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Practice of Epidemiology

Assessing Zika Virus Transmission Within Households During an Outbreak in Martinique, 2015–2016

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Since 2015, Zika virus (ZIKV) has caused large epidemics in the Americas. Households are natural targets for control interventions, but quantification of the contribution of household transmission to overall spread is needed to guide policy. We developed a modeling framework to evaluate this contribution and key epidemic features of the ZIKV epidemic in Martinique in 2015–2016 from the joint analysis of a household transmission study ($n = 68$ households), a study among symptomatic pregnant women ($n = 281$), and seroprevalence surveys of blood donors ($n = 457$). We estimated that the probability of mosquito-mediated within-household transmission (from an infected member to a susceptible one) was 21% (95% credible interval (CrI): 5, 51), and the overall probability of infection from outside the household (i.e., in the community) was 39% (95% CrI: 27, 50). Overall, 50% (95% CrI: 43, 58) of the population was infected, with 22% (95% CrI: 5, 46) of infections acquired in households and 40% (95% CrI: 23, 56) being asymptomatic. The probability of presenting with Zika-like symptoms due to another cause was 16% (95% CrI: 10, 23). This study characterized the contribution of household transmission in ZIKV epidemics, demonstrating the benefits of integrating multiple data sets to gain more insight into epidemic dynamics.

asymptomatic infections; final size model; household transmission; Zika virus

Abbreviations: CI, confidence interval; CrI, credible interval; ZIKV, Zika virus.

Zika virus (ZIKV) is an arbovirus transmitted by *Aedes* mosquitoes in tropical and subtropical regions (1). Discovered in 1947 (2) and regularly detected in Africa and Asia since then (3), ZIKV initially received little attention, mostly because ZIKV infections are usually asymptomatic or do not present severe symptoms, with Zika medical signs including fever, rash, conjunctivitis, arthralgia, myalgia, and headache. However, widespread ZIKV epidemics in Pacific Islands from 2007 (4) and in the Americas from 2015 (5, 6) have highlighted the risks of severe complications. In particular, ZIKV infection has been associated with Guillain-Barré syndrome and microcephaly (7–12). Currently, there is no curative treatment or vaccine for ZIKV infection (13). To develop effective control strategies against ZIKV, it is important to determine where ZIKV transmission occurs. Households might be natural targets for interventions because the abundance of *Aedes* breeding sites or the mosquito's feeding behavior and indoor resting, and the spatial proximity between household members might well facilitate mosquito-mediated transmission. However, a precise quantification of the contribution of household transmission to the overall spread is needed to guide policy.

Using data from a household transmission study where Zika-like symptoms were monitored in household contacts of laboratory-confirmed ZIKV cases, we characterized ZIKV household transmission in Martinique, a French island in the Caribbean that was affected by a large ZIKV outbreak in 2016 (14). We also investigated how such transmission studies, describing the clustering of symptomatic individuals in households, might be used to estimate other key epidemiologic

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parameters such as the proportion of asymptomatic infections. However, to be able to perform these assessments, we must first address a number of challenges and limitations inherent to our study design: the nonspecific nature of Zika symptoms means that 1) identified secondary cases might be unrelated to ZIKV infection; 2) fully asymptomatic ZIKV infections remain undocumented; and 3) because households necessarily include at least 1 symptomatic case (the index case), attack rates in the study might overestimate attack rates in the general population. We show how these challenges can be tackled with a statistical and modeling framework that integrates data sets documenting different aspects of this epidemic.

METHODS

Data

In this study, we used data from 3 different sources: a household transmission study, ZIKV testing of pregnant women, and a seroprevalence study among blood donors.

Household transmission study. Cohort of Patients Infected by an Arbovirus (CARBO) is a descriptive and prognostic cohort study of arbovirus infection in the French West Indies, French Guiana, and Metropolitan France (ClinicalTrials.gov identifier: NCT01099852) among people consulting in participating hospital centers (emergency room, full hospitalization, day hospitalization, or outpatient visit) (15). From December 2015 to October 2016, household contacts of laboratory-confirmed ZIKV cases included in the CARBO cohort in Martinique University Hospital were recruited for a household transmission study. Laboratory confirmation of recent ZIKV infection was performed by reverse-transcription polymerase chain reaction testing (RealStar Zika Virus reverse-transcription polymerase chain reaction kit 1.0; Altona Diagnostics, Hamburg, Germany) of serum or urine, or by direct detection of immunoglobulin M against ZIKV in serum (French National Reference Laboratory for arboviruses in Marseille, France). Immunoglobulin M antibodies were captured with rabbit antihuman immunoglobulin M antibodies (Interchim, Montluçon, France).

Initially, follow-up questionnaires and clinical data were collected on or after week 12 (week 1 corresponds to symptom onset in the index case). However, the protocol was amended in May 2016 to ensure more thorough follow-up, with additional visits planned nearer to the day of enrollment of the index case, on approximately day 10 and day 21. During each visit, household contacts were asked whether they were experiencing symptoms potentially associated with ZIKV infection such as fever, maculopapular rash, nonpurulent conjunctivitis, arthralgia, and myalgia since the beginning of the ZIKV epidemic, as well as the date of onset of any symptoms. In addition, study teams performed telephone interviews to obtain an update between 6 and 12 months after symptom onset in the index case.

We refer to the initial laboratory-confirmed ZIKV case as the index case. Other members of the household are denoted household contacts. A secondary case is defined as a household contact with at least 2 symptoms consistent with a Zika suspected case (acute onset of fever, maculopapular rash, nonpurulent conjunctivitis, arthralgia, and myalgia). The secondary clinical attack rate corresponds to the proportion of household contacts that are secondary cases.

This study was approved by a French ethics committee (Comité de Protection des Personnes–CPP Sud-Ouest et Outre-Mer).

ZIKV testing results for pregnant women with symptoms. Between February and November 2016, all pregnant women presenting Zika-like symptoms were routinely tested for ZIKV infection, due to the risk of microcephaly associated with ZIKV infection during pregnancy (16). Blood samples were tested using specific reverse-transcription polymerase-chain-reaction testing for ZIKV (RealStar Zika Virus reverse-transcription polymerase chain reaction kit 1.0;Altona Diagnostics). We analyzed the laboratory results for the subset of pregnant women that consulted at Martinique University Hospital. This data set brings information on the proportion of Zika-like symptoms related to a ZIKV infection.

Seroprevalence among blood donors. We used data from a published ZIKV seroprevalence survey among blood donors in Martinique (17) conducted during March 9–23 and June 6–13, 2016, using samples from blood donors. Details about the design and the laboratory tests used are published elsewhere (17) and available in Web Appendix 1 (available at https://academic.oup.com/aje). This data set gives information on the expected attack rate of ZIKV in the population.

Model

We initially adopted a classical final-size chain binomial model for viral transmission in and out of the household (18, 19) that describes the expected distribution of the number of infected household members according to household size. In this model, each household member has a probability p_C to acquire infection from outside the household during the course of the epidemic (hereafter, "community transmission"). If an individual is infected, there is a probability p_H of vector-mediated transmission toward another susceptible household member ("within-household transmission"). Under these assumptions, the chain binomial model can be used to derive the expected attack rate (defined as the overall probability of ZIKV infection during the epidemic) as a function of household size.

In our baseline analysis we assumed that the probability of within-household transmission was independent of household size. We also considered an alternative model using a frequency-dependent probability of within-household transmission (20–22) whereby p_H decreases with household size N according to $p_H = 1 - \exp(-\frac{\beta}{N})$.

We adapted this classical model to capture the characteristics of the data we used. First, we included the probability of asymptomatic ZIKV infection p_A. Because secondary cases were not laboratory confirmed, the probability p_{NZ} of presenting with symptoms unrelated to ZIKV infection was factored into the model. Finally, only households with at least 1 laboratory-confirmed and symptomatic ZIKV case detected by surveillance were included in our study. This constitutes a selection bias, given that it makes it more likely that we included households with a large number of symptomatic ZIKV cases. This bias was accounted for by conditioning inference on the

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probability that the household was recruited for the study. Technical details are provided in Web Appendix 1.

We assumed that the number of confirmed ZIKV infections among pregnant women with Zika-related symptoms followed a binomial distribution where the probability of ZIKV infection in a symptomatic individual was derived from the mathematical model described above (see Web Appendix 1).

Finally, because it takes about 2 weeks for an infected individual to seroconvert, we assumed that seroprevalence on a given week reflected the cumulative infection attack rate 2 weeks earlier. Under the assumption that the (unobserved) weekly number of ZIKV infections was proportional to the (observed) weekly number of consultations for ZIKV-related symptoms (given by surveillance data (17)), we were able to estimate the overall infection attack rate p_I from the cumulative infection attack rate measured by the serological studies for weeks 9 and 21 of 2016 and the proportion of consultations that occurred up to weeks 9 and 21 of 2016 (see Web Appendix 1).

To assess the effect of the selection bias mentioned above, we compared the observed secondary clinical attack rate in recruited households (i.e., where there is at least 1 symptomatic ZIKV case) with that expected in a typical household, using parameters drawn from the posterior distribution and the distribution of household sizes in Martinique (23).

Parameter estimation

The posterior distribution of model parameters was explored in a Bayesian framework using Markov chain Monte Carlo sampling (24), with uniform priors between 0 and 1 for model parameters. More details about the methods are presented in Web Appendix 2. We used the deviation information criterion for model comparison (25), with the smallest deviation information criterion value corresponding to the best fit. A difference of 4 in deviation information criterion units is considered substantial (26).

Validation of the model and of the statistical framework

We derived the expected distribution of secondary clinical attack rates in participating households, ZIKV seroprevalence in both March and June 2016, the proportion of persons with Zika-like symptoms that were infected by ZIKV, the size of households, and number of members reporting symptoms among recruited households. We compared these predictions with observed values.

A simulation study was also performed to evaluate the ability of our approach to estimate model parameters (see Web Appendix 3). We simulated 500 data sets according to our study design, using parameter values at the posterior mean. Our model was then used to analyze these data sets, and we compared the estimated parameter values with input parameters.

Sensitivity analysis

We performed several sensitivity analyses to assess the robustness of our results. Recruitment of households occurred between December 2015 and October 2016; however, the study documenting ZIKV infections in pregnant women started later, in February 2016. In our first sensitivity analysis, we assessed how our estimates were modified if the analysis was restricted to this shorter time period (see Web Appendix 4). Second, the observed distribution of household sizes is truncated for Martinique (23), with households of size ≥6 being reported in a single category. In the baseline analysis, we assumed these households were uniformly distributed between sizes 6, 7, and 8 (see Web Table 1). We performed a second sensitivity analysis (see Web Appendix 5) using a geometric distribution (see Web Table 2). Finally, our model assumes that households were followed until the end of the epidemic. In practice however, follow-up was often a bit shorter: Defining the follow-up as the proportion of Zika-like cases reported in Martinique (14) at the time of the last interview, 84% of households were followed for more than 90% of the epidemic, and 16% were followed up for 80% to 90% of the epidemic. In a third sensitivity analysis, we accounted for this censoring in the model (see Web Appendix 6).

RESULTS

Data

A total of 68 households were recruited between December 2015 and September 2016, summing to a total of 232 household members (68 index cases and 164 household contacts), see Web Table 3. Households had an average size of 3.4 members (range, 1–8) (Figure 1A). Among the households, 14 (21%) had a questionnaire at inclusion of the index case (range, 1–5 days after symptom onset for the index case), 15 (22%) at approximately day 10 (range, 6–10), 17 (25%) near day 21 (range, 18–32), 17 (25%) near week 12 (range, 78–96 days), and 40 (59%) between 6 and 12 months after inclusion (range, 229–374 days). The average duration of follow-up after the inclusion of the index case was 202 days (Figure 1B). Among the 164 household contacts, 79 (48%) developed Zika-like symptoms. The secondary clinical attack rate was similar, with overlapping confidence intervals, in households of size 2 (54%; 95% confidence interval (CI): 27, 80), 3 (53%; 95% CI: 30, 75), 4 (31%; 95% CI: 4, 57), and 5 (50%; 95% CI: 15, 85) (Figure 1C). Of the 281 pregnant women with Zika-like symptoms that were tested for ZIKV infection between February and November 2016, 204 (73%) were found to be infected with ZIKV. Finally, the seroprevalence among blood donors was 13.5% (95% CI: 6.2, 20.8) for 418 donors in March and 42.2% (95% CI: 34.9, 49.5) for 176 donors in June 2016 (17).

Transmission of Zika in the community and in the household

Results for Zika transmission are presented in Table 1. Posterior distributions and trace plots from the Markov chain Monte Carlo sampling are presented in Web Figures 1 and 2, respectively. The probability of acquiring ZIKV infection in the community was estimated at $p_C = 39\%$ (95% credible interval (CrI): 27, 50). The probability of mosquito-mediated within-household transmission from an infected member to a susceptible contact was estimated at $p_H = 21\%$ (95% CrI: 5, 51). The secondary clinical attack rate in recruited households was

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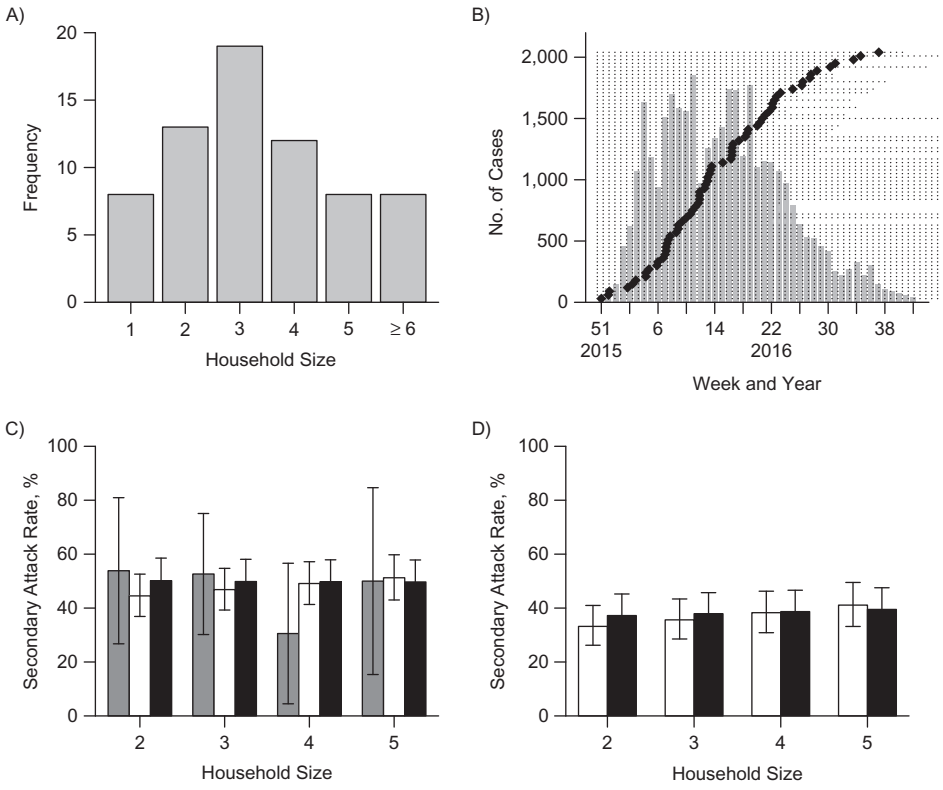


Figure 1. Observed and expected statistics for households in Martinique during a Zika virus outbreak, 2015–2016. A) Distribution of the sizes of the 68 recruited households. B) Timing of household inclusion in the survey. Each black dot indicates recruitment of a household; the dotted line represents the duration the household was followed. The gray bars represent the epidemic curve for Zika in Martinique, given by the number of Zika-like cases reported in Martinique in a sentinel network of general practitioners (14). C) Observed and expected secondary clinical attack rate in households recruited in the study as a function of household size in the data (gray) and for the baseline (white) and the frequency-dependent (black) models. D) Expected secondary clinical attack rate in a typical household in Martinique, as function of household size (i.e., once the effect of the selection bias has been removed). The secondary clinical attack rate is the proportion of household contacts who exhibit symptoms. Predictions are given for the baseline (white) and the frequency-dependent models (black). Whiskers represent 95% confidence intervals.

about 50%. However, once we corrected for the selection bias (i.e., the presence of at least 1 confirmed symptomatic Zika case seeking care in recruited households), our model predicted that the average secondary clinical attack rate was 39% (95% CI: 31, 46) in a typical household in Martinique (Figure 1D). The overall attack rate of ZIKV in the island population was estimated at 50%

Table 1. Estimates Obtained From the Model in the Main Analysis for Key Epidemic Features During the Zika Virus Outbreak in Martinique, 2015–2016[a]

Parameter	Main Analysis	
	Mean Value of the Posterior Distribution	95% CrI
Proportion of asymptomatic infections, p_A (%)	40	23, 56
Probability of infection from the community, p_C (%)	39	27, 50
Probability of within-household transmission, p_H (%)	21	5, 51
Probability of presenting symptoms due to another cause, p_{NZ} (%)	16	10, 23
Proportion of infections occurring at household level, %	22	5, 46
Attack rate, %	50	43, 58

Abbreviation: CrI, credible interval.

[a] The table shows mean (95% credible interval) of the posterior distribution obtained with Markov chain Monte Carlo sampling.

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(95% CrI: 43, 58). These results imply that 22% (95% CrI: 5, 46) of infections occurred within households and 78% (95% CrI: 54, 95) in the community.

ZIKV infection and the presence of Zika-like symptoms

We estimated that 40% of ZIKV infections (95% CrI: 23, 56) were asymptomatic and that the probability of presenting with Zika-like symptoms due to another cause was 16% (95% CrI: 10, 23) (Table 1).

Frequency-dependent household transmission

Under the assumption that the household transmission rate was frequency-dependent, we estimated that 30% (95% CrI: 8, 55) of infections occurred in the household setting, compared with 22% (95% CrI: 5, 46) in our main analysis (see Web Table 4). This model predicted an average secondary clinical attack rate of 38% in a typical household, compared with 39% in our baseline analysis (Figure 1D). However, the deviation information criterion was slightly higher for the frequency-dependent model: 452 versus 451 in the main analysis (see Web Appendix 7).

Model validation

There was a good agreement between observed values and expected distributions of key variables (Figure 2). The predicted secondary clinical attack rate in participating households was 50% (95% CrI: 42, 58) (observed: 48%). The seroprevalence in March and June 2016 was predicted at 15% (95% CrI: 13, 17) and 38% (95% CrI: 32, 44), respectively (observed: 14% and 44%, respectively). The predicted proportion of pregnant women with Zika-like symptoms testing positive for ZIKV infection was predicted at 73% (95% CrI: 68, 78) (observed: 73%). The expected distribution of the size of participating households and the number of members reporting symptoms is given in Web Table 5, and is consistent with the data. In a simulation study, we showed that our approach was able to reliably estimate key parameters (see Web Figure 3). True parameter values were within the 95% credible intervals in 97% of the simulations (see Web Table 6).

Sensitivity analysis

When the study period was restricted to the period from February to November 2016 (first sensitivity analysis), 51 households remained in the data set, with a secondary clinical attack rate of 43% and household transmissions representing 26% (95% CrI: 7, 52) of infections (see Web Table 7) (vs. 22% (95% CrI: 5, 46) in the main analysis). In addition, the proportion of asymptomatic ZIKV infections was slightly higher: 46% (95% CrI: 29, 62) versus 40% (95% CrI: 23, 56) in the main analysis. Using a geometric distribution for the tail of the household size distribution, we obtained results similar to those obtained in the main analysis (see Web Table 8). Finally, when we accounted for censorship in household follow-up, estimates remained largely unchanged, with a slightly higher contribution of households to ZIKV transmission: 24% (95% CrI: 6, 48) versus 22% (95% CrI: 5, 46) in the main analysis (see Web Table 9).

DISCUSSION

Household transmission studies constitute an important design that has been extensively used to assess the contribution of

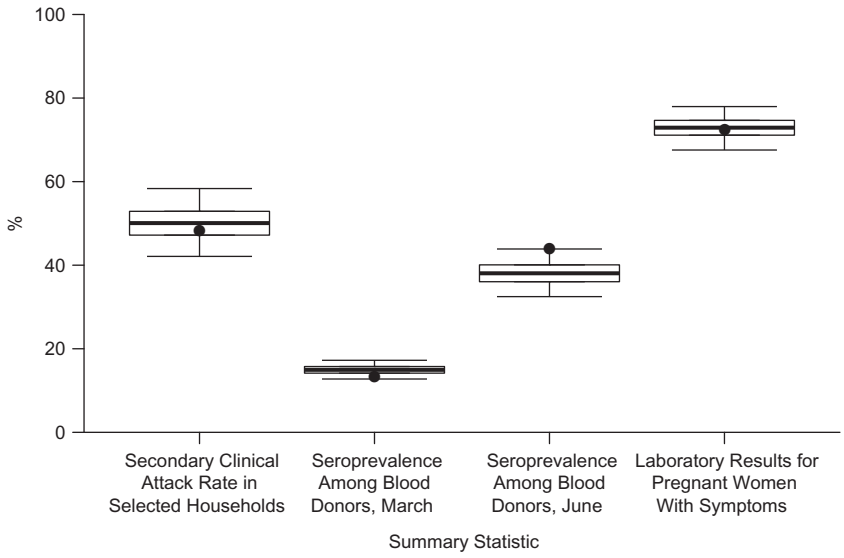


Figure 2. Expected distributions (boxplot) and observed values for the secondary clinical attack rate (defined as the proportion of nonindex household members with Zika-like symptoms) in the participating households recruited between December 2015 and September 2016, the seroprevalence among blood donors in Martinique in March and June 2016, and the proportion of pregnant women presenting Zika-like symptoms who tested positive for ZIKV infection during February–November 2016. The black dots represent the observed values in the data. The boxplots show the 2.5%, 25%, 50%, 75%, 97.5% quantiles of the distributions.

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households in the spread of a diverse set of pathogens including influenza, measles, Ebola, Middle East respiratory syndrome coronavirus, and chikungunya among others (20, 21, 27–34). To our knowledge, we are the first to use this design to obtain an assessment of ZIKV transmission in households. The development of dedicated statistical methods was necessary to properly account for specific features of the study design, while data integration was instrumental in tackling parameter identifiability issues.

We estimated that about a fifth of ZIKV infections in Martinique occurred in the household setting. This suggests that vector-control methods targeting households of cases and their neighbors might be beneficial, provided a sufficiently sensitive surveillance system (35). However, additional efforts will likely be necessary for effective control as a result of silent transmission and reporting delays, among other factors. Interestingly, estimates of the proportion of infections occurring in the household setting for pathogens such as influenza and chikungunya were relatively similar to the ones obtained here for ZIKV (31, 33).

Fifty percent of household contacts in recruited households exhibited clinical signs. However, by design, we were more likely to recruit households with a large number of ZIKV cases. As a consequence, secondary clinical attack rates were likely overestimated. Our statistical model was able to correct for such selection bias and produce more reliable estimates of household secondary clinical attack rates. Our model predicted that the secondary clinical attack rate in a typical household on the island was 39% (95% CrI: 27, 50) on average (i.e., substantially lower than what we observed in recruited households). This highlights the importance of developing statistical approaches that capture the specific features of the study design.

The proportion of asymptomatic infections (40%; 95% CrI: 23, 56) was low compared with previous estimates from a Yap Island outbreak (80%) (4) or among pregnant women in French Guiana (77%) (36). However, it was consistent with estimates obtained in a household investigation in Puerto Rico (43%) (37), a serosurvey in French Polynesia (50%) (38), a survey among blood donors Martinique (45%) (17), and the reanalysis of surveillance data from French overseas territories (<50%) (39). A number of factors could explain such variations. The risk of developing symptoms following infection might vary by population, for example, because of genetic factors. Age and sex might also affect the probability of asymptomatic infection (37), and thus the study population can explain some discrepancies. The variations could also be partly explained by differences in case definitions. For example, in Yap Island a symptomatic case was defined by an acute onset of generalized macular or papular rash, arthritis or arthralgia, or nonpurulent conjunctivitis (4), which is slightly different from the definition used in the present study. Other factors could also explain these discrepancies (e.g., the study designs or the way data were collected). These factors might have a larger effect for pathogens like ZIKV, whose symptoms are mostly mild. With an overall attack rate of ZIKV infection of 50% (95% CrI: 43, 58), this study suggests that about a third of the population in Martinique experienced symptoms due to ZIKV infection.

We developed an extension of the chain binomial model (18, 19) that addressed common limitations in studies based on household surveillance, namely: 1) the lack of laboratory confirmation for secondary cases; 2) the possibility of unobserved asymptomatic infections; and 3) a selection bias, given that only households with 1 symptomatic Zika case seeking care were included in the study. Identifiability problems were overcome by integrating 2 additional data sets collected during the outbreak: a seroprevalence study among blood donors (17) and laboratory results for pregnant women presenting Zika-like symptoms.

Our study has several limitations. First, the reporting of Zika-like symptoms by household members was done retrospectively, sometimes several months after the household inclusion. Thus, recall bias is likely in this study, particularly given the mild symptoms associated with Zika disease. This might have led to overestimating the proportion of asymptomatic infections. However, our estimate of the proportion of asymptomatic infections is at the lower end of those found in the literature, and it seems unlikely this proportion could be much below 40%. The imperfect follow-up of households also means that reported dates of symptom onset in household contacts are likely to be too imprecise to be used for inference (20, 32). As a consequence, we developed a statistical framework that did not use this information but relied only on the total number of cases per household. Second, it is possible that symptoms reported when Zika circulation was low were more likely related to another cause than were those reported around the peak of the outbreak. Such disparities between households included at different times during the epidemic could have an impact on estimates. However, we have shown in a sensitivity analysis that results remained stable when the analysis was restricted to the households recruited between February and October 2016. Finally, for a mild disease like Zika, with nonspecific symptoms, the definition of a symptomatic case can have an impact on the estimated proportion of asymptomatic infections.

In conclusion, we estimated that up to 60% (95% CrI: 44, 77) of ZIKV infections might have led to symptoms during the outbreak in Martinique, which implies that a third of the island inhabitants presented symptoms due to ZIKV. We also estimated that 78% (95% CrI: 54, 95) of infections were acquired from the community, which can limit the impact of within-household prevention measures. This study also highlights the importance of joint analysis of multiple data streams collected during an outbreak to get more insight on key epidemic features.

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REFERENCES

1. Benelli G, Romano D. Mosquito vectors of Zika virus. *Entomol Gen*. 2017;36(4):309–318.
2. Dick GW, Kitchen SF, Haddow AJ. Zika virus (I). Isolations and serological specificity. *Trans R Soc Trop Med Hyg*. 1952; 46(5):509–520.
3. Hayes EB. Zika virus outside Africa. *Emerg Infect Dis*. 2009; 15(9):1347–1350.
4. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med*. 2009;360(24):2536–2543.
5. Fauci AS, Morens DM. Zika virus in the Americas—yet another arbovirus threat. *N Engl J Med*. 2016;374(7):601–604.
6. Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. *Emerg Infect Dis*. 2015;21(10):1885–1886.
7. Cauchemez S, Besnard M, Bompard P, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *Lancet*. 2016;387(10033): 2125–2132.
8. França GV, Schuler-Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. *Lancet*. 2016; 388(10047):891–897.
9. Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly—Brazil, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(3): 59–62.
10. Brasil P, Pereira JP Jr, Moreira ME, et al. Zika virus infection in pregnant women in Rio de Janeiro. *N Engl J Med*. 2016; 375(24):2321–2334.
11. Hoen B, Schaub B, Funk AL, et al. Pregnancy outcomes after ZIKV infection in French territories in the Americas. *N Engl J Med*. 2018;378(11):985–994.
12. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*. 2016; 387(10027):1531–1539.
13. World Health Organization. Zika virus fact sheet. World Health Organization. http://www.who.int/mediacentre/factsheets/zika/en/. Accessed October 17, 2017.
14. Institut National de Veille Sanitaire. Situation épidémiologique du virus Zika aux Antilles. Point au 22 décembre 2016. 2016. http://invs.santepubliquefrance.fr/Publications-et-outils/Points-epidemiologiques/Tous-les-numeros/Antilles/2016/Situation-epidemiologique-du-virus-Zika-aux-Antilles.-Point-au-22-decembre-2016. Accessed June 21, 2017.
15. Rozé B, Najioullah F, Fergé JL, et al. Guillain-Barré syndrome associated with Zika virus infection in Martinique in 2016: a prospective study. *Clin Infect Dis*. 2017;65(9):1462–1468.
16. Haut Conseil de la Santé Publique. Personnes atteintes par le virus Zika. Actualisation des modalités de prise en charge. Paris, France: Haut Conseil de la Santé Publique; 2016. https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=532. Accessed May 25, 2018.
17. Gallian P, Cabié A, Richard P, et al. Zika virus in asymptomatic blood donors in Martinique. *Blood*. 2017; 129(2):263–266.
18. Longini IM Jr, Koopman JS. Household and community transmission parameters from final distributions of infections in households. *Biometrics*. 1982;38(1):115–126.
19. Ludwig D. Final size distribution for epidemics. *Math Biosci*. 1975;23(1–2):33–46.
20. Cauchemez S, Carrat F, Viboud C, et al. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. *Stat Med*. 2004;23(22): 3469–3487.
21. Fraser C, Cummings DA, Klinkenberg D, et al. Influenza transmission in households during the 1918 pandemic. *Am J Epidemiol*. 2011;174(5):505–514.
22. Kuan G, Ramirez S, Gresh L, et al. Seroprevalence of anti-chikungunya virus antibodies in children and adults in Managua, Nicaragua, after the first chikungunya epidemic, 2014–2015. *PLoS Negl Trop Dis*. 2016;10(6):e0004773.
23. Institut National de la Statistique et des Études Économiques. MEN1—Ménages par taille du ménage et catégorie socioprofessionnelle de la personne de référence en 2013.

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2013. https://www.insee.fr/fr/statistiques/2020330?geo=DEP-972&sommaire=2106091. Accessed June 21, 2017.
24. Gilks WR, Richardson S, Spiegelhalter D. *Markov Chain Monte Carlo in Practice*. Boca Raton, FL: CRC Press; 1995: 522.
25. Spiegelhalter DJ, Best NG, Carlin BP, et al. Bayesian measures of model complexity and fit. *J R Stat Soc Series B Stat Methodol*. 2002;64(4):583–639.
26. Burnham KP, Anderson DR. *Model Selection and Inference: A Practical Information-Theoretic Approach*. New York, NY: Springer Science & Business Media; 2013:373.
27. Longini IM Jr, Koopman JS, Monto AS, et al. Estimating household and community transmission parameters for influenza. *Am J Epidemiol*. 1982;115(5):736–751.
28. Gastañaduy PA, Budd J, Fisher N, et al. A measles outbreak in an underimmunized Amish community in Ohio. *N Engl J Med*. 2016;375(14):1343–1354.
29. Glynn JR, Bower H, Johnson S, et al. Variability in intrahousehold transmission of Ebola virus, and estimation of the household secondary attack rate. *J Infect Dis*. 2018;217(2): 232–237.
30. Drosten C, Meyer B, Müller MA, et al. Transmission of MERS-coronavirus in household contacts. *N Engl J Med*. 2014;371(9):828–835.
31. Cauchemez S, Ferguson NM, Fox A, et al. Determinants of influenza transmission in South East Asia: insights from a household cohort study in Vietnam. *PLoS Pathog*. 2014;10(8): e1004310.
32. Cauchemez S, Donnelly CA, Reed C, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med*. 2009;361(27):2619–2627.
33. Salje H, Lessler J, Paul KK, et al. How social structures, space, and behaviors shape the spread of infectious diseases using chikungunya as a case study. *Proc Natl Acad Sci U S A*. 2016; 113(47):13420–13425.
34. Lau MS, Cowling BJ, Cook AR, et al. Inferring influenza dynamics and control in households. *Proc Natl Acad Sci U S A*. 2015;112(29):9094–9099.
35. Vazquez-Prokopec GM, Montgomery BL, Horne P, et al. Combining contact tracing with targeted indoor residual spraying significantly reduces dengue transmission. *Sci Adv*. 2017;3(2):e1602024.
36. Flamand C, Fritzell C, Matheus S, et al. The proportion of asymptomatic infections and spectrum of disease among pregnant women infected by Zika virus: systematic monitoring in French Guiana, 2016. *Euro Surveill*. 2017;22(44).
37. Lozier MJ, Burke RM, Lopez J, et al. Differences in prevalence of symptomatic Zika virus infection by age and sex—Puerto Rico, 2016. *J Infect Dis*. 2018;217(11):1678–1689.
38. Aubry M, Teissier A, Huart M, et al. Zika virus seroprevalence, French Polynesia, 2014–2015. *Emerg Infect Dis*. 2017;23(4): 669–672.
39. Subissi L, Daudens-Vaysse E, Cassadou S, et al. Revising rates of asymptomatic Zika virus infection based on sentinel surveillance data from French overseas territories. *Int J Infect Dis*. 2017;65:116–118.

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