Reassessing serosurvey-based estimates of the symptomatic proportion of Zika virus infections

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WEB APPENDIX 1

Assay Sensitivity

After the acute phase of infection, IgM sensitivity is generally high with observed sensitivity of 91% over 6-20 days post onset among U.S. travelers (1) and 97-100% over 8-60 days in Puerto Rico (2). IgM persistence is not yet well described at longer intervals, but likely begins to decrease beyond two months (e.g. only 79% of participants in a viral persistence study had IgM antibodies beyond 60 days post onset) (2). In the Yap and Puerto Rico studies, the serosurveys took place approximately 2 months after the peak of the epidemic, when IgM sensitivity was likely high, though perhaps waning for those infected early in the epidemic. In French Polynesia, the serosurvey was conducted approximately 2–3 months after the peak of the outbreak using an IgG assay which is expected to have high sensitivity for a longer time period because of longer IgG persistence (3). Seropositivity among symptomatic individuals in each study gives a lower bound for possible sensitivity. This was 85% in Yap, 67% in French Polynesia, and 58% in Puerto Rico. Evaluations of IgM and IgG assays for related dengue viruses have found sensitivities of 61.5–100%, with the majority of assays on the higher end of this spectrum (4-7). Given this evidence, we assumed that sensitivity for all three studies was most likely in the range of 85-99% and assigned the parameter a beta prior distribution with a mean of 95% and a 95% uncertainty interval approximately matching the assumed range, $beta(35, 2)$ **(Table S1)**.

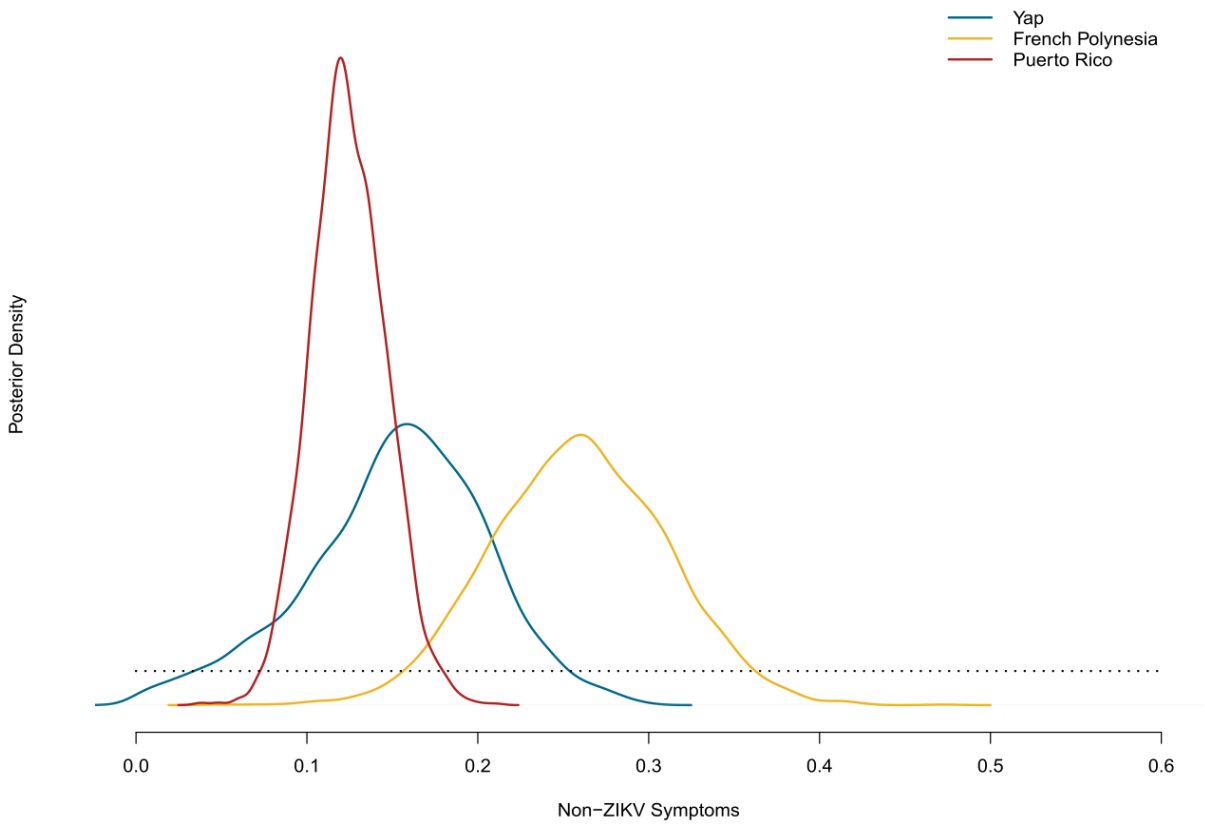
Assay Specificity

The specificity of serological assays for flaviviruses has long posed a challenge, especially in populations with previous exposure to dengue (e.g. Yap, French Polynesia, and Puerto Rico). Little quantitative evidence on the specificity of serological assays for ZIKV infection exists, but

numerous comparative studies of specificity for dengue virus ELISAs have been published (4-7). These studies have used a mix of negative control and challenge specimens for specificity assessment, ranging from only patients from dengue endemic areas (6) to only patients from non-endemic areas (7). Across the studies, specificity ranged from 80% to 100% for a wide variety of IgM and IgG ELISA assays. In the Zika serosurveys analyzed in here, additional analyses support an assertion that there was limited cross-reactivity and therefore reasonably high specificity in the specific studies. In Yap, there was no evidence of recent dengue; no patients with acute illness were positive for dengue virus RNA by RT-PCR (8). In French Polynesia, a serosurvey of blood donors prior to the Zika outbreak found that only 0.8% of donors (all with travel histories) were positive for ZIKV by IgG ELISA, despite 80% being positive by dengue virus IgG ELISA (9). This indicates that cross-reactivity for the ZIKV IgG ELISA was low in French Polynesia. For Puerto Rico, there was also no evidence of a concurrent dengue outbreak; during the study period the Department of Health reported 8,692 laboratory confirmed ZIKV infections and zero laboratory confirmed dengue virus infections (10). Given this evidence, we assumed that specificity was in the range of 80-100% with and assigned the parameter a beta prior distribution with a mean of 94% and a 95% uncertainty interval matching the assumed range, $beta(17, 1)$ **(Web Table 1)**.

Web Table 1 — Test Characteristic Prior Distributions

Parameter	Prior Distribution	2.5% quantile	Median	97.5% quantile
Sensitivity	beta(35, 2)	0.85	0.95	0.99
Specificity	beta(17,1)	0.80	0.96	1.00



Web Figure 1. Estimated probability of being symptomatic due to causes other than ZIKV infection. Each line is the posterior density of P_{SB} for the specified locations from 'Imperfect Test + Symptom Overlap' model, which allows for the possibility the symptoms may result from both ZIKV infection and another cause. The black dotted line indicates the prior distribution.

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