Web Material

Real-Time Assessment of Health-Care Requirements During the Zika Virus Epidemic in Martinique

Contents

Web Appendix 1

Mathematical Models

We used a deterministic SIR compartmental model to capture the ZIKV epidemic dynamics and the risk of GBS in ZIKV infected persons. The SIR model equations are:

$$\frac{dS}{dt} = -R_0\gamma\frac{SI}{N}$$
$$\frac{dI}{dt} = R_0\gamma\frac{SI}{N} - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

where R_0 is the reproduction number, $\gamma = T^{-1}$ is the inverse of the average infectious period, $S(t)$, $I(t)$, and $R(t)$ are respectively the number of susceptible, infectious, and recovered individuals at time t, and $N = S(t) + I(t) + R(t)$ is the number of individuals in the population - assumed to be constant over the course of the epidemic. As initial conditions we used $I(t=0) = I_0$ (where I_0 is one of the parameters estimated), $S(t=0) = N - I_0$, and $R(t=0) = 0$. For each set of parameters (R_0, γ, I_0), the system of differential equations was solved using the Runge-Kutta fourth-order method with a time step of 0.2 weeks.

The number of incident cases at week i is simply given by $Z_i = S(i-1) - S(i)$, while the expected number of consultations for ZIKV symptoms is $E_i = \rho Z_i$, where ρ is the probability of seeking care for ZIKV symptoms.

To capture overdispersion in the observed number C_i of consultations for week i we assumed that C_i had a negative binomial distribution $NegBinom(C_i; m, k)$ specified by its mean m and dispersion parameter k, with $m = E_i$, and $k = (E_i)^{\delta}$. Since the variance of $NegBinom(C_i; m, k)$ is $m + m^2 k^{-1}$, the above parametrization results in a negative binomial distribution with variance $m + m^{2-\delta}$ (with $m = E_i$), which approaches the variance of a Poisson distribution when δ is close to 2.

Finally, we assumed that persons infected by ZIKV had a probability p_{GBS} of developing GBS, so that the expected total number of GBS cases was given by $\lambda = Z\, p_{GBS}$, with Z the total number of estimated ZIKV infections.

Likelihood Function

The likelihood function summarizes the contribution of the different datasets to the likelihood:

- Epidemic time series: For each epidemic week *i* the likelihood function of our model contained the term $NegBinom(C_i; E_i, k_i)$ with E_i defined above and $k_i = (E_i)^{\delta}$.
- Data on GBS cases: The likelihood function included a Poisson term $Pois(G; \lambda = Z\, p_{GBS})$ for the total number *G* of GBS cases reported, with *Z* the total number of estimated ZIKV infections and p_{GBS} the probability of GBS following ZIKV infection.
- Serological data (when available): For French Polynesia, we additionally included a binomial term *Binom(314; 476, AR)* representing the probability of finding 314/476 seropositive individuals after the epidemic(1), given the estimated attack rate (*AR*).

The likelihood functions L for French Polynesia and Martinique were therefore:

French Polynesia: $$L = \left[\prod_i NegBinom(C_i; m = E_i, k = E_i^{\delta}) \right] Pois(G; \lambda = Zp_{GBS}) Binom(314; 476, AR)$$

Martinique: $$L = \left[\prod_i NegBinom(C_i; m = E_i, k = E_i^{\delta}) \right] Pois(G; \lambda = Zp_{GBS})$$

where the index *i* runs over all weeks for which we had data.

We note that for French Polynesia, the reproduction number could potentially be estimated by fitting our model i) to the final attack rate or ii) to the epidemic curve. Our likelihood framework makes it possible to analyze both datasets. Interestingly, our final estimate of R_0 for French Polynesia was close to the one that would be obtained if only the serological dataset had been used for inference, highlighting the important contribution of this dataset to inference.

Clinical management of GBS cases

To simulate the clinical management of GBS cases we sampled 100 sets of parameters from the posterior distributions and simulated 50 epidemics per set (for a total of 5000 = 100 x 50 simulated epidemics). For a GBS case, the probability of requiring intensive care p_{ICU} and the probability of requiring mechanical ventilation once in intensive care p_{MV} were estimated from the French Polynesia data: p_{ICU} = 16/42 = 0.38 and p_{MV} = 12/16 = 0.75. For each of the 100 sets of parameters, we proceeded as follows:

1. Simulate a ZIKV epidemic with the SIR model described above.
2. Compute the number of ZIKV incident cases Z_i for week i.
3. Draw the number of GBS cases G_i from $Binom(x; Z_i, p_{GBS})$.
4. Draw the number of GBS cases in ICU U_i from $Binom(x; G_i, p_{ICU})$.
5. Draw the number of mechanically ventilated GBS V_i from $Binom(x; U_i, p_{MV})$.
6. For each GBS case draw and assign a time interval from ZIKV symptoms to GBS.
7. For each GBS case in ICU draw and assign a time interval from GBS to admission to ICU, and the duration of the stay in ICU.
8. For each ventilated GBS case in ICU draw and assign a time interval from the admission to ICU to the start of mechanical ventilation, the duration of the mechanical ventilation, and the interval from the end of mechanical ventilation to ICU discharge.
9. Repeat steps 2 to 8 for week $i + 1$, until there are no more ZIKV cases.
10. Repeat steps 2 to 9 fifty times.

The distributions used for steps 6 to 8 were estimated from the French Polynesia data and are described in section “Analysis of Case Management Time Intervals in French Polynesia”.

Inference

As described above and in the main text, the model had 6 parameters: R_0 , $T = \gamma^{-1}$, I_0, ρ, p_{GBS}, and δ. For French Polynesia, estimates were obtained using uniform priors - see also the section “Influence of the Prior for French Polynesia” below. On the other hand, for Martinique, we fixed the average infectious period at T = 11 days, and we used Gaussian priors centered at the posterior means obtained for French Polynesia. In section “Sensitivity of Predictions for Martinique to the Average Infectious Period” below, we also present estimates for Martinique from a model in which the average infectious period was estimated using as prior the posterior distribution obtained for French Polynesia (T = 11.0 [9.5, 12.6] days).

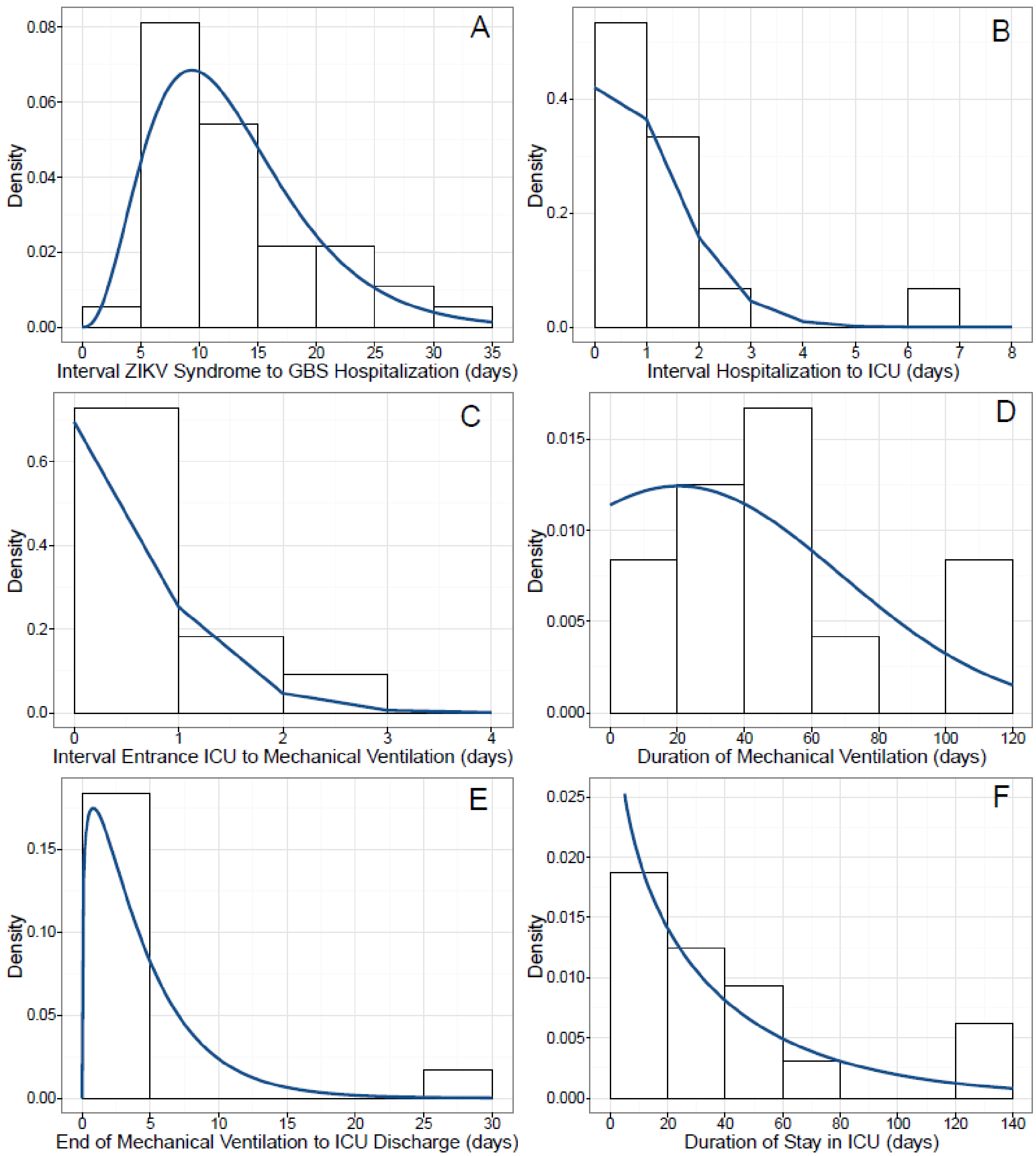
Web Appendix 2

Analysis of Case Management Time Intervals in French Polynesia

In order to characterize the clinical management of GBS cases we used the data on the 42 ZIKV-associated GBS cases recorded during the epidemic in French Polynesia. In particular, we used this dataset to fit six distributions corresponding to: 1) the time from ZIKV syndrome to hospitalization (Web Figure 1A); 2) the time from hospitalization to intensive care admission (Web Figure 1B); 3) the time between admission to intensive care and start of mechanical ventilation (Web Figure 1C); 4) the duration of mechanical ventilation (Web Figure 1D); 5) the time between the end of mechanical ventilation to the discharge from intensive care (Web Figure 1E); 6) the total duration of the stay in intensive care (Web Figure 1F). The distributions used for the fit were chosen by visual inspection of the quantile-quantile plots, and their corresponding parameters are reported in Web Table 1.

Web Figure 1

Case management time intervals in French Polynesia. In all panels the histogram shows the observed data while the blue line corresponds to our fit. A) Time from ZIKV syndrome to hospitalization. B) Time from hospitalization to intensive care admission. C) Time between admission to intensive care and start of mechanical ventilation. D) Duration of mechanical ventilation. E) Time between the end of mechanical ventilation and discharge from intensive care. F) Total duration of the stay in intensive care.



Web Table 1

Time intervals and distributions used to model them. The parameters are defined as follows: α and β are the shape and rate parameters for Gamma distributions; λ is the mean for Poisson distributions; μ and σ are the mean and the standard deviation for the Truncated Normal distribution having as support [0, +∞[. The intervals are assumed in units of days.

Time Interval	**Modeled as**	**Distribution Parameters**
ZIKV syndrome to hospitalization	Gamma	α = 3.75, β = 0.29
Hospitalization to ICU admission	Poisson	λ = 0.9
ICU admission to start of mechanical ventilation	Poisson	λ = 0.4
Duration of mechanical ventilation	Truncated Normal	μ = 20.3, σ = 48.5
End of mechanical ventilation to ICU discharge	Gamma	α = 1.23, β = 0.28
Total stay in ICU	Gamma	α = 0.80, β = 0.02

Web Appendix 3

Influence of the Prior for French Polynesia

In Web Table 2 we show that the choice of the prior does not strongly affect the parameter estimates for the 2013-2014 epidemic in French Polynesia. The results reported in the main text correspond to model M1, with uniform priors for all parameters. We explored two additional models (M2 and M3) with Gaussian priors for all parameters except I_0 and p_{GBS} and found the estimates practically unchanged, even when - as for M3 - the Gaussians are narrowly centered on values far from the posterior distribution obtained with M1.

Web Table 2

Parameter estimates for French Polynesia using different priors. *U*(a, b) denotes a uniform distribution over [a, b]. *N*(a, b) denotes a Gaussian distribution with mean μ = a and standard deviation σ = b. C_0 is the first reported number of consultations for suspected ZIKV infection, and *N* is the population of French Polynesia. The parameter γ is the inverse of the average infectious period.

Model	Parameter	Prior	Posterior Mean	95% CI
M1	R_0	$U(0, 10)$	1.61	1.53, 1.69
	$\gamma = T^{-1}$ (1/week)	$U(0.23, 7)$	0.64	0.56, 0.74
	I_0 (10^3)	$U(C_0, N)$	2.7	1.7, 3.9
	ρ	$U(0, 1)$	0.18	0.16, 0.21
	p_{GBS} (10^{-4})	$U(0, 1)$	2.48	1.81, 3.26
	δ	$U(0, 1)$	0.4	0.3, 0.5
M2	R_0	$N(2, 0.5)$	1.63	1.55, 1.71
	$\gamma = T^{-1}$ (1/week)	$N(0.5, 0.1)$	0.61	0.54, 0.69
	I_0 (10^3)	$U(C_0, N)$	2.9	2.0, 4.1
	ρ	$N(0.2, 0.05)$	0.18	0.16, 0.20
	p_{GBS} (10^{-4})	$U(0, 1)$	2.42	1.74, 3.18
	δ	$N(1, 0.25)$	0.4	0.3, 0.5
M3	R_0	$N(2, 0.1)$	1.69	1.61, 1.77
	$\gamma = T^{-1}$ (1/week)	$N(0.35, 0.1)$	0.57	0.50, 0.64
	I_0 (10^3)	$U(C_0, N)$	3.1	2.1, 4.5
	ρ	$N(0.7, 0.1)$	0.18	0.16, 0.20
	p_{GBS} (10^{-4})	$U(0, 1)$	2.33	1.71, 3.05
	δ	$N(1, 0.25)$	0.4	0.3, 0.5

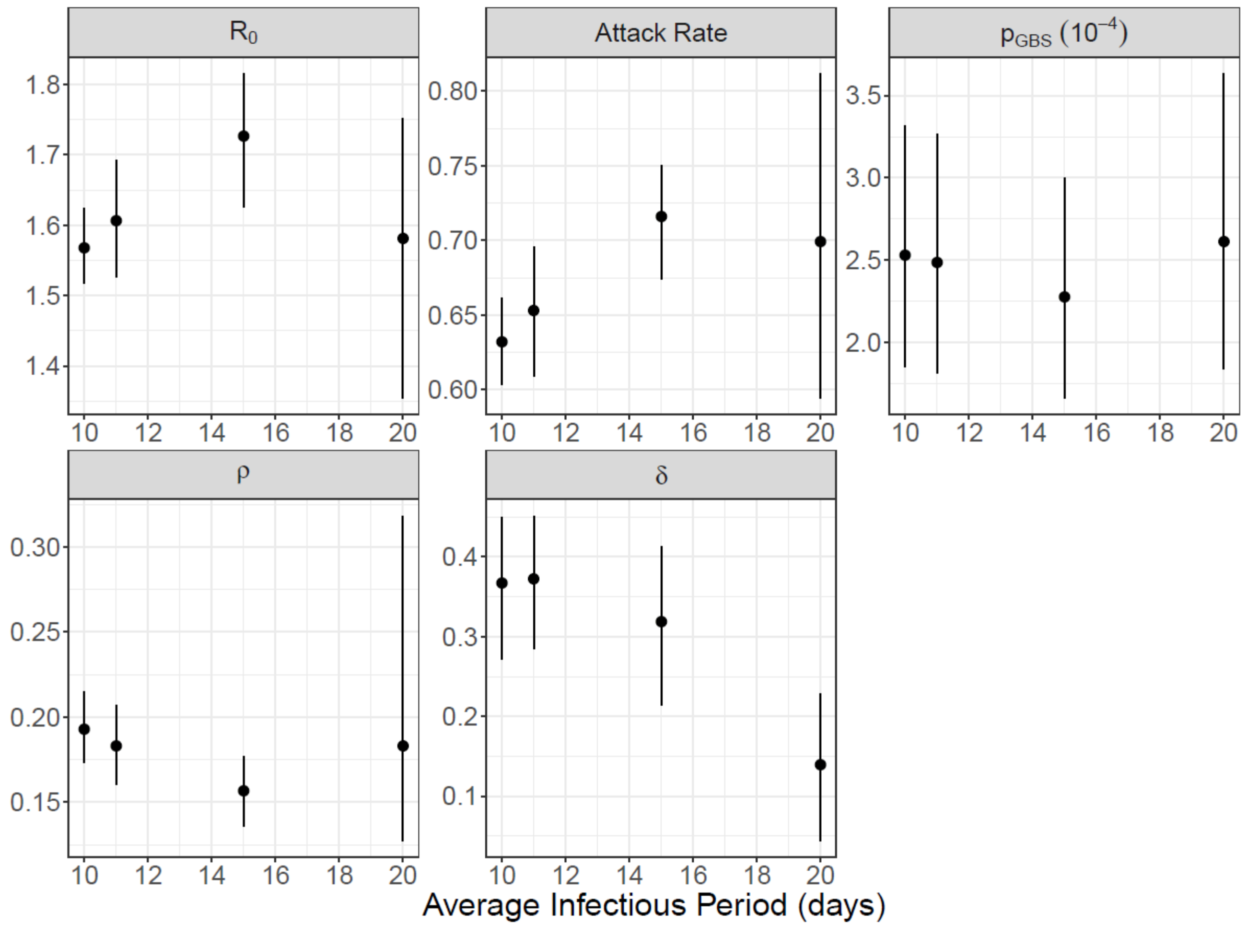
Web Appendix 4

Sensitivity Analysis for French Polynesia

In our main analysis, we estimate the ZIKV average infectious period from the French Polynesia outbreak data. Our 11-day estimate is consistent with a recent study showing that this parameter should be in the range (10-23) days(2). In Web Figure 2 we show how our estimates vary with the average infectious period, while in Web Figure 3 we compare the different fit obtained.

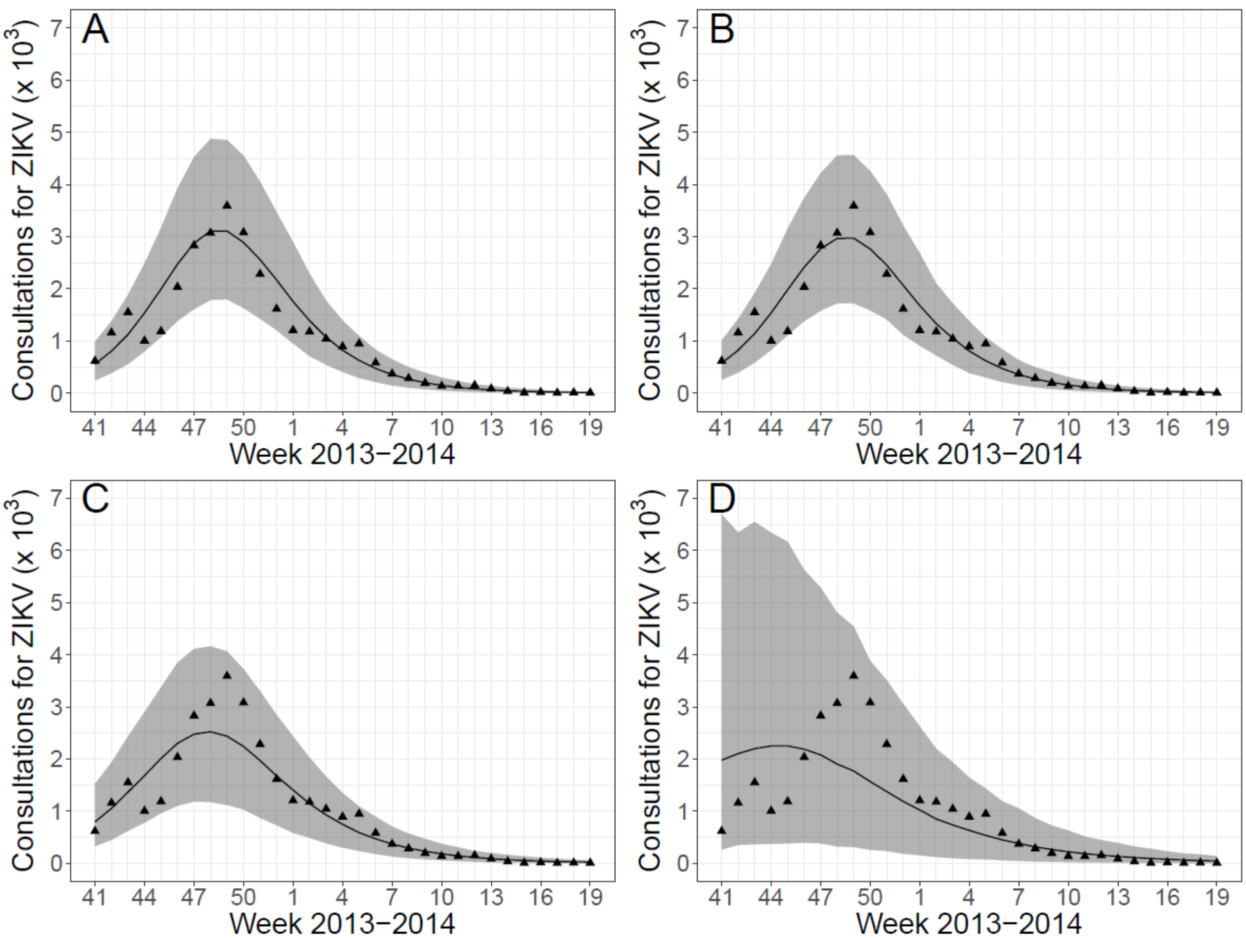
Web Figure 2

Sensitivity analyses for the French Polynesia epidemic. We report the estimates obtained from our model for a ZIKV average infectious period varying between ten and 20 days. The model with a (estimated) average infectious period of 11 days is the one used in the main text.



Web Figure 3

Fit obtained for the French Polynesia epidemic for different values of the average infectious period. We report the number of consultations for ZIKV obtained for models with an average infectious period fixed at 10 days (panel A), estimated (at 11 days, panel B), fixed at 15 days (panel C), and fixed at 20 days (panel D).



Web Appendix 5

Sensitivity of Predictions for Martinique to the Average Infectious Period

In Web Table 3 we show that the value of the average infectious period does not affect the predictions obtained for the Martinique epidemic.

Additionally, in Web Table 4, we report the parameter estimates obtained with a model where the average infectious period was also estimated - instead of being fixed at 11 days. In the latter case, we used as prior the posterior distribution obtained for French Polynesia (T = 11.0 [9.5, 12.6] days). We obtained a posterior distribution equal to the prior and parameter estimates practically identical to the ones reported in the main text (i.e. those from the baseline model in the table).

Web Table 3

Total number of GBS cases and resources needed to manage them for the epidemic in Martinique. The different rows represent model predictions at week 32-2016 for different fixed values of the average infectious period T.

	N. of GBS cases	N. of ICU beds		N. of ventilators	
T (days)	**Mean**	**Mean**	**95% CI**	**Mean**	**95% CI**
11	28	4	0, 8	3	0, 7
15	29	4	0, 9	3	0, 7
20	29	4	0, 8	3	0, 7

Web Table 4

Posterior mean and 95% credible intervals for the parameters of the model.

	Baseline Model		Estimated Infectious period	
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**
Reproduction number: R_0	1.36	1.30, 1.42	1.37	1.30, 1.46
Average infectious period: T (days)	Fixed at 11	-	11.4	9.9, 13.1
N. of initially infected: I_0 (10^3)	2.7	1.7, 3.9	2.7	1.7, 3.9
Probability of seeking care: ρ	0.22	0.20, 0.25	0.22	0.19, 0.25
Risk of GBS once infected with ZIKV: p_{GBS} (10^{-4})	1.58	1.04, 2.22	1.54	1.01, 2.19
Overdispersion parameter: δ	0.3	0.2, 0.4	0.3	0.2, 0.4

Web Appendix 6

Comparing SIR and SEIR Models

For arthropod-borne infections, the SIR model captures the complex natural history (including the extrinsic and intrinsic latent periods and the human infectious period) with a single parameter. To test whether explicitly adding a latent period could have an impact on the results of our model, we used the French Polynesia outbreak data to fit an SEIR model with a latent period fixed at six days(3). We found that the SIR and the SEIR models provided very similar results (Web Table 5) and almost identical fit (Web Figure 4). For this reason, we kept the simpler SIR model as our reference model.

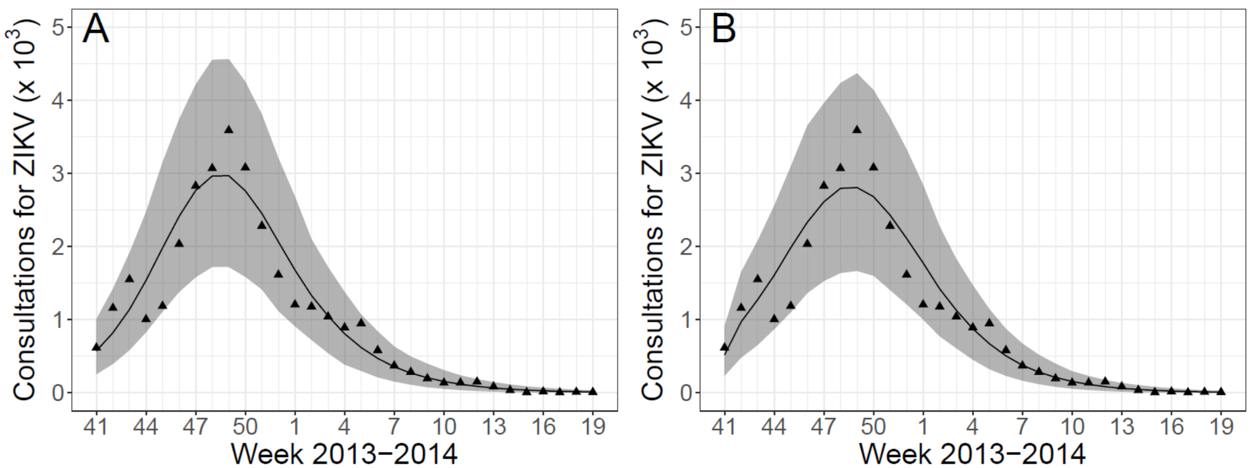
Web Table 5

SIR and SEIR model parameters for the 2013-2014 ZIKV outbreak in French Polynesia.

	SIR		SEIR	
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**
R_0	1.61	1.53, 1.69	1.64	1.55, 1.73
Latent Period (days)	NA		Fixed at 6	
Infectious Period (days)	11.0	9.5, 12.6	6.0	4.3, 8.2
I_0 (10^3)	2.7	1.7, 3.9	5.0	3.1, 7.4
ρ	0.18	0.16, 0.21	0.18	0.16, 0.21
p_{GBS} (10^{-4})	2.48	1.81, 3.26	2.41	1.77, 3.15
δ	0.4	0.3, 0.5	0.4	0.3, 0.5
Attack Rate	0.65	0.61, 0.70	0.65	0.61, 0.70

Web Figure 4

Fit obtained for the French Polynesia epidemic. A) SIR model. B) SEIR model with latent period fixed at six days.



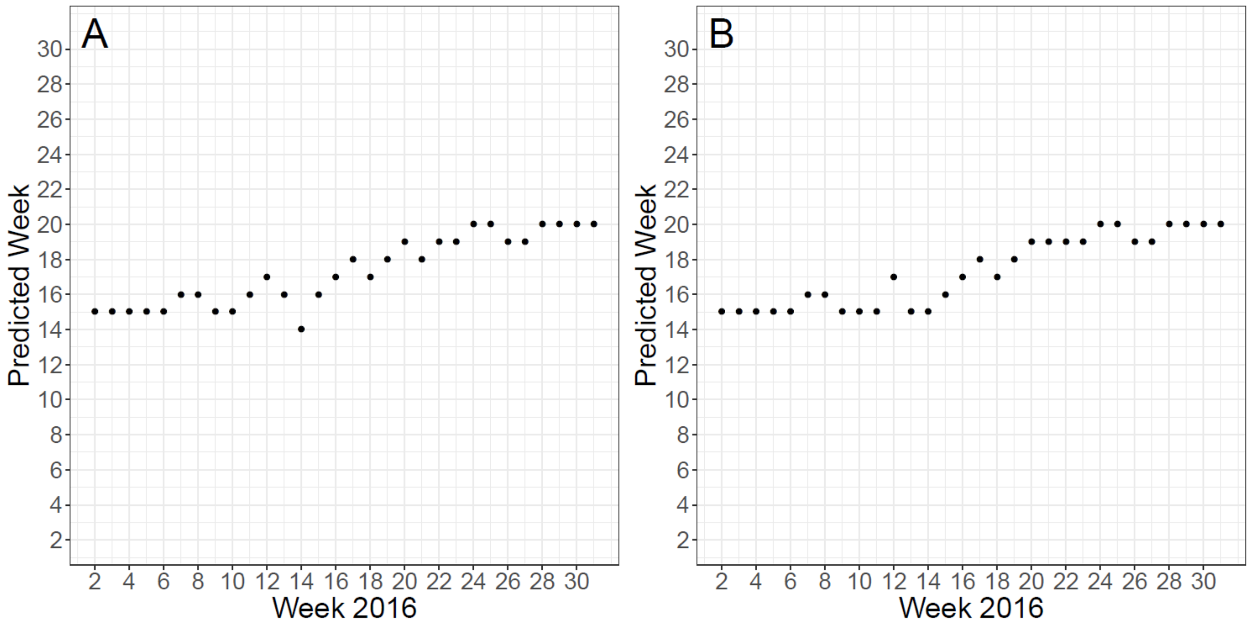
Web Table 6

Posterior mean and 95% credible intervals for the parameters of the model and for the attack rate.

	French Polynesia		Martinique	
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**
Reproduction number: R_0	1.61	1.53, 1.69	1.36	1.30, 1.42
Average infectious period: T (days)	11.0	9.5, 12.6	Fixed at 11	-
N. of initially infected: I_0 (10^3)	2.7	1.7, 3.9	2.7	1.7, 3.9
Probability of seeking care: ρ	0.18	0.16, 0.21	0.22	0.20, 0.25
Risk of GBS once infected with ZIKV: p_{GBS} (10^{-4})	2.48	1.81, 3.26	1.58	1.04, 2.22
Overdispersion parameter: δ	0.4	0.3, 0.5	0.3	0.2, 0.4
Attack Rate	0.65	0.61, 0.70	0.48	0.43, 0.53

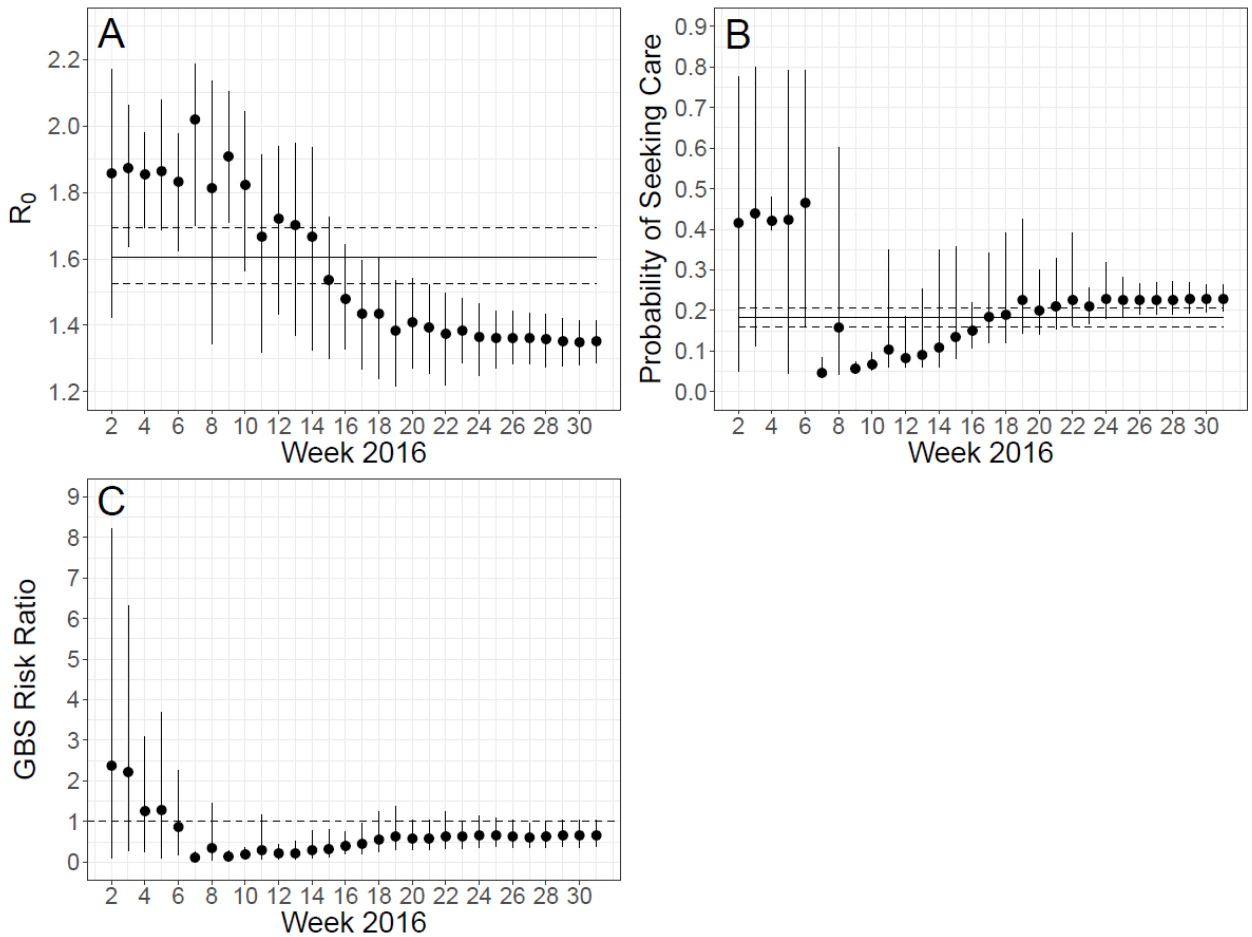
Web Figure 5

Real-time estimates of the week for which the maximum number of resources would be needed in Martinique. A) ICU beds. B) Ventilators. Observed values were weeks 18-19 for both ICU beds and number of ventilators.



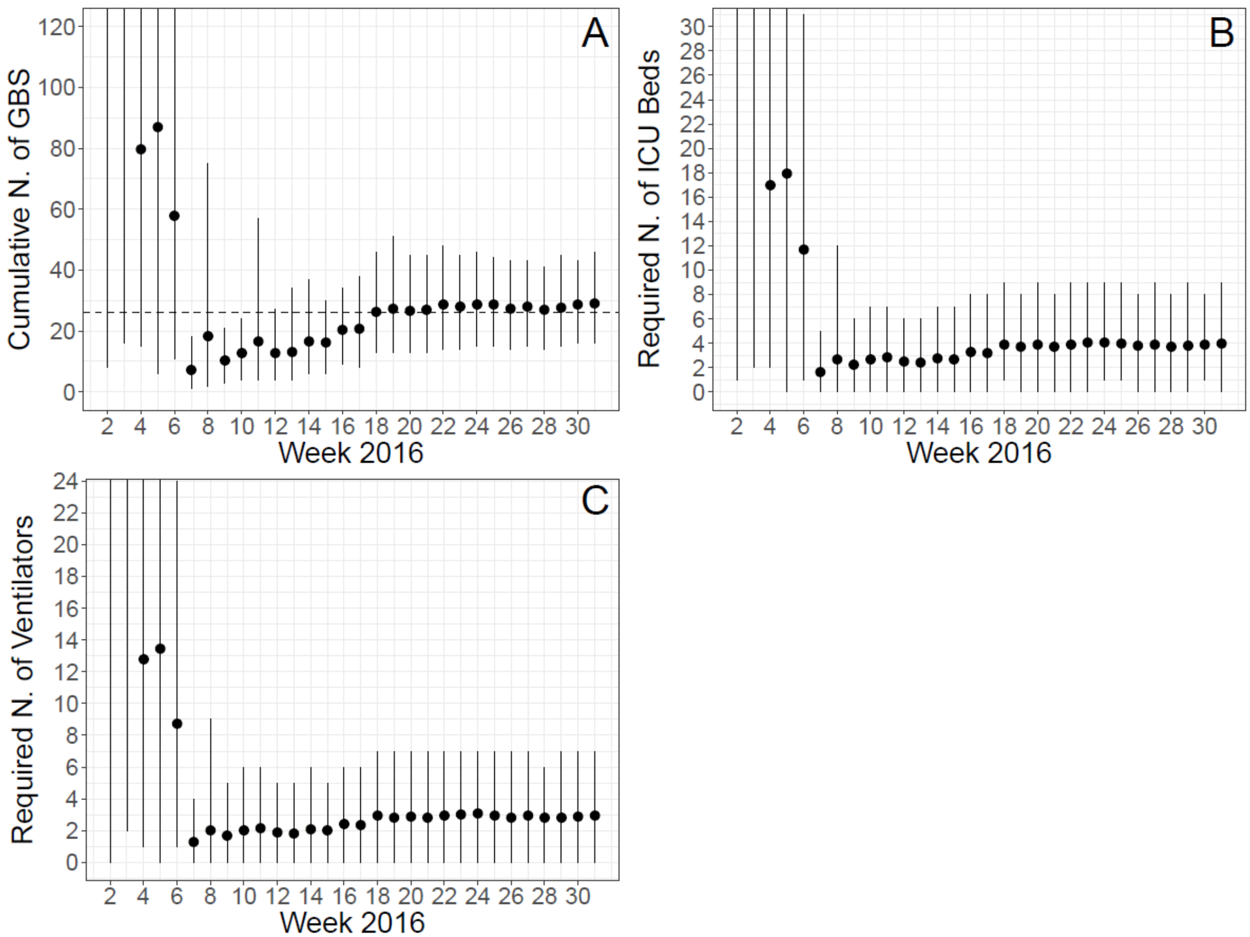
Web Figure 6

Real-time estimates of key model parameters for Martinique obtained using uniform priors for all parameters. A) Reproduction number R_0. B) Probability of seeking care for individuals infected by ZIKV. C) GBS risk ratio for Martinique relative to French Polynesia. Dots and bars denote the posterior means and 95% credible intervals obtained for Martinique. Similarly, the solid and dashed lines in panels A and B denote the posterior means and 95% credible intervals obtained for French Polynesia.



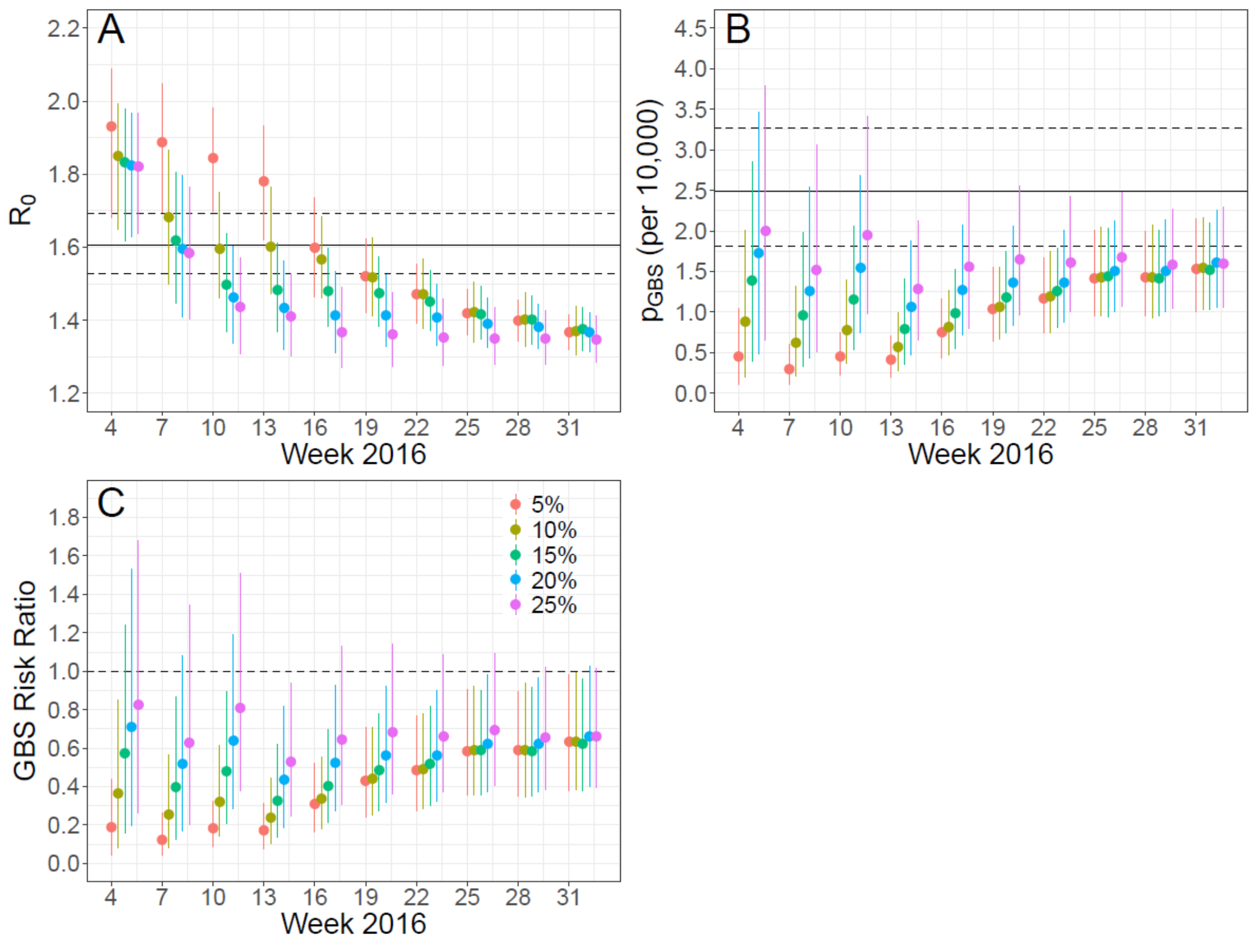
Web Figure 7

Real-time estimates of the resources needed to manage GBS cases in Martinique obtained using uniform priors for all parameters. A) Total number of GBS cases. B) Required number of ICU beds. C) Required number of ventilators. Dots and bars denote the posterior means and 95% credible intervals. The dashed line in panel A corresponds to the total number of hospitalized GBS cases in Martinique as of week 32-2016, i.e. 26 cases.



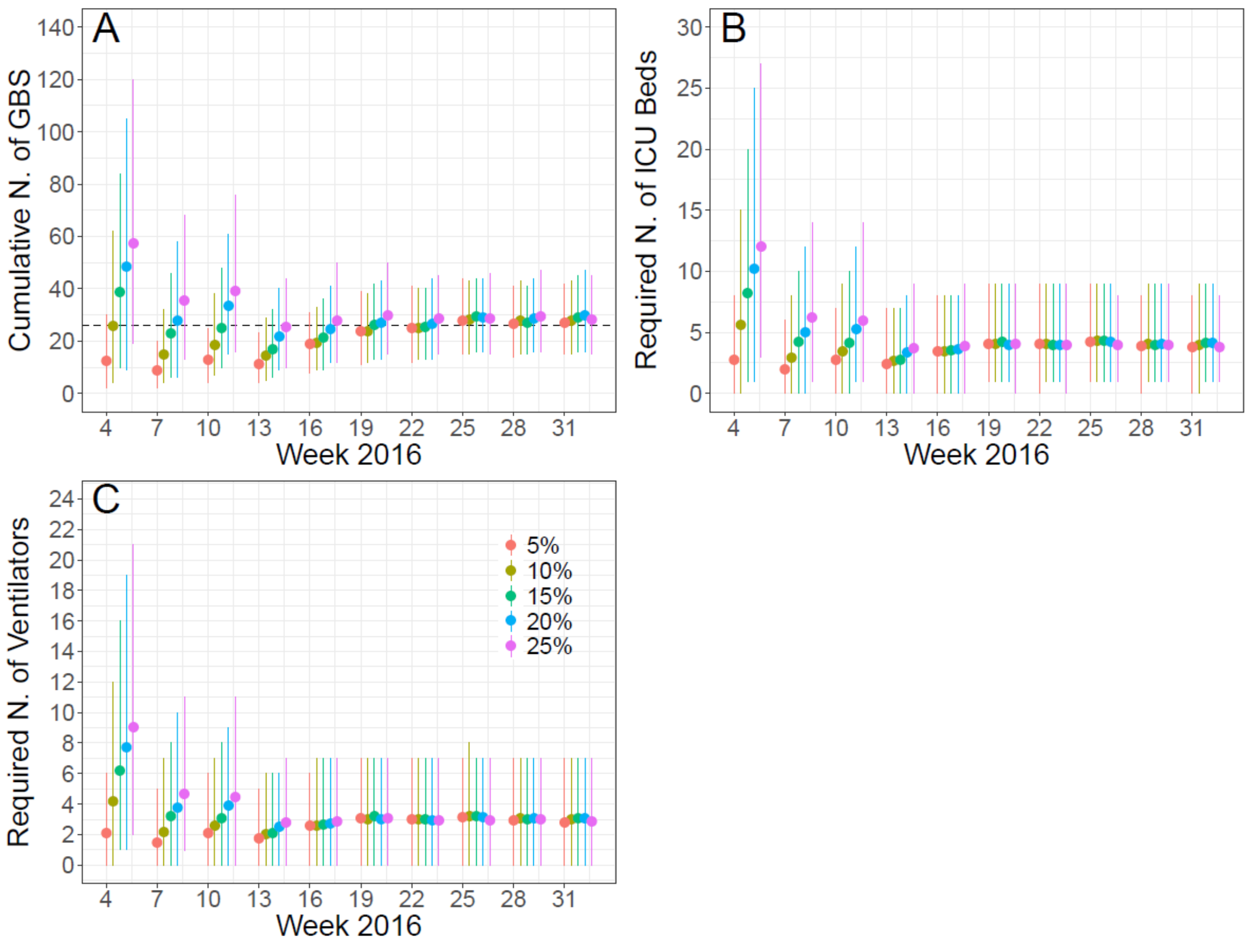
Web Figure 8

Real-time estimates of key model parameters for Martinique obtained for fixed probabilities of seeking care. A) Reproduction number. B) Probability of developing GBS following ZIKV infection. C) GBS risk ratio for Martinique relative to French Polynesia. The colored dots and bars denote the posterior means and 95% credible intervals obtained for Martinique. Similarly, the solid and dashed black lines in panels A and B denote the posterior means and 95% credible intervals obtained for French Polynesia. Different colors correspond to different fixed probabilities of seeking care, from 5% to 25%, with color code given in panel C.



Web Figure 9

Real-time estimates of the resources needed to manage GBS cases in Martinique obtained for fixed probabilities of seeking care. A) Cumulative number of GBS cases. B) Required number of ICU beds. C) Required number of ventilators. The colored dots and bars denote the posterior means and 95% credible intervals. The dashed line in panel A corresponds to the total number of hospitalized GBS cases in Martinique as of week 32-2016, i.e. 26 cases. Different colors correspond to different fixed probabilities of seeking care, from 5% to 25%, with color code given in panel C.



Web Appendix 7

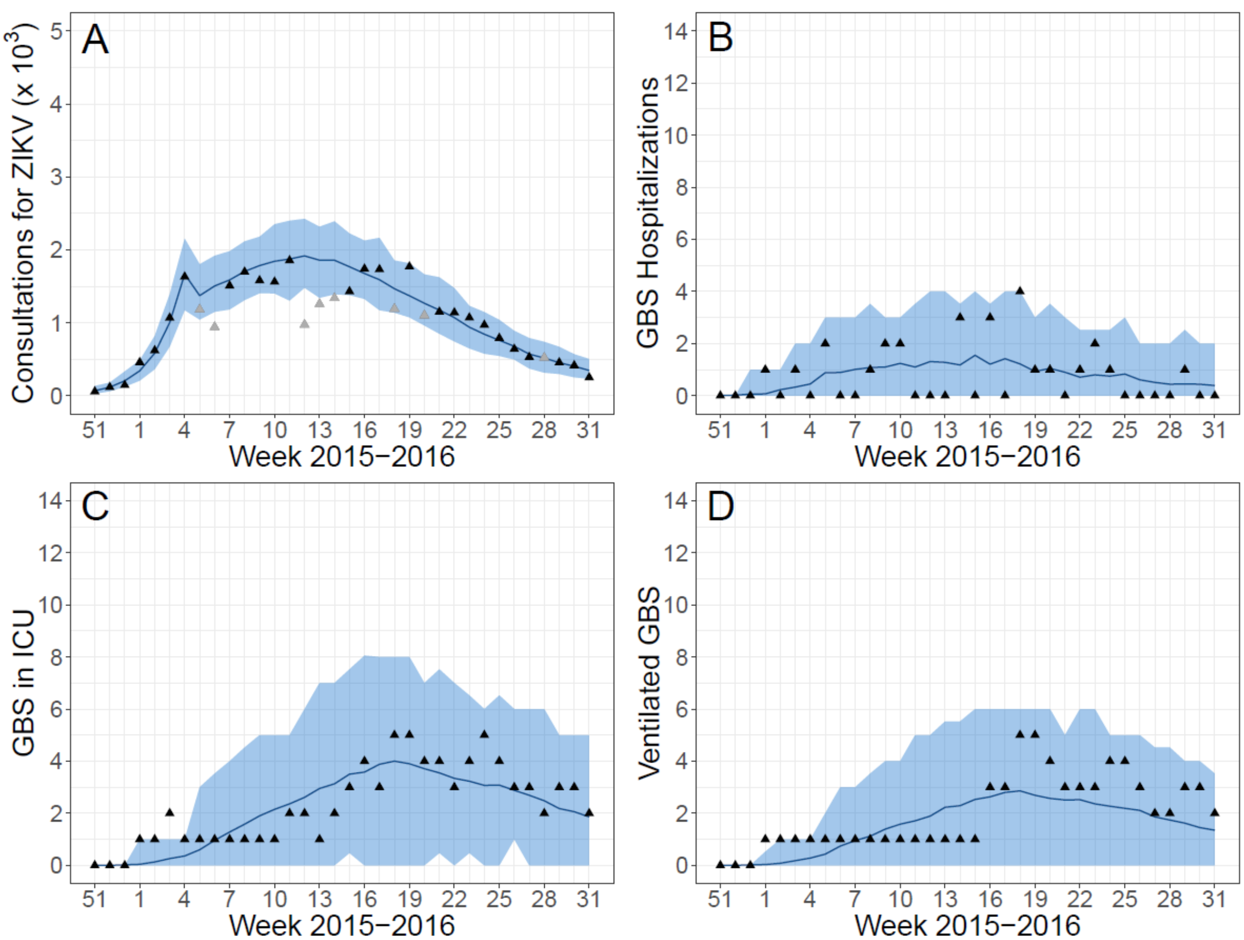
Time-varying Transmission Rate in Martinique

The model described in the main text assumes that the transmission rate was constant over time. However, we note in Figure 2A that the epidemic in Martinique was characterized by a quick increase in the number of cases with a subsequent slow-down and plateau. To test whether the hypothesis of constant transmission was too restrictive, we explored models in which the basic reproduction number changed over time, with a switch point estimated by choosing the model with the lowest deviance information criterion(4).

The best fitting model had a switch point at week 5 2016, with a reproduction number before week 5 of R_0 = 1.83 [1.71, 1.94] decreasing to R_0 = 1.21 [1.17, 1.25] afterwards. This model provided a slightly better fit to the ZIKV epidemic curve (Web Figure 10A) without substantially changing or improving the predictions concerning GBS cases (Web Figure 10B-D). Moreover, the predictions of this model were inconsistent with recent data documenting seroprevalence at two time points during the epidemic in Martinique (5), which were much better explained by the model assuming a constant transmission rate (Web Figure 11). This suggests that variations in reporting may have contributed in shaping the observed trajectory of consultations counts. In practice, it is likely that the truth lies somewhere between models with time-varying versus constant transmission rates, although the later one receives more support from the serological data.

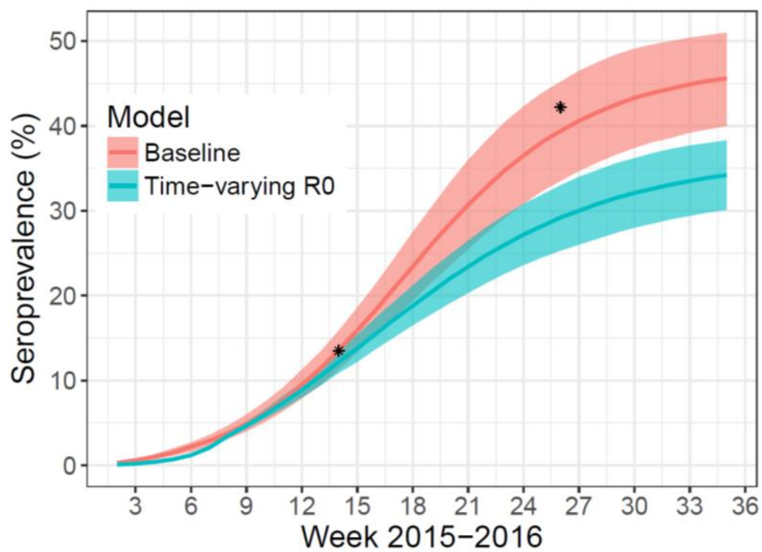
Web Figure 10

Epidemic curves and model fit for Martinique as of week 32-2016 for a model in which the transmission rate could switch once between two different values. The switch point was estimated at week 5 2016. A) Weekly number of consultations for suspected ZIKV infection. B) Weekly number of GBS cases by hospitalization date. C) Weekly number of GBS cases in intensive care unit (ICU). D) Weekly number of mechanically ventilated GBS cases. Triangles denote the data. The grey triangles in panel A indicate data points with large uncertainties - not used for model fitting - due to holidays. The solid line gives the predicted average, while the shaded area gives the 95% credible interval.



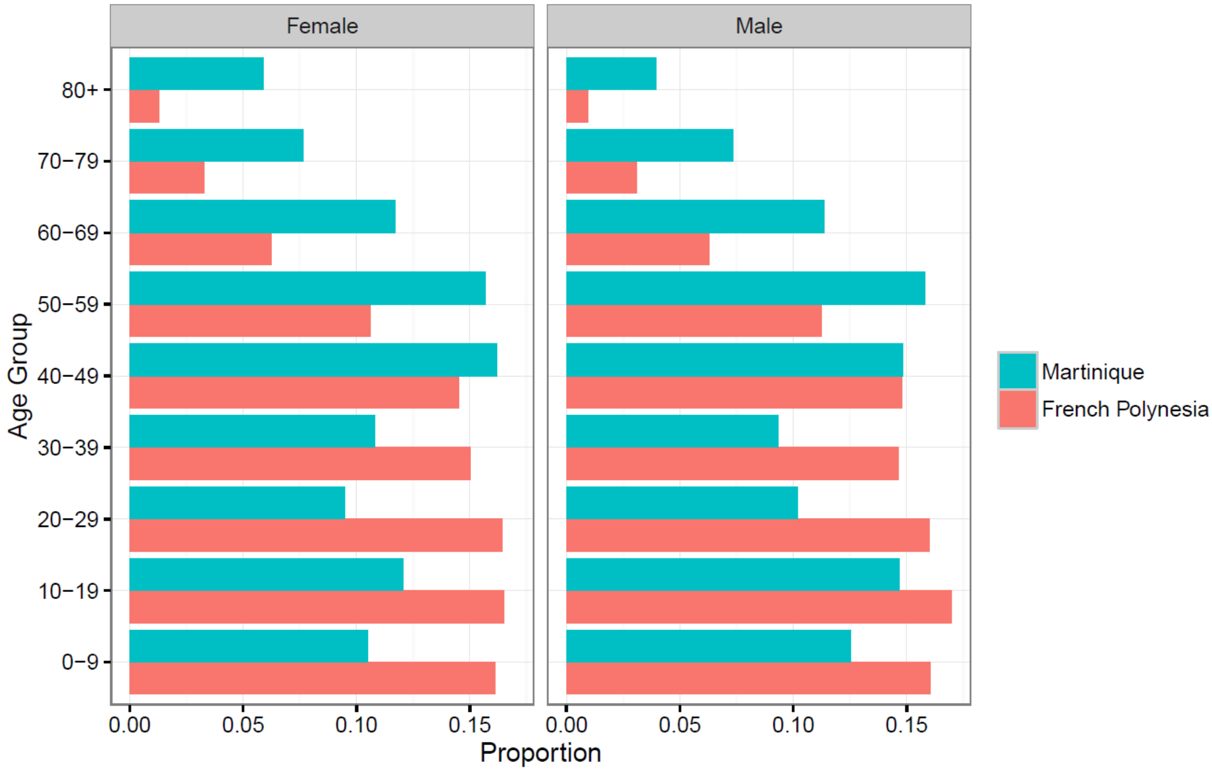
Web Figure 11

Seroprevalence of ZIKV in Martinique. Colored lines and shaded areas represent mean and 95% credible intervals obtained from our models. Red denotes the model used in the main text (baseline), while green (Time-varying R_0) denotes the model with a switch point at week 5 for the transmission rate. The two stars represent serology data taken from a recent publication(5).



Web Figure 12

Population pyramid for French Polynesia and Martinique. For French Polynesia, 2014 data were taken from the French Polynesia Statistical Institute website(6). For Martinique, 2015 data were taken from the French National Institute for Statistics and Economic Studies website(7).



Web Appendix 8

Using Serology Data to Estimate the Average Infectious Period in Martinique

Serological data became available for Martinique as this paper was under review (5). We therefore reran our model accounting for this information to estimate the average infectious period for Martinique. The results are shown in Web Table 7.

Web Table 7

Posterior mean and 95% credible intervals for the parameters of the model. The column "Baseline Model" corresponds to the results described in the main text (average infectious period fixed at 11 days). The column "Estimated Infectious Period" shows the results of a model that included the recently available serology data from blood donors(5) and in which the average infectious period was estimated.

	Baseline Model		**Estimated Infectious period**	
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**
Reproduction number: R_0	1.36	1.30, 1.42	1.40	1.32, 1.50
Average infectious period: T (days)	Fixed at 11	-	12.7	9.9, 16.1
N. of initially infected: I_0 (10^3)	2.7	1.7, 3.9	1.3	0.7, 2.1
Probability of seeking care: ρ	0.22	0.20, 0.25	0.21	0.17, 0.24
Risk of GBS once infected with ZIKV: p_{GBS} (10^{-4})	1.58	1.04, 2.22	1.47	0.97, 2.08
Overdispersion parameter: δ	0.3	0.2, 0.4	0.3	0.2, 0.4

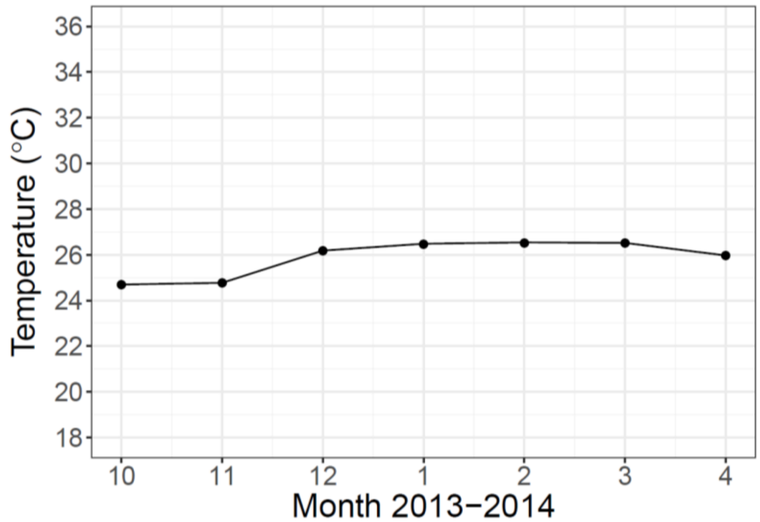
Web Appendix 9

Climate Data for French Polynesia and Martinique

Web Figures 13 and 14 show monthly temperatures for French Polynesia and Martinique. Temperatures were in the range 24.7°C-26.5°C (width: 1.8°C) in French Polynesia and 26.1°C-28.7°C (width: 2.6°C) for Martinique.

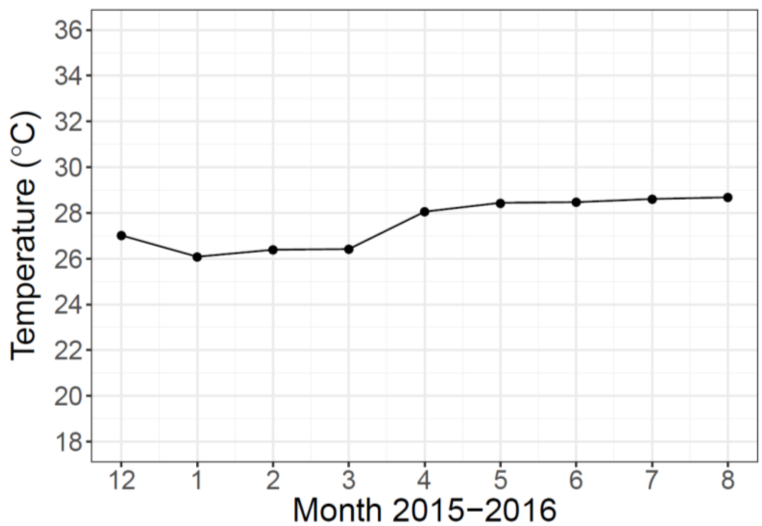
Web Figure 13

Average monthly temperature for French Polynesia in 2013-2014. Data were taken from the National Oceanic and Atmospheric Administration website(8).



Web Figure 14

Average monthly temperature for Martinique in 2015-2016. Data were taken from the National Oceanic and Atmospheric Administration website(8).



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