Estimation of the reproduction number of the 2015 Zika virus outbreak in Barranquilla, Colombia, and a first estimate of the relative role of sexual transmission

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Mathematical modelling estimation of the reproduction number of the 2015 Zika virus outbreak in Barranquilla, Colombia, and a first estimate of the relative role of sexual transmission

Summary

Background
In 2015, the Zika arbovirus (ZIKV) began circulating in the Americas, rapidly expanding its global geographic range in explosive outbreaks. Unusual among mosquito borne diseases, ZIKV has been shown to also be sexually transmitted. Critical to the assessment of outbreak risk, estimation of the potential attack rates, and assessment of control measures, are estimates of the basic reproduction number, $R_0$, and estimates of the relative role of sexual transmission in outbreak dynamics.

Methods
We estimate $R_0$, and relative role of sexual transmission, of the 2015 ZIKV outbreak in Barranquilla, Colombia, through an analysis of the exponential rise in identified syndromic ZIKV cases ($n = 1,470$ to the end of December, 2015).

Findings
The rate of exponential rise in cases was $\rho = 0.073 \text{ days}^{-1}$, with 95% CI $[0.064, 0.082]$ days$^{-1}$. Using a vector borne disease model, we estimated the reproduction number of this outbreak to be $R_0 = 4.4$ with 95% CI $[3.0, 6.2]$, and a one standard deviation uncertainty of 0.9. Using a novel vector borne disease model with additional direct sexual transmission, we find that sexual transmission is not likely significant enough to achieve sustained transmission in the absence of mosquitoes. The percentage of cases due to sexual transmission is $<30\%$ (95% CL).

Interpretation
This is among the first estimates of $R_0$ for a ZIKV outbreak in the Americas, and the first quantification of the relative role of sexual transmission. While potentially responsible for a significant fraction of cases, we find sustained sexual transmission
alone is unlikely.

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1 Introduction

Zika virus (ZIKV), a mosquito borne arbovirus, was first identified in Uganda in 1947. Similar to the dengue and chikungunya viruses, ZIKV is primarily spread by the tropical and sub-tropical domestic mosquito, Aedes aegypti. Recent outbreaks of ZIKV disease have occurred in French Polynesia in 2013-14, and Yap Island in the Pacific in 2007, and since 2015, ZIKV has rapidly spread through many countries in South America, Central America, and the Caribbean where the Aedes aegypti species is endemic.

ZIKV disease is usually asymptomatic, and is typically mild even with clinical presentation, with symptoms similar to that of dengue and chikungunya arbovirus infection. However, the disease has been linked to an apparent increased risk of the neurological disorder Guillain-Barré syndrome, and also to neonate microcephaly. The latter is of particular concern, because pregnant women may not even know they have been infected, and the damage to their unborn infants may result in subsequent lifelong disabilities. In addition, there is evidence that there is also a direct sexual transmission component to the disease, although it has been hitherto unknown how significant a factor this aspect is in overall transmission in Aedes aegypti infested areas. There is currently no vaccine or specific treatment for ZIKV infection, leaving control of the vector populations, use of mosquito repellents, and avoidance of sexual contact as the only means to control the spread of the disease. Quantification of the role of sexual transmission is crucial to the assessment of the relative efficacy of avoidance of sexual contact in case reduction.

Critical to the assessment of outbreak risk, and to the design, development, and evaluation of control strategies, are mathematical models that simulate the underlying dynamics of the transmission of the disease within a population. A particularly important quantity in infectious disease epidemiology that can be estimated with such models is the basic reproduction number, $R_0$, which is the average number of secondary cases produced in a completely naïve population by the introduction of a single infectious individual. Very few estimates of the reproduction number of ZIKV disease have been published in the literature at the time of this writing (March, 2016), likely largely due to
the surveillance challenges posed by this typically asymptomatic disease in countries
with limited human and capital resources for surveillance.

Here we examine the outbreak of ZIKV that began in 2015 in Barranquilla, Colombia. Barranquilla is the major Colombian port city on the Caribbean coast, with a population of 1.4 million. It is a center of development in Colombia, and in recent years has experienced a rapid expansion of urbanisation. It has a tropical savannah climate, with an average daytime temperature of 32°C year round, with day/night average of 28-4°C. Rainy seasons are from April to June and August to November, with a yearly average precipitation of just over 800 mm, providing an ideal habitat for the *Aedes aegypti* mosquito.

The public health department of the city has had a long-standing programme of surveillance of arboviral diseases in both the human and vector populations; dengue viruses (DENV) have been endemic in the city for many years, with three serotypes co-circulating prior to 2007 (DENV-1, -2 and -4), and all four DENV serotypes circulating since then. Since 2014, chikungunya virus (CHIKV) also emerged in a major outbreak in Barranquilla, and affected a large fraction of the population.

In this work we examined the clinically identified cases of ZIKV in Barranquilla from the beginning of October to the end of December, 2015; we employed a mathematical model for vector borne disease transmission to assess the reproduction number for ZIKV disease spread, by fitting the parameters of the model to the initial exponential rise in cases. We also developed a novel mathematical model that includes direct sexual transmission, and used this model to examine the potential relative contribution of sexual transmission to the overall final size of the epidemic.

## 2 Methods and Materials

### 2.1 Data

The data used consisted of the daily incidence of ZIKV disease cases identified during 2015 in Barranquilla, Colombia, by the Colombian National System for the Public Health Surveillance (Sistema de Vigilancia en Salud Publica: SIVIGILA).
cases were identified based on the clinical presentation (fever, rash, joint pain, or conjunctivitis) of patients who consulted any of the primary public health facilities. All data were de-identified to protect the privacy of the individuals.

A total of \( n = 1,470 \) cases were identified between the beginning of October and the end of December, 2015. The gender and age demographics of those cases are shown in Table 1. The dates of initial symptoms were available for \( n = 1,146 \) (78%) of these cases. The incidence data, aggregated by day of initial symptoms, are shown in Figure 1.

Of the \( n = 1,470 \) cases, 3% were pregnant women. Because concern over fetal birth defects may have prompted women to seek testing for ZIKV when they otherwise would not, there is potential surveillance bias. In the following we thus determine the exponential rise in cases including pregnant women, and cross-check the analysis by excluding pregnant women.

### 2.2 Statistical method for fitting the exponential rise in incidence

In the early stages of an outbreak of infectious disease, the number of incident cases grows exponentially in time as the effect of the increasing incidence on the depletion of the susceptible population remains small.\(^{15}\)

We employed maximum likelihood methods to fit an exponential curve to the initial rise in daily ZIKV incidence data, by date of initial symptoms, to determine the initial exponential growth rate, \( \rho \), using a Negative Binomial likelihood to account for over-dispersion in the data.\(^{16,17}\) Using the methods described in Chowell et al. (2012),\(^{17}\) we determined that the exponential rise in cases occurred up to approximately the end of November, 2015 (\( n = 304 \)). Surveillance during that period by the SIVIGILA system was constant, and no unusual vector control measures were implemented during that time.

We cross-checked the robustness of the assumptions and fit results by fitting to the initial rise only during the month of October (\( n = 26 \)), and again for the month of November (\( n = 278 \)). If the rate of exponential rise was constant (as it should be when surveillance is constant and no unusual vector control measures are taken in the initial
phase of the outbreak), the two fits should yield statistically consistent results.\cite{18}

2.3 Estimation of the reproduction number, and fraction of cases due to sexual transmission

ZIKV is primarily a mosquito borne disease; a mosquito bites an infectious human, whereupon the virus replicates in the mosquito’s mid gut, and then its salivary gland cells.\cite{19} After several days (known as the “extrinsic incubation period”), ZIKV can be found in the mosquito’s saliva, which then can be transmitted to other humans the mosquito bites.\cite{19} A human, once bitten by an infected mosquito, incubates the virus for several days, whereupon they become infectious for a period of several more days.\cite{20}

Here we employed a compartmental mathematical model of vector borne disease to simulate these dynamics. This model has previously been used to estimate the reproduction number of DENV and CHIKV fever outbreaks,\cite{21,22} and the reproduction number of the 2013-14 outbreak of ZIKV in French Polynesia in 2007.\cite{23} The model includes compartments corresponding to Susceptible, Exposed, Infected, and Recovered humans, and Susceptible, Exposed, and Infected mosquitoes (and is thus known as an SEIR/SEI model).

In a population of $N_h$ humans and $N_v$ adult female mosquitoes, the susceptible humans, $S_h$, are bitten by infectious mosquitoes, whereupon the human incubates the virus for an average period, $1/\kappa$ days, before becoming infectious, $I_h$. After an average of $1/\gamma$ days, the human then moves to the recovered and immune compartment, $R_h$.

Susceptible adult female mosquitoes, $S_v$, upon biting an infectious human, incubate the virus for an average period, $1/\eta$, and then move to the infectious compartment, $I_v$. They die after an average of $1/\mu$ days.

The system of ordinary differential equations and the compartmental flow diagram describing this model are shown in Appendix A.

As discussed in Appendix A, the expression that relates the reproduction number of the model to the rate of exponential rise, $\rho$, of infectious cases is

$$ R_0 = \frac{(\kappa + \rho)(\gamma + \rho)(\mu + \eta + \rho)(\mu + \rho)}{\gamma \mu \kappa (\eta + \mu)}. $$

(1)
Thus, given the rate of exponential rise in cases, and estimates of the latent and infectious periods and the mosquito lifetime, we can estimate the reproduction number. ZIKV has a high rate of asymptomatic infection, thus the observed cases represent a small fraction of the true number. However, this scale factor does not change the rate of exponential rise in cases; thus estimation of the rate of exponential rise with only partial observation of cases is a robust means to estimate the reproduction number.

In order to estimate the probability distribution for $R_0$, given probability distributions for $\rho$, $\kappa$, $\gamma$, $\eta$, and $\mu$, we performed one million Monte Carlo iterations, whereby we randomly sampled values of $\rho$ and the model parameters from their probability distributions, and calculated the resulting estimate of $R_0$ at each iteration. The serial interval of ZIKV is the sum of the incubation periods plus half the infectious periods, $T = 1/\kappa + 1/\eta + 0.5/\mu + 0.5/\gamma^{24}$; we thus used the constraint that the serial interval derived from the sampled parameters had to be within the observed serial interval of 10 to 23 days. The resulting distribution of the estimates of $R_0$ forms the estimate of the probability density for that quantity.

The probability distributions for $\kappa$, $\gamma$, $\eta$, and $\mu$ were derived from the ranges of the literature estimates for these quantities, assuming a Uniform probability distribution over the range. The estimates used to assess the range of the Uniform probability distributions for these parameters are shown in Table 2.

The probability distribution for the rate of exponential rise, $\rho$, was derived from the likelihood fit to the data, and was Normally distributed about the best-fit estimate.

We expanded the vector borne disease model to include additional direct sexual transmission. However, based on the exponential rise in incidence alone, the contribution of sexual transmission to the incidence cannot be disentangled from the vector borne transmission; but under assumptions of the reproduction number of the vector borne transmission (estimated, for instance, from the $R_0$ of another arboviral disease like CHIKV, which is not sexually transmitted), the sexual transmission component can be estimated. This is the first mathematical model of its kind developed to simulate the dynamics of combined vector borne and direct sexual transmission. Full details of the model are shown in Appendix A. Uncertainties on the estimates are derived using the Monte Carlo procedure, described above.
Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3 Results

The results of the fit of an exponential rise to the daily incidence data of ZIKV cases in Barranquilla from the beginning of October up to the end of November are shown overlaid on the data in Figure 1. The estimated rate of exponential rise was $\rho = 0.073$ days$^{-1}$, with 95% confidence interval [0.064, 0.082] days$^{-1}$.

We cross-checked our assumption of a constant rate of exponential rise in the initial data by fitting only up to the end of October, yielding $\rho = 0.061$ [0.040, 0.086] days$^{-1}$. We additionally fit to the data between the beginning to the end of November, yielding $\rho = 0.055$ [0.029, 0.080] days$^{-1}$. These two rates of rise were statistically consistent ($\chi^2_{1}$ test $p = 0.73$), thus the exponential rate of rise in cases appeared to be consistent over the entire period from the beginning of October to the end of November. These two fits are also shown overlaid on the incidence data in Figure 1.

Excluding pregnant women from the fit only excluded two cases up the end of November, and resulted in negligible changes to the estimated exponential rise.

We then performed the Monte Carlo procedure for the estimation of the uncertainty on the $R_0$, by sampling the probability distributions of the model parameters and our estimate of $\rho$. With the use of Equation 1, we obtained the average value of the estimated reproduction number $R_0 = 4.4$ with 95% CI [3.0, 6.2], and a one standard deviation uncertainty of 0.9.

The estimates of the reproduction number due to sexual transmission alone, and the fraction of cases due to sexual transmission, versus hypothesized values of the reproduction number in the absence of sexual transmission, are shown in Figure 1.
4 Discussion

Here we have estimated the $R_0$ of a ZIKV outbreak occurring in an area typical of the regions in the Americas that are currently being affected by the disease. Despite the pressing need to estimate the reproduction number for a newly emerging pandemic disease, there is currently only one other estimate of the reproduction number of a ZIKV disease outbreak of which the authors are aware; the reproduction number of the 2013-14 ZIKV outbreak in French Polynesia has recently been estimated to be between 1·9 to 3·23 (note that the description of the study is currently only available as a preprint). The estimate of the reproduction number obtained by this analysis, $R_0 = 4·4 \pm 3·0\text{ to } 6·2$, is significantly larger than that estimated for the French Polynesia outbreak, but the reasons for the discrepancy are unclear. Increased levels of urbanisation in Colombia compared to French Polynesia may play a role,26 as may the warmer temperature in Barranquilla compared to the Pacific islands. For instance, the extrinsic incubation period for DENV has been shown to be shorter when temperatures are warmer,27 and shorter extrinsic incubation times have been offered as a potential explanation of patterns of explosive outbreaks of arboviral disease.28

Immediately after the 2007 Yap Island outbreak, a seroprevalence study revealed that 73\% [68\%, 77\%] of the population had been recently infected,3 a remarkably large fraction. The larger the reproduction number, generally the more people that ultimately be infected with a disease,7 and thus qualitatively the observed high attack rate is in agreement with our result.

SEIR/SEI model estimates for the reproduction number of DENV outbreaks generally fall between around 1·5 to 3 (see, for instance,21,22), and around 4 for CHIKV outbreaks.23,29 The estimated reproduction number of the ZIKV outbreak in Barranquilla is significantly larger than the estimates for DENV outbreaks, despite the fact that the vector species is the same for the two diseases. This could be due to a variety of reasons, including a sexual transmission component to ZIKV,4 and/or partial prior immunity to DENV in hyperendemic areas, and/or shorter incubation periods for ZIKV in the vectors, and/or a longer infectious period in humans.

It is important to note here that our estimate of the ZIKV reproduction number is model
dependent, as indeed are all such estimates in the literature. However, for ease of comparison of results we have been careful to use the same model that was employed to analyse the French Polynesia ZIKV outbreak, DENV outbreaks, and a CHIKV outbreak. While we have not explored other model formulations in this analysis, it is a trivial matter for our estimate of the exponential rise to be used with other compartmental model formulations, and/or other model parameter values, in order to extract alternative estimates of $R_0$.

There is currently a great deal of uncertainty related to the epidemiological parameters of ZIKV infection, such as the human and mosquito latent periods, which are almost wholly responsible for the somewhat broad confidence interval on our estimate of $R_0$. Further study will help to constrain these parameters, and allow for more precise estimates of the reproduction number. Again, because we have provided our estimate of the exponential rise in cases for this outbreak, it is a trivial matter in the future to re-calculate the reproduction number once these parameters are better known.

Our study is based on syndromic surveillance data, similar to many other studies of arboviral outbreaks (for instance, References), due to limited laboratory testing resources in developing countries where many of these outbreaks occur. Further study is needed in the future to determine how potential mis-diagnosis may affect apparent temporal dynamics, particularly in places where other arboviral diseases may be co-circulating.

Sexual transmission has been noted to play a role in ZIKV transmission, but the relative contribution of direct transmission cannot be determined based on exponential rise in incidence alone unless an assumption is made about $R_0$ in the absence of sexual transmission. Studies of CHIKV outbreaks in naïve populations have determined the reproduction number to be around 4. If this is used as an estimate of the approximate $R_0$ of ZIKV without sexual transmission, we see in Figure 1 that the reproduction number of sexual transmission alone is likely below 0.75, which is too low to achieve sustained transmission in the absence of mosquitoes ($R_0 > 1$ is required to achieve sustained transmission). However, as seen in Figure 1, the estimated fraction of cases due to sexual transmission when mosquitoes are also present may be as high as 30%, thus safe sexual practices may significantly reduce incidence.
5 Conclusions

ZIKV has spread explosively in the Americas in recent months. Here we have employed an SEIR/SEI mathematical model of the spread of vector borne disease to estimate the basic reproduction number, $R_0$, of the ZIKV outbreak that began in October, 2015, in Barranquilla, Colombia. We estimate the $R_0$ to be $4.4$ with 95% CI $[3.0, 6.2]$, and a one standard deviation uncertainty of 0.9. This is among the very first estimates of the $R_0$ of a ZIKV outbreak in the Americas, and is important to assessment of outbreak risk in new areas.

In addition, we developed a novel mathematical model for combined vector borne and direct sexual transmission. With the model, we have obtained the first estimate of the relative contribution of sexual contact to the transmission cycle when mosquitoes are also present. If the $R_0$ of ZIKV in the absence of sexual transmission is similar to that observed for CHIKV outbreaks, our modelling analysis estimates that up to 30% of ZIKV cases may be due to sexual contact alone. Thus safe sexual practices may significantly reduce incidence during ZIKV outbreaks in tropical and semi-tropical areas.

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Contributors

AKIF and CMERV collected the data used in these studies, and assisted in the analysis and interpretation. FB, CCC, AM, and ST analysed the data, and performed the modelling analysis to estimate the reproduction number. All authors assisted in the writing and editing of the manuscript.

Conflicts of Interest

We declare that we have no conflicts of interest.

Research in Context

Evidence before this study
A literature review of Scopus, MEDLINE, PubMed, and Google Scholar without date restrictions, with search terms “Zika” and “reproduction number”, yielded only one peer-reviewed estimate of the reproduction number of past ZIKV outbreaks, and no peer-reviewed estimates the reproduction number of the recent outbreaks in the Americas.

Added value of this study
Our study provides one of the first estimates of the reproduction number of a ZIKV outbreak in the Americas, and the first quantification of the relative role of sexual transmission.
Implications of all the available evidence
Estimates of the reproduction number are critical to the assessment of the relative efficacy of potential disease control strategies.
Additionally, while potentially responsible for a significant fraction of cases, we find sustained sexual transmission alone of ZIKV is unlikely.

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Table 1: Number of confirmed cases of Zika virus disease in Barranquilla, Colombia, between October 1, 2015 and December 31, 2015

|                | n = 1,470 |
|----------------|-----------|
| Total          | 1,470     |
| Male           | 610 (41%) |
| Non-pregnant Female | 817 (56%) |
| Pregnant Female | 43 (3%)   |
| Age 0 to 17    | 232 (16%) |
| Age 18 to 44   | 901 (61%) |
| Age 45 to 64   | 289 (20%) |
| Age 65 and over| 48 (3%)   |
Table 2: **Model parameters used in this analysis**

The incubation and infectious periods, and the mosquito average lifespan, were determined from the cited references, and the references therein.

| Parameter | Definition | Estimate | Reference |
|-----------|------------|----------|-----------|
| $1/\kappa$ | intrinsic (human) latent period | 3 to 12 days | 20 |
|           |            | 2 to 7 days | 1 |
|           |            | $\sim 2$ to $\sim 6$ days | 2 |
|           |            | assume Uniform(2,12) days |   |
| $1/\gamma$ | human infectious period | 3 to 5 days | 20 |
|           |            | $\sim 3$ to $\sim 7$ days | 2 |
|           |            | assume Uniform(3,7) days |   |
| $1/\eta$  | extrinsic (mosquito) latent period | 4 to 6 days | 20 |
|           |            | 10 to 15 days | 5 |
|           |            | $\sim 8$ to $\sim 13$ days | 2 |
|           |            | assume Uniform(4,15) days |   |
| $1/\mu$   | average mosquito lifespan | 6 to 15 days | 21, 22 |
|           |            | 10 to 20 days | 23 |
|           |            | $\sim 6$ to $\sim 10$ days | 2 |
|           |            | assume Uniform(6,20) days |   |
| $1/\eta + 1/\kappa + 0.5/\gamma + 0.5/\mu$ | serial interval | 10 to 23 days | 20 |
Confirmed Zika virus cases, Barranquilla, CO:
October to December, 2015

Figure 1: Results of the analysis
The top plot shows the time series of confirmed Zika virus disease cases in Barranquilla, Colombia, with the best-fit exponential curves to the initial rise overlaid. Shown in the bottom left hand plot is the estimated $R_0$ of ZIKV due to sexual transmission alone, vs hypothesized values of the $R_0$ due to vector borne transmission alone, based on the observed exponential rise in cases. The bottom right hand plot shows the estimated fraction of ZIKV cases due to sexual transmission, vs hypothesized values of the $R_0$ due to vector borne transmission alone.
Appendix A

A1: Vector borne disease model with no sexual transmission

ZIKV is primarily a mosquito borne disease; a mosquito bites an infectious human, whereupon the virus replicates in the mosquito’s mid gut, and then its salivary gland cells. After several days (known as the “extrinsic incubation period”), ZIKV can be found in the mosquito’s saliva, which then can be transmitted to other humans the mosquito bites. A human, once bitten by an infected mosquito, incubates the virus for several days, whereupon they become infectious for a period of several more days.

We employed a compartmental mathematical model of vector borne disease to simulate these dynamics. This model has previously been used to estimate the reproduction number of DENV and CHIKV fever outbreaks, and the reproduction number of the 2013-14 outbreak of ZIKV in French Polynesia in 2007. The model includes compartments corresponding to Susceptible, Exposed, Infected, and Recovered humans, and Susceptible, Exposed, and Infected mosquitoes (and is thus known as an SEIR/SEI model).

In a population of $N_h$ humans and $N_v$ adult female mosquitoes, the susceptible humans, $S_h$, are bitten by infectious mosquitoes, whereupon the human incubates the virus for an average period, $1/\kappa$ days, before becoming infectious, $I_h$. After an average of $1/\gamma$ days, the human then moves to the recovered and immune compartment, $R_h$.

Susceptible adult female mosquitoes, $S_v$, upon biting an infectious human, incubate the virus for an average period, $1/\eta$, and then move to the infectious compartment, $I_v$. They die after an average of $1/\mu$ days.

The diagram of the flows and interactions between model compartments is as follows:
The equations describing the dynamics of the model are:

\[
\begin{align*}
    dS_h/dt &= -\beta S_h I_h / N_h \\
    dE_h/dt &= +\beta S_h I_h / N_h - \kappa E_h \\
    dI_h/dt &= +\kappa E_h - \gamma I_h \\
    dR_h/dt &= +\gamma I_h \\
    dS_v/dt &= -\beta_v S_v I_h / N_v + \mu N_v - \mu S_v \\
    dE_v/dt &= +\beta_v S_v I_h / N_v - \eta E_v - \mu E_v \\
    dI_v/dt &= +\eta E_v - \mu I_v,
\end{align*}
\]

where the parameters $\beta$ and $\beta_v$ describe the relative transmission rates from mosquitoes to humans, and humans to mosquitoes, respectively, $N_h = S_h + E_h + I_h + R_h$, and $N_v = S_v + E_v + I_v$. We assumed that disease induced mortality in humans was negligible, and that the outbreak occurred on a short time scale relative to the vital dynamics of the human population. We also assumed in the model that asymptomatic individuals transmitted the virus similar to symptomatic individuals, thus we included both in the same compartment (which is additionally motivated by the fact that we did not use this model in this analysis to assess intervention or treatment measures aimed at symptomatic individuals). The model assumes exponentially distributed sojourn times.
in each of the states, and also assumes a closed population, with homogeneous mixing between the humans and the vectors.

**A1.1: Reproduction number of the vector borne model with no sexual transmission**

The basic reproduction number is defined as the number of secondary disease cases caused by introducing a single infective into a wholly susceptible population of both hosts (humans) and vectors (mosquitoes). For the model in Equations 2, this may be calculated directly. There are two stages. First, the infected human infects mosquitoes, at a rate $\beta_v N/N_v$ over an average time $1/\gamma$. This produces $\beta_v N/N_v \gamma$ infected mosquitoes, of whom a fraction $\eta/(\eta + \mu)$ proceed to become infectious. The second stage is that the infected mosquitoes infect humans at a rate $\beta N_v/N$ for an average time $1/\mu$, producing $\beta N_v/N\mu$ infected humans per mosquito. The net result of these two stages is

$$[\beta_v N/N_v \gamma \eta/(\eta + \mu)] [\beta N_v/N\mu] = \frac{\beta_v \beta \eta}{\mu \gamma (\eta + \mu)}, \quad (3)$$

infected humans, and this is the basic reproduction number $R_0$.

To calculate the basic reproduction number $R_0$, we can also use the next generation matrix approach, slightly modified. We form the next generation matrix with large domain [9, Chapter 3], [10, Chapter 7]. This is the matrix product $K_L = FV^{-1}$, with $F$ the matrix of transmission terms, whose $(i, j)$ entry is the expected number of secondary infections in compartment $i$ caused by individuals originally in compartment $j$, and $V$ is the matrix such that the $(i, j)$ entry of the matrix $V^{-1}$ is the expected time that an individual initially introduced in compartment $j$ spends in disease compartment $i$. 

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For the model in Equations 2 the disease states are \((E_h, I_h, E_v, I_v)\). The matrices are

\[
F = \begin{bmatrix}
0 & 0 & 0 & \beta N_v \frac{N_h}{N_v} \\
0 & 0 & 0 & 0 \\
0 & \beta N_v \frac{N_h}{N_v} & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}
\] (4)

\[
V = \begin{bmatrix}
\kappa & 0 & 0 & 0 \\
-\kappa & \gamma & 0 & 0 \\
0 & 0 & \mu + \eta & 0 \\
0 & 0 & -\eta & \mu
\end{bmatrix}
\] (5)

Thus the next generation matrix with large domain is

\[
K_L = \begin{bmatrix}
0 & 0 & \beta N_v \frac{N_h}{N_v} \frac{\eta}{\mu + \eta} & \beta N_v \frac{N_h}{N_v} \frac{1}{\mu} \\
0 & 0 & 0 & 0 \\
0 & \beta N_v \frac{1}{N_h} & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}
\] (6)

It is possible to reduce the next generation matrix with large domain to the number of states at infection \([9, \text{Chapter 3}],[10, \text{Chapter 7}]\). The states at infection are those disease states in which there can be new infections. Suppose that there are \(n\) disease states and \(k\) states at infection with \(k < n\). Then we may define an auxiliary \(n \times k\) matrix, \(Q\), in which each column corresponds to a state at infection and has 1 in the corresponding row and 0 elsewhere. Then the next generation matrix is the \(k \times k\) matrix

\[
K = Q^T K_L Q.
\] (7)

It is easy to show, using the fact that \(Q^T K_L = K_L\), that the \(n \times n\) matrix \(K_L\) and the \(k \times k\) matrix \(K\) have the same non-zero eigenvalues and therefore the same spectral radius.

The disease states of the model of Equations 2 at infection are \(E_h, E_v\), thus the matrix
\( Q \) is

\[
Q = \begin{bmatrix}
1 & 0 \\
0 & 0 \\
0 & 1 \\
0 & 0
\end{bmatrix},
\]

and thus the next generation matrix \( K \) is the \( 2 \times 2 \) matrix

\[
K = \begin{bmatrix}
0 & \beta \frac{N_h}{N_v} \frac{\eta}{\mu(\mu + \eta)} \\
\beta \frac{N_v}{N_h} \frac{1}{\gamma} & 0
\end{bmatrix}.
\]

The largest positive eigenvalue of this matrix is

\[
B = \beta \beta_v \frac{\eta}{\mu \gamma (\mu + \eta)}.
\]

The LHS of Equation 10 can be interpreted as the reproduction number. However, it has been pointed out in the literature that the LHS of Equation 10 can equally reasonably be interpreted as \( R_0^T \), rather than \( R_0^{\text{SEIR}} \). The form in Equation 10 is referred to as the “type reproduction number” and is the total number of secondary infections in humans originating from a human infection. In practice, we note that several past SEIR/SEI model estimates of the reproduction number for DENV, CHIKV, and ZIKV outbreaks have also used the formulation as we have it here for consistency of comparison between our result and those estimates, we thus use the formulation as we have presented, with \( R_0 = B \).

A1.2: Exponential rise of the vector borne disease model with no sexual transmission

In order to determine the initial exponential growth rate from the vector borne disease model in Equations 2, a quantity that can be compared with experimental data, we linearise Equations 2 about the disease-free equilibrium: \( S_h = N_h, E_h = I_h = 0, S_v = \)
\( N_v \cdot E_v = I_v = 0 \). If we let \( y = N_h - S_h, z = N_v - S_v \), we obtain the linearisation

\[
\begin{align*}
y' &= \beta N_h \frac{I_v}{N_v} \\
E_h' &= \beta N_h \frac{I_v}{N_v} - \kappa E_h \\
I_h &= \kappa E_h - \gamma I_h \\
z' &= -\mu z - \beta N_i \frac{I_h}{N_h} \\
E_v &= \beta N_i \frac{I_h}{N_h} - (\mu + \eta) E_v \\
I_v' &= \eta E_v - \mu I_v
\end{align*}
\]

Solutions of the linearisation of Equations (11) are linear combinations of exponentials whose exponents are the roots of the characteristic equation (the eigenvalues of the coefficient matrix of Equations (11)).

The characteristic equation of Equation (11) is

\[
\det \begin{bmatrix}
-\lambda & 0 & 0 & 0 & 0 & \beta N_h \\
0 & -(\lambda + \kappa) & 0 & 0 & 0 & \beta N_v \\
0 & \kappa & -(\lambda + \gamma) & 0 & 0 & 0 \\
0 & 0 & -\beta N_i \frac{I_h}{N_h} & -(\lambda + \mu) & 0 & 0 \\
0 & 0 & \beta N_i \frac{I_h}{N_h} & 0 & -(\lambda + \mu + \eta) & 0 \\
0 & 0 & 0 & 0 & \eta & -(\lambda + \mu)
\end{bmatrix} = 0. \quad (12)
\]

We can reduce Equation (12) to a product of two factors and a fourth degree polynomial equation

\[
\lambda(\lambda + \mu) \det \begin{bmatrix}
-(\lambda + \kappa) & 0 & 0 & \beta N_v \\
\kappa & -(\lambda + \gamma) & 0 & 0 \\
0 & \beta N_i \frac{I_h}{N_h} & -(\lambda + \mu + \eta) & 0 \\
0 & 0 & \eta & -(\lambda + \mu)
\end{bmatrix} = 0. \quad (13)
\]

The initial exponential growth rate is the largest root of this fourth degree equation,
which reduces to
\[ g(\lambda) = (\lambda + \kappa)(\lambda + \gamma)(\lambda + \mu + \eta)(\lambda + \mu) - \beta \beta \kappa \eta = 0. \] (14)

Since \( g(0) < 0 \) if \( R_0 > 1 \), \( g(\lambda) \) is positive for large positive \( \lambda \) and \( g'(\lambda) > 0 \) for positive \( \lambda \), there is a unique positive root of the equation \( g(\lambda) = 0 \), and this is the initial exponential growth rate.

The initial exponential growth rate may be measured experimentally, and if the measured value is \( \rho \), then from Equation 14 we obtain
\[ (\rho + \kappa)(\rho + \gamma)(\rho + \mu + \eta)(\rho + \mu) = \beta \beta \kappa \eta = R_0 \kappa \mu \gamma (\mu + \eta). \] (15)

From this, we obtain
\[ R_0 = \frac{(\rho + \kappa)(\rho + \gamma)(\rho + \mu + \eta)(\rho + \mu)}{\kappa \mu \gamma (\mu + \eta)} \] (16)

This provides a way to estimate the basic reproduction number from measurable quantities.

**A1.3: Estimation of the reproduction number for the vector borne disease model from observed exponential rise**

In Table 3 on page 8, we show literature estimates for the human and mosquito ZIKV incubation periods (\( 1/\kappa \) and \( 1/\eta \), respectively), the human infectious period (\( 1/\gamma \)), and the mosquito lifespan (\( 1/\mu \)). There is wide variation in all estimates, reflecting a great deal of uncertainty in the disease cycle parameters. We assume Uniform probability distributions for the model parameters, over the range of the literature estimates.

The rate of exponential rise in initial incidence in the 2015 ZIKV outbreak in Barranquilla, Colombia, was \( \rho = 0.073 \) days\(^{-1} \), with 95% CI \([0.064, 0.082]\) days\(^{-1} \). The probability distribution for the rate of exponential rise was derived from the likelihood fit to the data, and was Normally distributed about the best-fit estimate.

We performed a Monte Carlo procedure for the estimation of the uncertainty on the \( R_0 \),
Table 3: Model parameters for Equations 2. The incubation and infectious periods, and the mosquito average lifespan, were determined from the cited references, and the references therein.

| Parameter | Definition                               | Estimate          | Reference |
|-----------|------------------------------------------|-------------------|-----------|
| $1/\kappa$| intrinsic (human) latent period          | 3 to 12 days      | [3]       |
|           |                                           | 2 to 7 days       | [3]       |
|           |                                           | ~ 2 to ~ 6 days   | [7]       |
|           | assume Uniform(2,12) days                |                   |           |
| $1/\gamma$| human infectious period                   | 3 to 5 days       | [2]       |
|           |                                           | ~3 to ~7 days     | [7]       |
|           | assume Uniform(3,7) days                 |                   |           |
| $1/\eta$  | extrinsic (mosquito) latent period        | 4 to 6 days       | [2]       |
|           |                                           | 10 to 15 days     | [3]       |
|           |                                           | ~8 to ~13 days    | [7]       |
|           | assume Uniform(4,15) days                |                   |           |
| $1/\mu$   | average mosquito lifespan                 | 6 to 15 days      | [12]      |
|           |                                           | 10 to 20 days     | [5]       |
|           |                                           | ~6 to ~10 days    | [7]       |
|           | assume Uniform(6,20) days                |                   |           |
| $1/\eta + 1/\kappa + 0.5/\gamma + 0.5/\mu$| serial interval   | 10 to 23 days     | [2]       |

by sampling the probability distributions of the model parameters and our estimate of $\rho$. We used the constraint that the serial interval derived from the sampled parameters had to be within the observed serial interval of 10 to 23 days. With the use of Equation 16, we then obtained the average value of the estimated reproduction number $R_0 = 4.4$ with 95% CI [3.0, 6.2], and a one standard deviation uncertainty of 0.9.

**A2: vector borne disease model with additional direct sexual transmission**

For the Zika virus, it has been established that in addition to vector transmission of infection there is also the potential for direct transmission through sexual contact.
To model this, we expand the model of Equations 2 to include direct transmission:

\[
\begin{align*}
\frac{dS_h}{dt} &= -\beta S_h I_v / N_v - \alpha S_h I_h / N_h \\
\frac{dE_h}{dt} &= +\beta S_h I_v / N_v + \alpha S_h I_h / N_h - \kappa E_h \\
\frac{dI_h}{dt} &= +\kappa E_h - \gamma I_h \\
\frac{dR_h}{dt} &= +\gamma I_h \\
\frac{dS_v}{dt} &= -\beta_v S_v I_h / N_h + \mu N_v - \mu S_v \\
\frac{dE_v}{dt} &= +\beta_v S_v I_h / N_h - \eta E_v - \mu E_v \\
\frac{dI_v}{dt} &= +\eta E_v - \mu I_v,
\end{align*}
\] (17)

where \(\alpha\) is the direct transmission rate, and all other parameters are as in the vector borne disease model without direct transmission, as shown in Equations 2.

The model includes direct transmission, regardless of gender. We note that if transmission is only one-way male to female, sexual transmission by itself cannot sustain an outbreak in a population, regardless of the value of \(\alpha\). However, if transmission occurs bi-directionally, then if \(\alpha\) is large enough, sustained transmission via direct sexual contact alone is possible. Thus, including in the model bi-directional transmission allows us to assess the worst case scenario for the possibility of sustained sexual transmission in the population.

We also note here that the direct transmission rate, \(\alpha\), incorporates not only the sexual contact rate of individuals, but also the probability of transmission on contact with an infectious person. Thus, if some fraction of people that are infectious via the vector transmission route are not infectious via the sexual transmission route, \(\alpha\) incorporates the effect.

**A2.1: reproduction number of the vector borne disease model with direct sexual transmission**

To calculate the basic reproduction number of the model in Equations 17, we use the same direct approach we employed in Section A2.2; if there is sexual transmission, this
operates independent of the host-vector interaction, and produces $\alpha$ cases in average time $1/\gamma$, adding a simple term $\alpha/\gamma$ to the reproduction number

$$R_0 = \frac{\beta_v \beta \eta}{\mu \gamma (\eta + \mu)} + \alpha/\gamma. \quad (18)$$

We note here that if we attempted to use the next generation matrix approach to this calculation, we would obtain an incorrect answer because of the inclusion of two different generations.

**A2.2: The initial exponential growth rate of the vector borne disease model with sexual transmission**

In order to determine the initial exponential growth rate from the model in Equations 17, a quantity that can be compared with experimental data, we linearise the model Equations 17 about the disease-free equilibrium: $S_h = N_h, E_h = I_h = 0, S_v = N_v, E_v = I_v = 0$. If we let $y = N_h - S_h, z = N_v - S_v$, we obtain the linearisation

$$\begin{align*}
y' &= \beta N_h \frac{I_v}{N_v} + \alpha I_h \\
E_h' &= \beta N_v \frac{I_h}{N_v} + \alpha I_h - \kappa E_h \\
I_h' &= \kappa E_h - \gamma I_h \\
z' &= -\mu z - \beta_v N_v \frac{I_h}{N_h} \\
E_v &= \beta_v N_v \frac{I_h}{N_h} - (\mu + \eta) E_v \\
I_v' &= \eta E_v - \mu I_v.
\end{align*}$$

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The corresponding characteristic equation is

\[
\begin{vmatrix}
-\lambda & 0 & \alpha & 0 & 0 & \beta \frac{N_v}{N_h} \\
0 & -(\lambda + \kappa) & \alpha & 0 & 0 & \beta \frac{N_v}{N_h} \\
0 & \kappa & -(\lambda + \gamma) & 0 & 0 & 0 \\
0 & 0 & -\beta_v \frac{N_v}{N_h} & -(\lambda + \mu) & 0 & 0 \\
0 & 0 & \beta_v \frac{N_v}{N_h} & 0 & -(\lambda + \mu + \eta) & 0 \\
0 & 0 & 0 & 0 & \eta & -(\lambda + \mu)
\end{vmatrix} = 0. \quad (20)
\]

Solutions of the linearisation Equations 19 are linear combinations of exponentials whose exponents are the roots of the characteristic equation (the eigenvalues of the coefficient matrix of Equations 19).

We can reduce Equation 20 to a product of two factors and a fourth degree polynomial equation

\[
\lambda(\lambda + \mu)\det \begin{vmatrix}
-\lambda - \kappa & \alpha & 0 & \beta \frac{N_v}{N_h} \\
\kappa & -(\lambda + \gamma) & 0 & 0 \\
0 & \beta_v \frac{N_v}{N_h} & -(\lambda + \mu + \eta) & 0 \\
0 & 0 & \eta & -(\lambda + \mu)
\end{vmatrix} = 0. \quad (21)
\]

The initial exponential growth rate is the largest root of this fourth degree equation, which reduces to

\[
g(\lambda) = (\lambda + \kappa)(\lambda + \gamma)(\lambda + \mu + \eta)(\lambda + \mu) - \beta \beta_v \kappa \eta - \kappa \alpha (\lambda + \mu)(\lambda + \eta + \mu) = 0. \quad (22)
\]

If the observed value of the exponential rise is \( \rho \), then from (22) we obtain

\[
(\rho + \kappa)(\rho + \gamma)(\rho + \mu + \eta)(\rho + \mu) - \beta \beta_v \kappa \eta - \kappa \alpha (\rho + \mu)(\rho + \eta + \mu) = 0. \quad (23)
\]

The reproduction number of the model of Equations 17 reduces to that of an SEIR model when mosquitoes are absent. The reproduction number of the reduced model is

\[
\hat{R}_0 = \alpha / \gamma. \quad (24)
\]
In Section A1.1, we showed that the reproduction number of the model with vector-borne transmission alone is

\[ R_0^* = \frac{\beta \beta_v \eta}{\mu \gamma (\mu + \eta)}. \]  

(25)

From this we obtain

\[ \beta \beta_v = R_0^* (\mu + \eta) \mu \gamma / \eta. \]  

(26)

Substituting Equations 24 and 26 into Equation 23 and solving for \( \hat{R}_0 \) yields

\[ \hat{R}_0 = \frac{(\rho + \kappa)(\rho + \gamma)}{\kappa' \gamma} - \frac{R_0^* \mu (\mu + \eta)}{(\rho + \mu)(\rho + \eta + \mu)}. \]  

(27)

and

\[ \alpha = \frac{(\rho + \kappa)(\rho + \gamma)}{\kappa} - \frac{R_0^* \mu \gamma (\mu + \eta)}{(\rho + \mu)(\rho + \eta + \mu)}. \]  

(28)

A2.3: Estimation of the reproduction number for the vector borne disease model with sexual transmission from the observed exponential rise

Given hypotheses for the disease cycle parameters, and the reproduction number of the disease without any sexual transmission, \( R_0^* \), we can use Equation 27 with the rate of exponential rise in incidence to obtain estimates of the transmission due to sex alone, \( \hat{R}_0 \).

The estimates for the disease cycle parameters from the literature are shown in Table 3 on page 8. As above, we assumed Uniform probability distributions for the model parameters, over the range of the literature estimates, with the constraint that the serial interval derived from the sampled parameters had to be within the observed serial interval of 10 to 23 days.

The rate of exponential rise in initial incidence in the 2015 ZIKV outbreak in Barranquilla, Colombia, was \( \rho = 0.073 \) days\(^{-1} \), with 95% CI \([0.064, 0.082]\) days\(^{-1} \). The probability distribution for the rate of exponential rise was derived from the likelihood
fit to the data, and was Normally distributed about the best-fit estimate.

The only remaining unknown in Equation 27 is thus the reproduction number of the disease without any sexual transmission, $R_0^*$. Because mosquito borne transmission of ZIKV so far has always occurred in populations that also have sexual transmission, we cannot determine the value of $R_0^*$ independently of the value of $\hat{R}_0$ from the Barranquilla data, or from similar data.

In Figure 2 on page 13, we thus show the estimate of $\hat{R}_0$ versus hypothesized values of $R_0^*$; for each hypothesis of $R_0^*$, we performed the Monte Carlo procedure for the estimation of the uncertainty on the $\hat{R}_0$, by sampling the probability distributions of the model parameters and our estimate of the exponential rise, $\rho$, from the Barranquilla data. We used the constraint that the serial interval derived from the sampled parameters had to be within the observed serial interval of 10 to 23 days.

If the mosquito borne transmission dynamics for ZIKV are similar to that of CHIKV, there is the potential to use CHIKV outbreaks as a reference to estimate $R_0^*$ (because CHIKV is not sexually transmitted, and many recent CHIKV outbreaks largely occurred in naïve populations). Studies of CHIKV outbreaks in naïve populations have determined the reproduction number to be around 4.6, 16 In Figure 2 on this page, we see that if $R_0^* \sim 4$, the 95% upper confidence limit on $\hat{R}_0$ is around 0.75. A reproduction number of more than 1 is needed to achieve sustained transmission of a disease in a population, thus it is unlikely that sexual transmission alone can result in sustained ZIKV transmission in a population.

A2.4: Estimation the fraction of cases due to sexual transmission

Here we again assumed Uniform probability distributions for the model parameters, over the range of the literature estimates shown in Table 3 on page 8, with the constraint that the serial interval derived from the sampled parameters had to be within the observed serial interval of 10 to 23 days.

Under hypotheses of $R_0^*$, estimates of $A = \beta \beta_r$ were derived from Equation 26. Under assumptions of their relative transmission $q$, we obtained $\beta_r = \sqrt{qA}$, and $\beta = \sqrt{A/q}$. In addition, as described in the preceding section, with an estimate of the exponential
rise in cases, one can estimate the 95% confidence interval on the values of $\hat{R}_0$, given hypotheses of $R^*_0$. Because $\hat{R}_0 = \alpha/\gamma$, these estimates can be converted to estimates of $\alpha$.

Numerical simulations of Equations [17] with the assumptions of $\kappa$, $\gamma$, $\eta$, $\mu$, $\beta$, $\beta_v$, and $\alpha$ were used to obtain final size estimates of hypothetical outbreaks that match the exponential rise of the 2015 Barranquilla ZIKV outbreak. The final size estimates were divided into the cases that were produced by sexual transmission, and those that were produced by transmission from mosquitoes.

The resulting 95% CI on the fraction of total cases due to sexual transmission versus hypothesized values of $R^*_0$ are shown in Figure 3 on page 17. Cross-checks of the analysis with various values of $q$ and relative numbers of humans and mosquitoes, $N_h$ and $N_v$, respectively, confirm that the results in Figure 3 on page 17 are insensitive to these assumptions.

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Assessed using the initial exponential rise in incidence during the 2015 ZIKV outbreak in Barranquilla, CO

Figure 2: Estimates of $\hat{R}_0$ (the reproduction number of the disease model with only direct sexual transmission) versus hypothesized values of $R^*_0$ (the reproduction number of the vector borne disease model with no sexual transmission). The estimates are derived from the initial exponential rise in incidence in the 2015 ZIKV outbreak in Barranquilla, Colombia.
Assessed using the initial exponential rise in incidence during the 2015 ZIKV outbreak in Barranquilla, CO

Figure 3: Estimates of the fraction of cases due to sexual transmission for the vector borne disease model with sexual transmission versus hypothesized values of $R_0^*$ (the reproduction number of the vector borne disease model with no sexual transmission). The estimates are derived from the initial exponential rise in incidence in the 2015 ZIKV outbreak in Barranquilla, Colombia.