirect ELISA) and/or commercial or hospital laboratories (assays not known). Sending specimens for additional testing significantly increased the time to classify cases. While control measures for the two confirmed cases described were enacted before cases were confirmed due to a high level of suspicion, this additional time may impact the timeliness of implementation of control measures for low-suspicion cases and increase anxiety in patients awaiting test results.

In a postelimination setting, rubella surveillance can be improved by reducing the number of false-positive rubella IgM results. Strategies to achieve this reduction include limiting rubella IgM tests to patients for whom a clinically compatible diagnosis is suspected and use of a more specific rubella IgM assay by laboratories. Reducing the burden of unnecessary rubella testing can lead to a more effective use of resources and ultimately a more appropriate public health response.

## MATERIALS AND METHODS

**Reports to DOHMH: case ascertainment and investigation.** In NYC, rubella is a reportable condition (38). Laboratories with test results consistent with rubella infection (e.g., positive IgM or RT-PCR) and providers who suspect rubella infection clinically are required to report to NYC DOHMH. This evaluation included all rubella reports received by NYC DOHMH in 2012 and 2013. Suspected measles cases reported to DOHMH that were tested for both measles and rubella were excluded from the evaluation ( $n = 17$ ; none confirmed as rubella cases).

DOHMH staff investigated reports to obtain clinical and epidemiological information from health care providers, as per routine surveillance. DOHMH asked providers for the reason the rubella IgM tests were ordered. In this analysis, we defined IgM tests ordered as a result of clinical suspicion of rubella as diagnostic. An example of appropriate testing includes ordering a rubella IgM test for a symptomatic individual, particularly for one who has traveled to a country where rubella is endemic. We defined IgM tests ordered unintentionally or inappropriately as "inappropriate testing." Examples of inappropriate testing include ordering a rubella IgM test when there was no concern for rubella infection either to determine evidence of immunity to rubella (i.e., only rubella IgG should have been ordered) or because the IgM test was part of a panel of tests ordered for other reasons.

**Laboratory testing.** Various commercial laboratories or NYC DOHMH Public Health Laboratory performed initial serologic testing for rubella IgM. Serum specimens collected from symptomatic patients or pregnant women without prior evidence of immunity, including those tested inappropriately, that tested IgM positive at DOHMH were sent to the Centers for Disease Control and Prevention (CDC) laboratory for repeat IgM testing and for IgG avidity testing (Fig. 1). The CDC also performed RT-PCR on urine, nasopharyngeal swab, or throat swab specimens when appropriate specimens were available for clinically suspected cases (39).

DOHMH performed rubella IgM testing using an indirect enzyme-linked immunosorbent assay (Wampole Rubella IgM ELISA II, 425350CE; Cranbury, NJ). The CDC performed rubella IgM testing using a capture EIA (Diamedix Rubella IgM Capture; Erba Scientific, Miami, FL). Capture assay plates are coated with anti-human IgM antibody to increase specificity for IgM molecules (14).

To perform the CDC laboratory-developed assay for rubella IgG avidity, the rubella-specific IgG IU per milliliter of test serum values were determined using an indirect ELISA (Wampole Rubella IgG ELISA II, 425300CE; Cranbury, NJ). Sera containing  $<10$  IU/ml were not tested, and sera containing  $>70$  IU/ml

were diluted to <70 IU/ml with the kit dilution buffer. The avidity of the rubella-specific IgG antibodies was determined by parallel washing of wells after the serum incubation step with the standard buffer and the buffer modified by the addition of 35 mM diethylamine (DEA). Standard wash buffer alone was used after the conjugate incubation. The avidity index was calculated as the ratio between the ELISA absorbance for serum tested with and without DEA. Serum samples with avidity indexes of <30% were considered to be low avidity, while indexes of >30% were high avidity. A high avidity index indicated that infection with rubella was remote, occurring 3 months or more prior to the serum collection date. Low-avidity IgG antibodies can persist for up to 4 months following vaccination (37).

**Case classification.** We classified reports as confirmed or discarded based on criteria from the Council of State and Territorial Epidemiologists, with the exception of asymptomatic, nonpregnant patients tested for IgM inappropriately, who were classified as discarded cases without further laboratory testing (40).

**Characterization of reports.** We characterized reports to DOHMH by sex, age, pregnancy status, rubella symptoms, source of first report to DOHMH, and purpose of IgM testing (diagnostic versus inappropriate testing). Reports indicating pregnant and postpartum status at the time of report, including miscarriage and stillbirth, were grouped together in analyses. We described the clinical presentations and travel histories of individuals with confirmed rubella, as well as the control measures enacted by DOHMH.

**IgM assays: positive predictive value and specificity.** Results of IgM testing by indirect ELISA performed at the DOHMH and capture EIA performed at the CDC were analyzed and compared. Case classification status was considered the gold standard in these analyses. For each assay, the PPV was calculated by dividing the number of individuals with positive IgM results who were classified as confirmed by the total number of individuals with positive IgM results. In order to make comparisons of PPVs between IgM assays, only individuals tested both by indirect and by capture assays were included in the calculation of PPV for each assay.

For each IgM assay, specificity was calculated by dividing the number of individuals with negative IgM results who were classified as discarded by the total number of individuals classified as discarded. The PPV and specificity for each assay were calculated separately by testing purpose (diagnostic versus inappropriate testing). For calculations of the PPV and specificity, we considered indeterminate results to be neither positive nor negative.

Exact 95% confidence intervals (CI) were calculated where noted; otherwise, 95% CI were calculated assuming a normal distribution. Specificities were compared using Pearson's chi-square and Fisher's exact tests. PPVs were compared between IgM assay formats using a generalized score statistic and between testing purposes using Fisher's exact test (41).

**Timeliness.** Timeliness was measured by the mean number of days between specimen collection for serologic testing and case classification. The date of case classification was documented beginning in March 2013, so cases classified prior to March 2013 were excluded from the timeliness analysis. We compared timeliness between individuals requiring serologic testing at the CDC and those without by Student's *t* test.

**Analysis.** For all statistical tests, significance was set at *P* levels of <0.05. Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

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