Tropical Medicine and International Health doi:10.1111/tmi.12924

VOLUME 22 NO 10 PP 1249–1265 OCTOBER 2017

Stratifying the potential local transmission of Zika in municipalities of Antioquia, Colombia

Juan Ospina[1], Doracelly Hincapie-Palacio[2], Jesús Ochoa[2], Adriana Molina[2], Guillermo Rúa[3], Dubán Pájaro[4], Marcela Arrubla[4], Rita Almanza[5], Marlio Paredes[6,7] and Anuj Mubayi[6]

1 *Eafit University, Medellín, Colombia*
2 *National School of Public Health, 'Héctor Abad Gómez', Epidemiology Group, University of Antioquia, Medellín, Colombia*
3 *Group of Entomology, Faculty of Medicine, University of Antioquia, Medellín, Colombia*
4 *Secretary Regional Health and Social Protection of Antioquia, Medellin, Colombia*
5 *Secretary of Health, Medellin, Colombia*
6 *Simon A. Levin Mathematical Computational and Modeling Sciences Center, Arizona State University, Tempe, AZ, USA*
7 *Department of Mathematics and Physics, University of Puerto Rico, Cayey, Puerto Rico*

Abstract

OBJECTIVE To stratify and understand the potential transmission processes of Zika virus in Colombia, in order to effectively address the efforts on surveillance and disease control.

METHODS We compare R_0 of Zika for municipalities based on data from the regional surveillance system of Antioquia, Colombia. The basic reproduction number (R_0) and its 95% confidence intervals were estimated from an SIR model with implicit vector dynamics, in terms of recovered individuals in each time unit, using an approximate solution. These parameters were estimated fitting the solution of the model to the daily cumulative frequency of each Zika case according to symptoms onset date relative to the index case reported to the local surveillance system.

RESULTS R_0 was estimated for 20 municipalities with a median of 30 000 inhabitants, all located less than 2200 m above sea level. The reported cases ranged from 17 to 347 between these municipalities within 4 months (January to April of 2016). The results suggest that 15 municipalities had a high transmission potential ($R_0 > 1$), whereas in five municipality transmissions were potentially not sustaining ($R_0 < 1$), although the upper bound of the confidence interval of the R_0 for 3 of these 5 was greater than one, indicating the possibility of an outbreak later on.

CONCLUSION The study identified high-risk municipalities ($R_0 > 1$) and provide a technique to optimise surveillance and control of Zika. Health authorities should promote the collection, analysis, modelling and sharing of anonymous data onto individual cases to estimate R_0.

keywords Zika, basic reproductive number, mathematical model, Colombia

Introduction

In May 2015, PAHO/WHO issued an epidemiological alert for the Zika epidemic in the Americas, after confirmation of autochthonous transmission in Brazil. On 1 February 2016, WHO declared the Zika epidemic in the Americas a *Public Health Emergency of International Concern* [1, 2].

Zika is a disease spread by an arbovirus of the genus *Flavivirus* (family Flaviviridae) and is transmitted by the *Aedes aegypti* mosquito, which is also vector of dengue and chikungunya [3]. In 2015–2016, because of its high incidence, the Zika epidemic was considered a public health problem in the Americas due to its rapid spread compared to previous epidemics in Africa and Asia, frequent occurrence of severe neurological complications (Guillain–Barré syndrome) and occurrence of congenital syndromes related to Zika infection [4].

Around 40 countries/territories in the Americas reported autochthonous transmission in 2015–2016. By July 2016, Brazil had reported 78% of confirmed cases (64 311/81 914), 38.7% of suspected cases (161 241/416 958) and 1656 cases of congenital syndrome with suggestive evidence of congenital infection and 255 laboratory-confirmed cases. Colombia was the second country in Americas to report a large number of cases: 10.4% (n = 8506) of confirmed cases, 21.1% of suspected cases (n = 87 844), 11 confirmed cases of microcephaly related to Zika and 102 cases under study. Puerto Rico (2.6% of confirmed cases) and Venezuela (2% of confirmed cases and 11.8% of suspected cases) also report high incidence [5].

PAHO/WHO recommended countries to establish integrated control programme to reduce virus transmission, including the identification of areas with high risk of transmission [2]. In this study, we estimate the basic reproductive number (R_0), an indicator of potential for local Zika transmission in Antioquia. R_0 is formally defined as the average number of secondary cases generated by an infected individual when introduced into a completely susceptible population during his infectious period [6].

Antioquia in northwestern Colombia has more than 6 million inhabitants living in 125 municipalities divided into nine subregions (Figure 1). *Aedes aegypti* is distributed in more than 80% of its land area due to its tropical climate. Antioquia reported the highest number of municipalities with laboratory-confirmed cases at week 28 of 2016 [7] and it had a rapid spread of the disease in some subregions and cases presented more aggressive symptoms than from other arboviruses such as joint pain, conjunctivitis and emerging neurological conditions.

PAHO established some entomological indices to determine the risk of dengue transmission [8]; however, these indices are not accurate. For example, Focks [9] found a weak relationship between larval indices and production of adult mosquitoes, responsible for transmission. It has also been determined that less than 20% of larvae deposits are usually responsible for over 80% of *Aedes* adults [10]. Similar results have been reported by Bowman [11] and Boyer [12]. Particularly the latter suggest that traditional infestation indexes of *Aedes* should not be considered indicators of epidemiological risk. In Medellin, the capital of Antioquia, a relationship between traditional entomological indexes and the incidence of the disease was not observed for dengue epidemic registered in 2010 [13].

Given the poor relationship between the transmission of dengue and entomological indicators, this paper estimated R_0 from an SIR model with implicit vector dynamics, based on the work of Pandey [14] and Bailey [15]. The SIR model proposed in our paper recognises the importance of vector transmission summarising, in the beta transmission parameter, the cycle of vector–human transmission. We use epidemiological surveillance data to establish the potential for local transmission, estimating R_0 for the ongoing Zika epidemic.

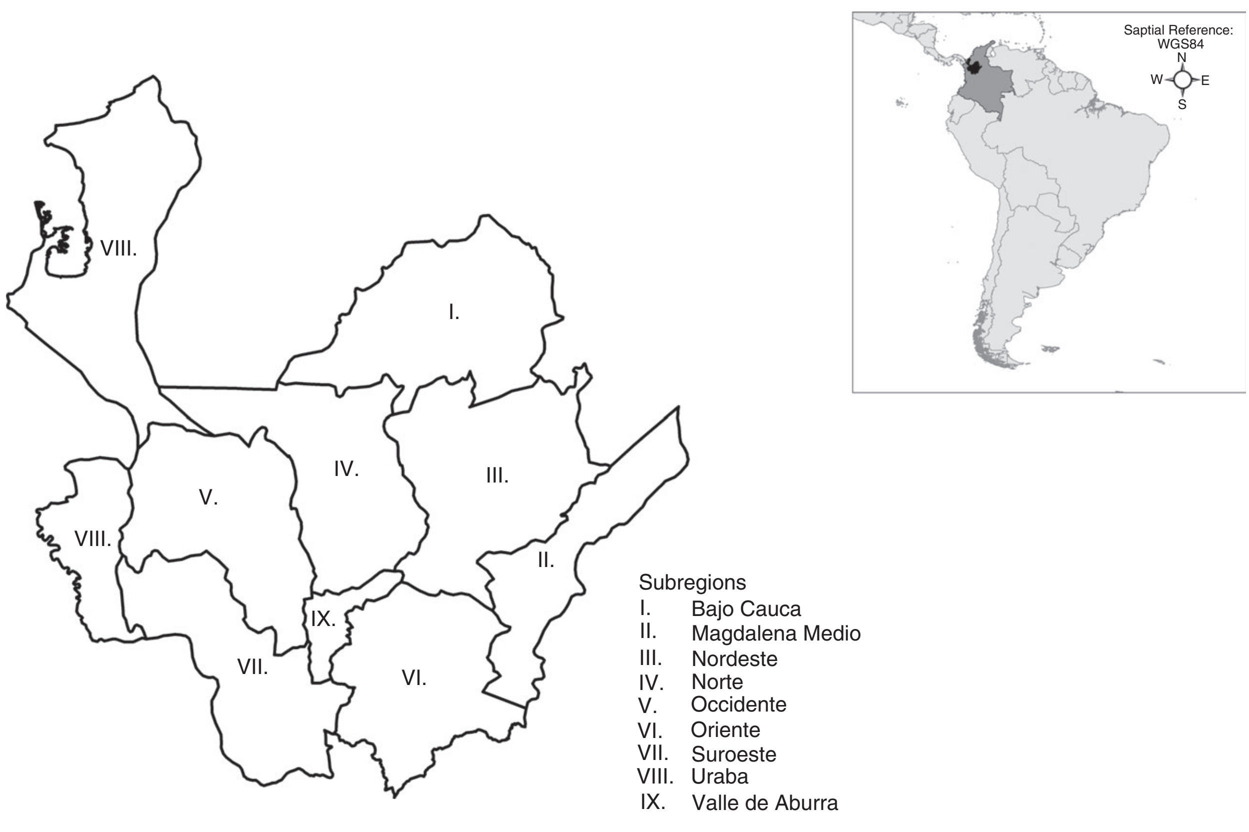

Figure 1 Subregions of Antioquia, Colombia.

Methods

We estimated and compared the basic reproductive number of Zika in municipalities of Antioquia, Colombia. The solution to an SIR model with implicit vector dynamic in the transmission term was adjusted to the daily cumulative frequency of Zika cases, reported to the epidemiological surveillance system of Antioquia ('SIVIGILA') by municipality.

The approximate solution of a model was obtained as follows. First, the vector SIR model with explicit vector dynamics was reduced to a simple SIR model with an implicit vector dynamics via simple assumptions on the transmission terms. The resulting effective simple SIR model incorporated the transmission parameter, which is a weighted average of vector-to-host and host-to-vector transmission parameters of the original vector SIR model. That is, the transmission term β includes the average number of new infected humans generated by an infectious mosquito and the average number of new infected mosquitoes generated by a single infected human (Equation 17 in Appendix 1).

The original vector SIR model consisted of five coupled differential equations which described explicitly the transmission of the disease from vectors-to-humans and humans-to-vectors. The human population was classified into susceptible, infected and removed individuals, and the vector population was classified into susceptible and infected mosquitoes.

The second, analytical solution of the vector SIR model was difficult to compute. In Appendix 1, we show that an analytic solution is possible if the model is simplified under a certain approximation, which assumes that the number of infected mosquitoes remains approximately constant during the epidemic. Such an assumption is reasonable under certain specific climatic (i.e., rainfall, temperature) and ecological conditions in the region. For the resulting effective simple SIR model, it was possible to use the well-known approximated analytical solution proposed by Kermack and Mackendrick [16] (Equation 18 in Appendix 1).

We assumed that the temporal evolution of the number of removed human individuals is directly observed from the notifications of the epidemiological surveillance. The epidemic parameters were assumed constants over time, and the effect of a possible spatial migration was assumed negligible.

Using the simplest model, which assumed a closed population during the transmission of Zika, the effect on the transmission of asymptomatic individuals and the possibility of sexual or vertical transmission are not considered. Homogeneous mixing between humans and vectors is assumed in such a way that the classical mass action law is applicable.

The deterministic model is used because the population of municipalities is large enough and the effect of stochastic processes on the model parameter estimates is extremely low.

Data sources

Data were obtained from the anonymous database of the epidemiological surveillance system ('SIVIGILA') of Antioquia, which contains daily data onto the onset date of symptoms of each patient by municipality. Case reporting is required by all hospitals or clinics. Case definition and data management are based on the guidelines of the Ministry of Health and Social Protection and the National Institute of Health of Colombia (NIH). We included only Antioquia′s residents in the analysis. Suspected cases, laboratory confirmed and confirmed clinical criteria were included. Cases were reported from the first 4 months of 2016 when the peak of the epidemic ocurred.

Parameter estimation

The epidemic parameters were estimated using NLREG® (version 6.5 – P. Sherrod, TN, USA) by fitting the mathematical expression of recovered individuals per unit time R (t) to the daily cumulative number of reported Zika cases according to symptoms onset date relative to the index case (Appendix 1 Equation 18; Appendix 2).

NLREG® is a flexible, stable and easy to handle software. It is a non-linear regression procedure which uses a least squares method for fitting. In order to perform the estimation, it is necessary to introduce some 'seed' or *ad hoc* values for the relevant parameters. These values are neither initial values of the model parameters nor initial states as needed in the case of a dynamical system. Hence, there is no need for any sensitivity analysis on it. The code used to estimate the parameters is included in Appendix 1.

We verified that the time between the index case and the successive case was approximately the extrinsic incubation period, which is around 3 weeks [17]. The seed values of the parameters were taken as $\gamma_h = 0.02$, $R_0 = 20$, $s = 100$ with their 95% confidence interval. Goodness of fit test was used to compare observed and estimated data.

Ethics approval for the study was not required, as all analysis used depersonalised routine notification data.

Results

From 1 January 2016 to 11 April 2016 (i.e., week 1–15), 1935 cases of Zika were reported to the Secretary of Health in 74 of the 125 municipalities of Antioquia and nine subregions. Of these, 1864 cases were from Antioquia residents (96.3%) in municipalities that were located below 2200 metres above sea level. The population of the municipalities varied between 14 000 and 2.5 million, with a median of 30 000 inhabitants per municipality (Table 1).

1841 cases were analysed, after discarding 23 cases due to other diagnoses. Laboratory confirmed cases accounted for less than 1% of total cases (=15/1841). Data on the onset date of symptoms were available in 99.5% of cases. Laboratory-confirmed cases data were used only for small number of municipalities. Due the rarity of laboratory-confirmed cases, data based on suspected and clinical confirmed cases were used for 11 municipalities and only suspected cases were used for seven municipalities (Table 1).

Cases were primarily women (67.1%), aged 15–44 years old (63.7%) and residents in urban areas (81.8%). The age and gender distributions were found to be similar between municipalities Table 1. We estimated R_0 for 20 municipalities that had reported more than 15 cases in the analysed period. Most index cases began showing symptoms in January 2016. Outbreaks were reported during 43–98 days (median 79 days) in the municipalities. A median of 38 cumulative cases was reported by municipality, with a minimum of 17 cases in *Sopetrán* and maximum of 347 cases in *Medellin*. Also, the next two highest reporting of the cumulative frequency of cases was found in *Apartadó* (n = 311) and *Turbo* (n = 228).

As shown in Figures 2–3, the cumulative number of cases was growing abruptly in *Caceres* and *Medellin*, while in 12 municipalities it stabilised around a fixed number. In the remaining six municipalities, the cumulative curve showed a slow growth initially, eventually approaching to a stable value of cumulative number of cases.

The adjusted coefficient of multiple determination ranged between 96.27% and 99.97%, obtaining a suitable adjustment of accumulated cases per day and the number of recovered individuals per unit time $R(t)$ estimated from the model according to equation 18 (Figures 2–3).

The median R_0 was estimated as 1.12. The R_0 upper 95% confidence interval was >1 in all 15 municipalities.

The greatest potential for transmission occurred in 14 municipalities, with a maximum $R_0 > 1$ of 2.2 (CI 95% 1.54–2.86) in *Nechí* and a maximum value of 56.38 in *Caceres* (Figure 4). The last two municipalities are part of the *Bajo Cauca* subregion, where the epidemic was growing during the analysis, as can be seen in Figure 2.

In the subregion of Valle of Aburrá, Medellin, R_0 = 22.2, followed by the subregion of Urabá, where six municipalities had $R_0 > 1$.

Potential to maintain transmission locally was lower in five municipalities, where the estimated R_0 was <1, but the upper confidence interval included some R_0 values >1 during the analysed period (see Figures 3–4).

Discussion

Mathematical models have been developed to help understand the epidemiology of vector-borne diseases and support decision making. Some of these models explicitly include dynamics of vector population. In this study, we developed a procedure to estimate the reproduction number (R_0) of a vector-borne disease via analytical expression of cumulative cases that includes a weighted average of effective vector-to-host and host-to-vector transmission. The vector-borne model used in this article is first reduced to the effective direct transmission model before explicitly finding its approximate solution under certain assumption and estimating R_0. The approximation of the solution to the model provided a simple relationship between the reported cases in the field and the estimated cases from the model without explicitly incorporating all the entomological variables and data, following the work of Pandey [14] and Bailey [15].

Models that explicitly include entomological variables are complex due to the requirement of greater number of parameters, including parameters describing the infection cycle between mosquito and humans, for which data may be difficult to obtain. Hence, simple models with relatively few parameters and with consistency with real data are often preferred, as in the current analysis. However, to formulate a model that incorporates all the complexities of Zika are mathematically more complicated, making it difficult to derive algebraic expression of R_0, to obtain approximated analytical solutions and to perform regression procedures that let us estimate the epidemiological parameters.

However, we would like to note that this study considers certain strict modelling assumptions including constant vector density. For the current study, this assumption may be reasonable as the analysis covered only ~3 months, but it may not hold for other vector-borne diseases or if we consider other regions with significant fluctuations in climatic variables. Models with explicit vector dynamics and parameters depending on weather conditions (i.e. rainfall and temperature) may be required if an outbreak lasts longer.

Table 1 Zika cases of residents in Antioquia, Colombia, 2016 by subregion and municipality

Subregion/ Municipality	Metres above sea level	Population	Type of cases	Dates of index case and last case reported	Total cases	Ratio urban/ rural	Age – number (per cent) <15	15–44	45 +
Bajo Cauca									
Cáceres	200	38 850	Suspect	03/01/2016 15/02/2016	45	1.0	14 (31.1)	21 (46.6)	10 (22.2)
Nechí	30	27 238	Suspect	30/01/2016 20/03/2016	29	4.8	9 (31.3)	12 (41.4)	8 (17.8)
Caucasia	150	114 902	Suspect & Confirmed	10/01/2016 05/04/2016	59	13.8	11 (18.6)	37 (66.1)	11 (18.6)
Zaragoza	150	31 129	Suspect	29/01/2016 07/04/2016	49	7.2	7 (14.3)	34 (69.4)	8 (16.3)
Valle Aburrá									
Medellín	1538	2 486 723	Suspect & Confirmed	12/09/2015 09/04/2016	351	13.0	35 (10.0)	231 (65.8)	85 (24.2)
Bello	1450	464 614	Suspect & Confirmed	11/01/2016 01/04/2016	32	7.0	10 (31.3)	15 (46.8)	7 (21.9)
Envigado	1575	227 644	Suspect & Confirmed	01/01/2016 03/04/2016	21	6.0	2 (9.5)	12 (57.1)	7 (33.3)
Itagüí	1550	270 903	Suspect & Confirmed	13/01/2016 03/04/2016	40	3.4	3 (8.1)	31 (83.8)	3 (8.1)
Urabá									
Chigorodó	34	78 148	Suspect & Confirmed	02/01/2016 06/04/2016	164	17.2	31 (18.9)	105 (64.1)	28 (17.0)
San Pedro de Urabá	200	31 539	Suspect & Confirmed	06/01/2016 30/03/2016	23	2.3	4 (17.4)	9 (39.1)	10 (43.5)
Carepa	28	57 220	Suspect & Confirmed	07/01/2016 06/04/2016	102	4.1	14 (13.7)	75 (73.5)	13 (12.7)
Turbo	2	163 525	Suspect & Confirmed	02/01/2016 02/04/2016	228	4.4	44 (19.3)	153 (67.1)	31 (13.6)
Necoclí	8	63 991	Suspect & Confirmed	25/01/2016 07/04/2016	36	1.0	5 (13.9)	22 (61.1)	9 (25.0)
Apartadó	30	183 716	Suspect & Confirmed	02/01/2016 10/04/2016	315	7.1	64 (20.3)	196 (62.2)	55 (17.5)
Mutatá	75	21 077	Suspect & Confirmed	26/01/2016 03/04/2016	19	1.7	6 (31.6)	11 (57.9)	2 (10.5)
Nordeste									
Remedios	700	29 898	Suspect	16/02/2016 04/04/2016	18	3.5	3 (16.7)	15 (83.3)	0 (0.0)
Magdalena Medio									
Puerto Berrío	125	47 717	Suspect	31/01/2016 02/04/2016	61	3.7	10 (16.4)	34 (55.7)	17 (27.9)
Puerto Triunfo	150	20 483	Suspect	06/01/2016 02/04/2016	27	0.6	7 (25.9)	17 (63.0)	3 (11.1)
Occidente									
Sopetrán	750	14 821	Suspect	15/01/2016 01/04/2016	17	1.8	0 (0.0)	8 (47.0)	9 (52.9)
Oriente									
Rionegro	2125	122 231	Suspect & Confirmed	26/12/2015 02/04/2016	18	1.3	0 (0.0)	15 (83.3)	3 (16.7)

Our work has the advantage of using data on reported cases to stratify the potential transmission at municipalities during an ongoing outbreak. As mentioned by King *et al.* [18], it is preferable to estimate R_0 using disaggregated data. Thus, available data on the date of symptom onset of each patient are needed to implicitly model the

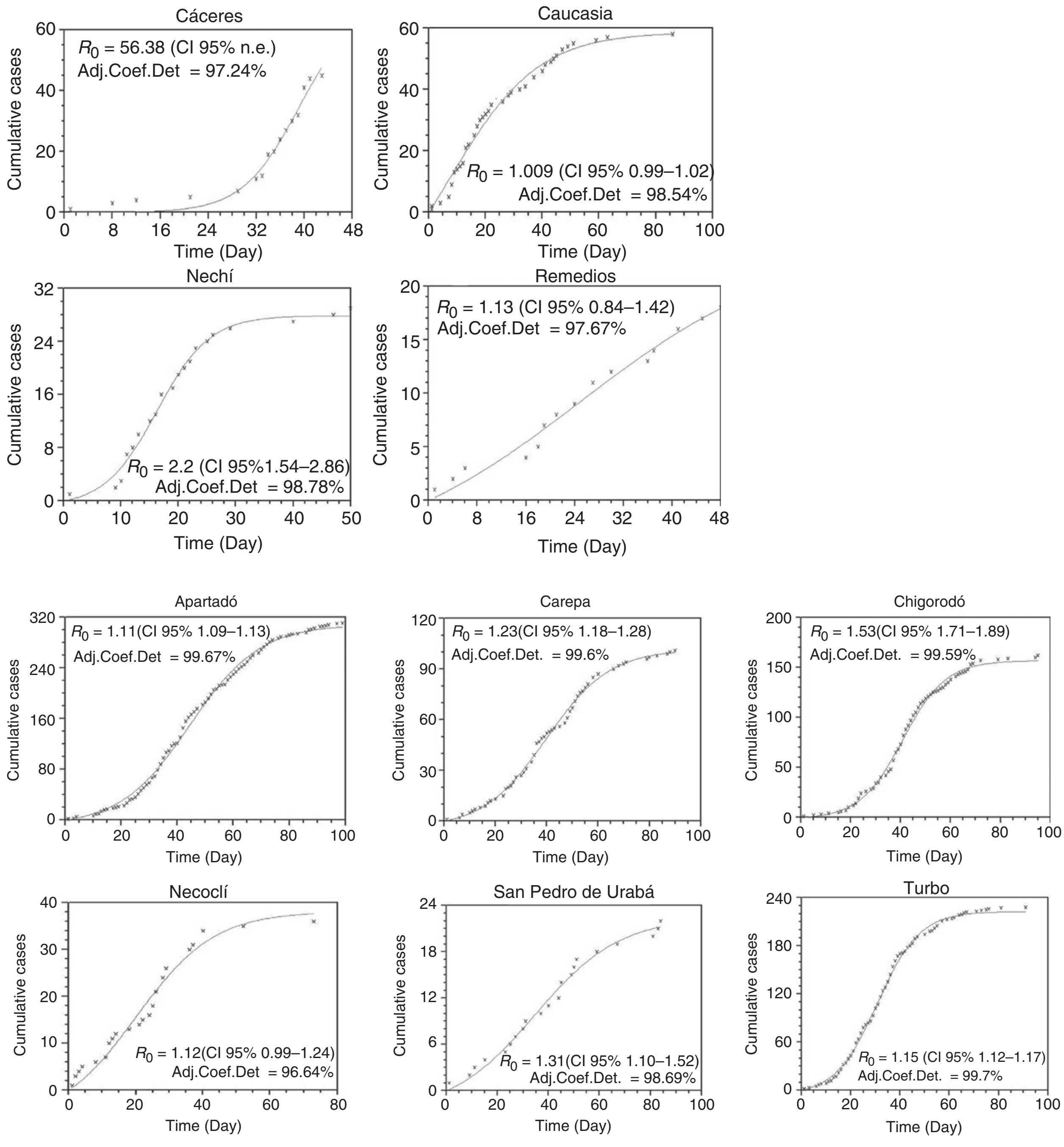

Figure 2 High Potential transmission (R_0 > 1) of Zika by municipality Antioquia, Colombia, 2016.

dynamics of transmission. These data are usually collected in epidemiological surveillance but not analysed or disseminated and shared.

Various studies have analysed the dynamics of transmission of vector-borne diseases by explicitly taking into account the spatial dissemination aspect [19]. We excluded the spatial link because of the short time scale. Typically, the transmission of a disease may depend on climatic, environmental and socio-economic factors that may go beyond the administrative limits of the

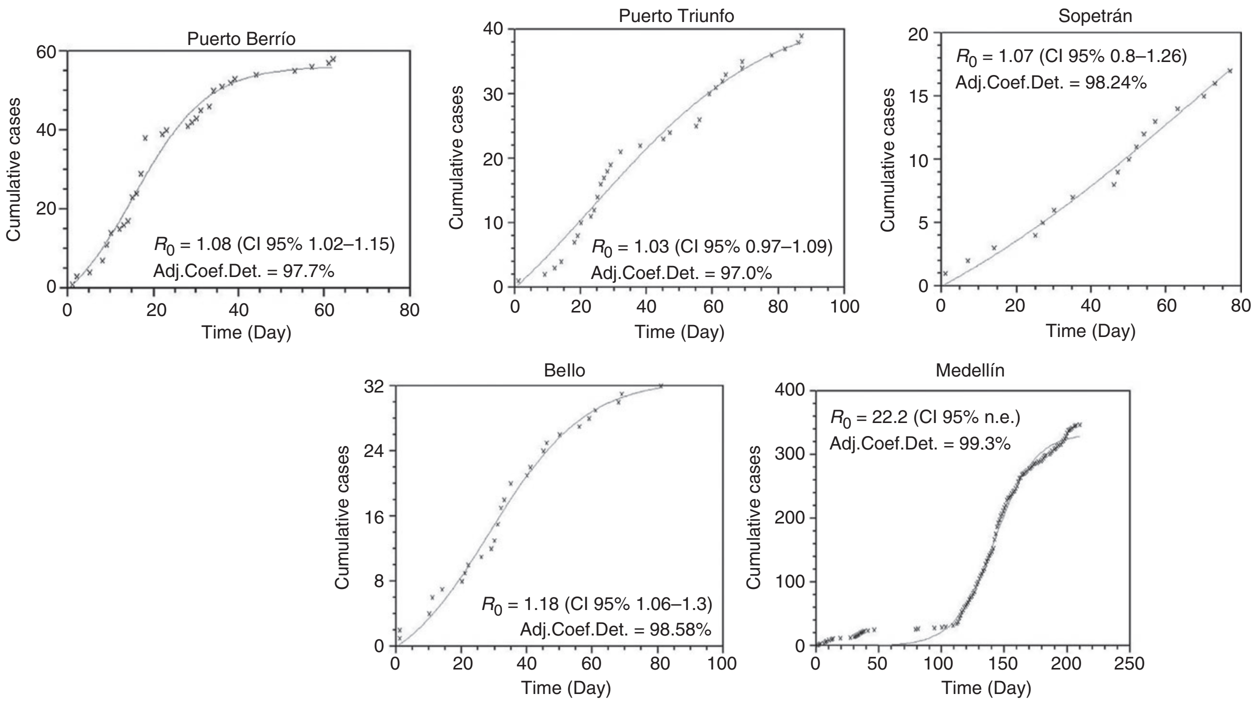

Figure 2 continued.

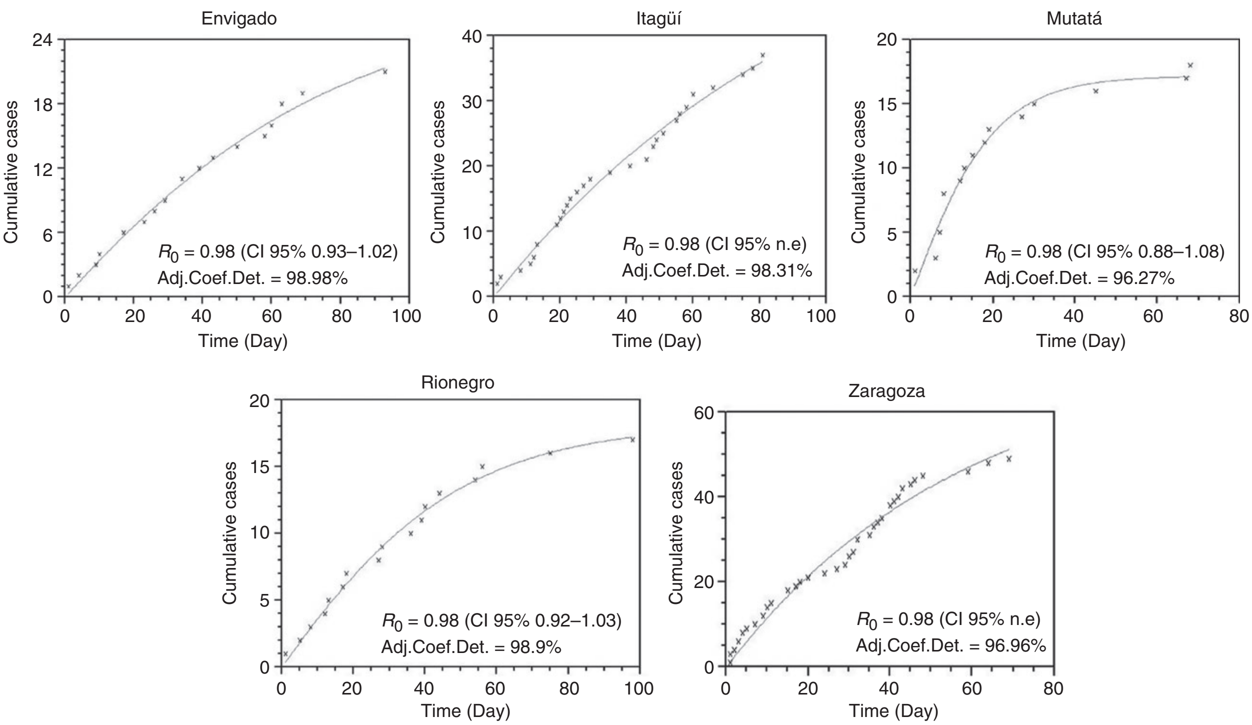

Figure 3 Less potential transmission (R_0 < 1) of Zika by municipality Antioquia, Colombia, 2016.

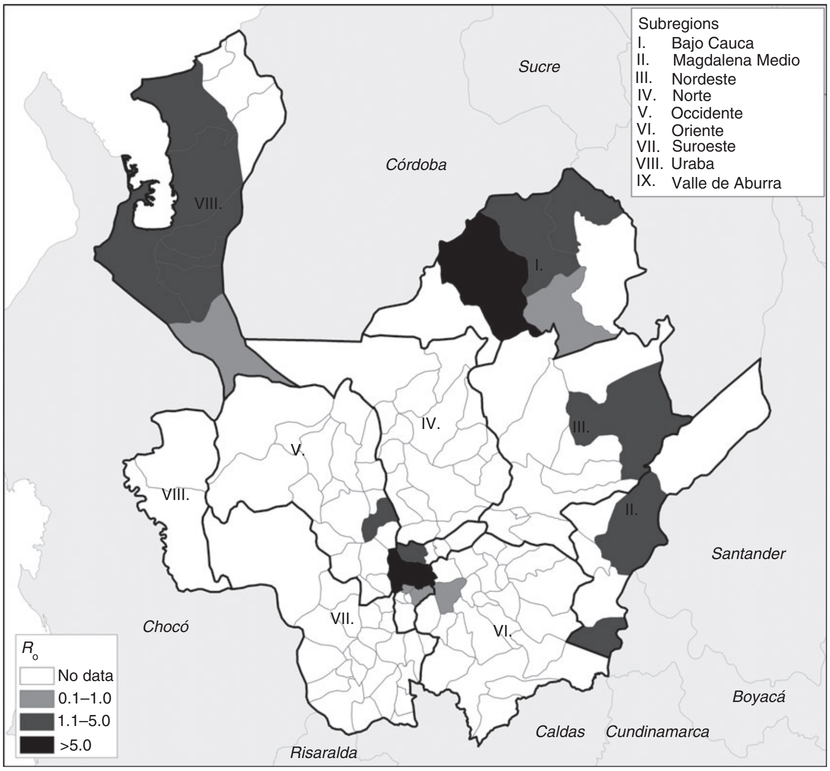

Figure 4 Reproductive number of Zika in municipalities of Antioquia, Colombia.

municipalities or regions. However, the choice of factors to be taken in the study should depend on the goal of the work, types of data that could be readily obtained from the field and availability of mathematical tools capable of estimating required quantities.

It should be emphasised that estimations of R_0 values provide approximations to the local transmission dynamics of Zika. As illustrated here, R_0 is used basically to compare the transmission potential between municipalities and accordingly, to identify and suggest effective local control measures [20]. Municipalities with higher or lower risk of Zika transmission were identified based on estimated R_0. There is no 'gold standard' to assess the external validity of our results; however, our findings on stratification of potential local transmission coincide with the risk perception of health personnel in charge of epidemiological surveillance (personal communications with Antioquia Secretary of health).

In this study, we used a deterministic model because of large populations in each of the municipalities. Additionally, vector transmission occurring in a municipality as a whole, make the modelling of epidemics in small groups like schools, hospitals, homes or workplaces, a hard task.

Like any other modelling study, this study also has some limitations including only few laboratory-confirmed cases and under-diagnosis or underreporting of cases, though, some stochasticity capturing measurement errors were included in the fitting procedure.

This work includes the stratification of the potential transmission of Zika for large and small outbreaks, guided by R_0 estimates depending on whether R_0 is bigger or smaller than one. Equation (18) is an approximate solution of our simple SIR model and this solution exists and can be applied for all values of R_0. In case $R_0 > 1$, the equation (18) produces a rising curve or S-shaped logistic function, which asymptotically saturates. If $R_0 < 1$, we obtain a curve of monotonically decreasing cases.

The presence of asymptomatic individuals so far estimated at 80% in other contexts [3,21] could affect estimation of R_0 in our model, which assumes that we are counting all infectious cases. In case of a high level of underreporting, inclusion of asymptomatic cases will merely provide high uncertainty in our estimates. Our aim was to use a simple model for an ongoing epidemic of Zika to capture local disease dynamics and compute a rigorous closed form expression to estimate R_0 using limited available data.

It was assumed in this model that each municipality has a closed population, which may be appropriate in the short term, in relation to the relatively short time of occurrence of Zika transmission. We also assumed negligible migration and internal mobility between municipalities. Moreover, data on disaggregated vital statistics are scarce, and there is no official reporting of internal mobility rates/residence times of the population. In future, we plan to consider the flow of individuals from endemic municipalities to the capital (Medellin) and metropolitan area (Valle of Aburra), mainly due to the difference in socio-economic conditions and work opportunities.

Our R_0 estimates for Zika fall are similar to ranges in the literature. However, the exact comparison of our estimates of R_0 with the reported values in the literature is difficult to carry out because of different models, and assumptions were used by other published studies.

Towers *et al.* [22]. used a SEIR/SEI model with vector dynamics for estimating R_0. They used data from the daily incidence of suspected Zika cases reported in Barranquilla, Colombia from October to November 2015 to estimate the exponential growth rate of an outbreak. In their fitting procedure, they fixed their entomological parameters obtained from other regions in the literature. According to authors, R_0 was estimated to be 3.8 (95% CI 2.4–5.6). The authors used a similar expression as given in equation 17 but some parameters were obtained assuming the epidemic being in its initial exponential phase when interventions are not yet applied. As only data from the beginning of the outbreak were only used, the exponential growth may overestimate the reproduction number. In our model we used Equation 16, a shortened form of Equations 17 and 18 representing the complete course of the epidemic instead of just its initial phase; therefore our method may underestimate the reproduction number.

Other authors also have analysed data from the initial phase of the epidemic based on the exponential growth rate, using phenomenological models. Majumder *et al.* [23]. used exponential smoothing models as well as the Incidence Decay and Exponential Adjustment (IDEA) model to estimate R_0 for Colombia and other countries, using the data published by HealthMap and the NIH. They estimated an average R_0 of around 4.82 (range 2.34–8.32). Nishiura *et al.* [24]. estimated R_0 from Colombia using maximum likelihood methods. They assumed that the confirmed cases from week 35 of 2015 had an exponential growth. The estimates of R_0 ranged from 3.0 to 6.6.

Rojas *et al.* [25] analysed surveillance data from San Andres and Girardot, Colombia using a maximum likelihood method to fit a chain-binomial model to daily incidence data. The estimated R_0 in San Andres was 1.41 (95% CI: 1.15–1.74) and in Girardot it was 4.61 (95% CI: 4.11–5.16). Hsieh [26] used a phenomenological model to estimate parameters by fitting the Richards model to the weekly reported case data from Colombia provided by the Pan American Health Organization (PAHO) website. The estimated R_0 ranged from 1.75 (95% CI: 1.34–2.16) to 1.79 (95% CI: 1.29–2.30) in the first wave of cases (week 32–43/2015) and in the second one (week 49/2015–week 16/2016), respectively.

Chowell *et al.* [27] estimated R_0 by calculating the polynomial growth profile of the initial trajectory of the epidemic with data from the daily incidence of Antioquia globally. Assuming a gamma distributed generation interval (average: 14 days S.D 2), they estimated R_0 of 10.3 (CI 95%: 8.3–12.4) in the first generation of Zika to 2.2 (CI 95%: 1.9–2.8) in the second generation. When the exponential distributed generation interval was assumed, R_0 was estimated from 2.8 (CI 95%: 2.4–3.1) to 1.8 (CI 95%: 1.7–2.0) for the two generations, respectively. The latter values were lower than those estimated by Nishiura *et al.* [24], who used weekly data from Colombia, but they are closer to those obtained in our work, for each of the municipalities despite using different models.

Anaya *et al.* [28] estimated R_0 assuming an exponential growth rate model and a gamma distribution for the generation time as described by Chowell *et al.* [27] of daily data of cases reported of Cucuta from 29 June 2015 to 30 July 2016. According to the authors, R_0 ranged between 2.68 (95% CI 2.542.67) and 4.57 (95% CI 4.18–5.01).

In this paper, we show that data based on the cumulative incidence give a better model fit than fitting the model to the incidence data. From a practical point of view, incidence data are limited because daily or weekly incidence may change with the confirmation of cases, usually 4 weeks after the notification of cases.

The age and sex distribution of cases of Antioquia are similar to those reported in Colombia [5]. As it has been documented, the tendency of women to consult a practitioner is related to concerns about the risk of having congenital malformations in infected pregnant women. The occurrence of cases primarily in urban areas and in the population aged 15–44 suggest that these populations have high exposure to vector density or are more susceptible to infection.

The results show a greater transmission potential of Zika in municipalities of Bajo Cauca, Uraba subregions and Medellin. The high R_0 in these municipalities is in line with the observed incidence rate, hence it suggests the need to strengthen the capacity of case detection and management as well as integrated vector control programmes.

Our results demonstrate the advantage of having individual patient data to estimate R_0 instead of analysing weekly accumulated data. Moreover, they are extremely useful in designing both regional and global policies. Public health departments will be able use such data and methods for future outbreaks of emerging and remerging disease.

Acknowledgements

We gratefully acknowledge useful comments on earlier drafts by Gerardo Chowell, Georgia State University, and Francisco J. Diaz, University of Antioquia. This work was partially funded by University of Antioquia.

References

1. World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations, Feb 1 2016. Geneva 2016. (Available from: http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/) [01 February 2016].
2. World Health Organization. Zika virus outbreaks in the Americas. *Wkly Epidemiol Rec* 2015: **90**: 609–610.
3. Weaver SC, Costa F, Garcia-Blanco MA *et al.* Zika virus: history, emergence, biology, and prospects for control. *Antiviral Res* 2016: **130**: 69–80.
4. Petersen E, Wilson ME, Touch S *et al.* Rapid spread of Zika virus in the Americas–implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic games. *Int J Infect Dis* 2016: **44**: 11–15.
5. Pacheco O, Beltran M, Nelson CA *et al.* Zika virus disease in Colombia - preliminary report. *N Engl J Med* 2016: doi: 10.1056/NEJMoa1604037.
6. Heffernan JM, Smith RJ, Wahl LM. Perspectives on the basic reproductive ratio. *J R Soc Interface* 2005: **2**: 281–293.
7. Instituto Nacional de Salud. Boletín Epidemiológico Semanal. Número 28: 10 – 16 julio Bogotá; 2016. (Available from: http://www.ins.gov.co/boletin-epidemiologico/Boletn%20Epidemiolgico/2016%20Bolet%C3%ADn%20epidemiol%C3%B3gico%20semana%2028.pdf) [30 July 2016].
8. Pan American Health Organization. *Dengue and Dengue Hemorrhagic Fever in the Americas: Guidelines for Prevention and Control*. PAHO: Washington DC, 1994.
9. Focks D. A review of entomological sampling methods and indicators for dengue vectors. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; 2004. (Available from: http://www.who.int/iris/handle/10665/68575#sthash.OmTDGEBh.dpuf) [20 August 2016].
10. Focks D, Alexander N. *Multicountry study of Aedes aegypti* pupal productivity survey methodology Document TDR/IRM/DEN/06.1 56. World Health Organization: Geneva; 2006.
11. Bowman LR, Runge-Ranzinger S, McCall PJ. Assessing the relationship between vector indices and dengue transmission: a systematic review of the evidence. *PLoS Negl Trop Dis* 2014: **8**: e2848.
12. Boyer S, Foray C, Dehecq JS. Spatial and temporal heterogeneities of *Aedes albopictus* density in La Reunion Island: rise and weakness of entomological indices. *PLoS ONE* 2014: **9**: e91170.
13. Calle D, Henao E, Rojo R, Almanza R, Rúa-Uribe G. Experiencias en el control integrado de la epidemia de dengue del año 2010 en Medellín. *Revista Salud Pública de Medellín* 2011: **5**: 77–87.
14. Pandey A, Mubayi A, Medlock J. Comparing vector-host and SIR models for dengue transmission. *Math Biosci* 2013: **246**: 252–259.
15. Bailey NTJ. *The Mathematical Theory of Epidemics*. Charles Griffin and Company Limited: London, 1957.
16. Kermack WO, McKendrick AG. A contribution to the mathematical theory of epidemics. *Proc R Soc Lond A* 1927: **115**: 700–721.
17. Musso D, Gubler DJ. Zika Virus. *Clin Microbiol Rev* 2016: **29**: 487–524.
18. King AA, Domenech de Celles M, Magpantay FM, Rohani P. Avoidable errors in the modelling of outbreaks of emerging pathogens, with special reference to Ebola. *Proc Biol Sci* 1806: **2015**: 20150347.
19. Lee S, Castillo-Chavez C. The role of residence times in two-patch dengue transmission dynamics and optimal strategies. *J Theor Biol* 2015: **374**: 152–164.
20. Fine PE. Herd immunity: history, theory, practice. *Epidemiol Rev* 1993: **15**: 265–302.
21. Duffy MR, Chen TH, Hancock WT *et al.* Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009: **360**: 2536–2543.
22. Towers S, Brauer F, Castillo-Chavez C, Falconar AK, Mubayi A, Romero-Vivas CM. Estimate of the reproduction number of the 2015 Zika virus outbreak in Barranquilla, Colombia, and estimation of the relative role of sexual transmission. *Epidemics* 2016: **17**: 50–55.
23. Majumder MS, Santillana M, Mekaru SR, McGinnis DP, Khan K, Brownstein JS. Utilizing nontraditional data sources for near real-time estimation of transmission dynamics during the 2015-2016 Colombian Zika virus disease outbreak. *JMIR Public Health Surveill* 2016: **2**: e30.
24. Nishiura H, Mizumoto K, Villamil-Gomez WE, Rodriguez-Morales AJ. Preliminary estimation of the basic reproduction number of Zika virus infection during Colombia epidemic, 2015-2016. *Travel Med Infect Dis* 2016: **14**: 274–276.
25. Rojas DP, Dean NE, Yang Y *et al.* The epidemiology and transmissibility of Zika virus in Girardot and San Andres island, Colombia, September 2015 to January 2016. *Euro Surveill* 2016: **21**: 1–21.
26. Hsieh YH. Temporal patterns and geographic heterogeneity of Zika virus (ZIKV) outbreaks in French Polynesia and Central America. *PeerJ* 2017: **5**: e3015.
27. Chowell G, Hincapie-Palacio D, Ospina J *et al.* Using phenomenological models to characterize transmissibility and

forecast patterns and final burden of Zika epidemics. *PLoS Curr* 2016: **31**: 1–21.

28. Anaya JM, Rodriguez Y, Monsalve DM *et al.* A comprehensive analysis and immunobiology of autoimmune neurological syndromes during the Zika virus outbreak in Cucuta, Colombia. *J Autoimmun* 2017: 77: 123–138.

Appendix 1

From the Vector SIR Model to the simple SIR model

The standard SIR vector model is given by the following system of non-linear and coupled differential equations where the equations (1), (2) and (3) describe the human population classified as susceptible (S_h), infected (i_h) and removed (R_h); and equations (4) and (5) describe the mosquito population classified as susceptible (S_m) and infected (i_m) [16]. We assumed that the mortality, migration and natality were negligible because the short time scale of the epidemic occurrence.

$$\frac{dS_h(t)}{dt} = -\beta_{mh}S_h(t)i_m(t) \tag{1}$$

$$\frac{di_h(t)}{dt} = \beta_{mh}S_h(t)i_m(t) - \gamma_h i_h(t) \tag{2}$$

$$\frac{dR_h(t)}{dt} = \gamma_h i_h(t) \tag{3}$$

$$\frac{dS_m(t)}{dt} = \mu_m N_m - \beta_{hm}S_m(t)i_h(t) - \mu_m S_m(t) \tag{4}$$

$$\frac{di_m}{dt}(t) = \beta_{hm}S_m(t)i_h(t) - \mu_m i_m(t) \tag{5}$$

where

$$\beta_{hm} \approx b\widetilde{\beta_{hm}}$$
$$\beta_{mh} \approx b\widetilde{\beta_{mh}}\frac{N_m}{N_h}$$

And the model parameters are as follows:
b: bitting rate.
$\beta_{h,m}$: probability of effective transmission from human to mosquito by bite.
$\beta_{m,h}$: probability of effective transmission from mosquito to human by bite.
γ_h: per capita recovery rate of Zika infection in humans
μ_m: per capita mortality rate in mosquitoes.
N_h: total human population
N_m: total mosquito population.
We assume that the densities of susceptible mosquitoes and infected mosquitoes are constant over time and obtain a simplified SIR model as below. That is,

$$i_m(t) = i_m \tag{6}$$

$$S_m(t) = S_m \tag{7}$$

Substituting (6) and (7) in (5) we obtain:

$$0 = \beta_{hm}S_m i_h(t) - \mu_m i_m \tag{8}$$

From (8), it follows that:

$$i_m = \frac{\beta_{hm}S_m i_h(t)}{\mu_m} \tag{9}$$

Using (6) and (9) in (1) we obtain:

$$\frac{dS_h}{dt}(t) = -\frac{\beta_{mh}S_h(t)\beta_{hm}S_m i_h(t)}{\mu_m} \tag{10}$$

Using (6) and (9) in (2) we obtain:

$$\frac{di_h}{dt}(t) = \frac{\beta_{mh}S_h(t)\beta_{hm}S_m i_h(t)}{\mu_m} - \gamma_h i_h(t) \tag{11}$$

Since S_m is assumed constant, we define average effective infectivity as in Pandey *et al.* (2013) [8]

$$\beta = \frac{\beta_{mh}\beta_{hm}S_m}{\mu_m} \tag{12}$$

Hence the equations (10) and (11) can be rewritten as:

$$\frac{d}{dt}S_h(t) = -\beta S_h(t)i_h(t) \tag{13}$$
$$\frac{d}{dt}i_h(t) = \beta S_h(t)i_h(t) - \gamma_h i_h(t) \tag{14}$$

Rewriting the equation (3)

$$\frac{d}{dt}R_h(t) = \gamma_h R_h(t) \tag{15}$$

It shows that the human population satisfies a simple SIR model given by equations (13), (14) and (15).
For the *effective* SIR model ((13), (14) and (15)) the basic reproduction number R_0 is given by:

$$R_0^2 = \frac{S_h(0)\beta}{\gamma_h} \tag{16}$$

Substituting (12) in (16), we obtain an R_0 which is similar to the reproduction number of the classic Ross–Macdonald model

$$R_0^2 = \frac{S_h(0)\beta_{mh}\beta_{hm}S_m}{\mu_m\gamma_h} \tag{17}$$

it is to say

$$R_0^2\left[= \frac{S_h(0)\beta_{mh}}{\gamma_h}\cdot\frac{\beta_{hm}S_m}{\mu_m}\right]$$

where $\frac{S_h(0)\beta_{mh}}{\gamma_h}$ is the average number of new infected humans generated by an infectious mosquito, and $\frac{S_m\beta_{hm}}{\mu_m}$ represents the average number of new infected mosquitoes generated by a single infected human.

An approximate solution for the effective SIR model and obtaining R_0

The SIR model (13), (14) and (15) can be solved approximately: [14–16]

$$R(t) = \frac{\rho^2\left(\frac{s}{\rho} - 1 - \alpha\tan h(-0.5\alpha\gamma_h t + \phi)\right)}{s} \tag{18}$$

where $s = S_h(0)$; and

$$\alpha = \sqrt{\left(\frac{s}{\rho} - 1\right)^2 + \frac{2s}{\rho^2}} \tag{19}$$

$$\phi = \frac{1}{2}\ln\left(\frac{\alpha\rho + s - \rho}{\alpha\rho - s + \rho}\right) \tag{20}$$

$$\rho = \frac{\gamma_h}{\beta} \tag{20A}$$

The saturation value obtained from (18) takes the form

$$R(\infty) = 2\rho(1 - \frac{\rho}{s}) \tag{20B}$$

The equation (20B) gives the final total size of the outbreak. The equation (18) gives the evolution through the time of the accumulated cases of the infection. The equation (18) will be used to fix the observed trends of the epidemic.

Algorithm to estimate the basic reproductive number using NLREG ® version 6.5 (P. Sherrod, TN, USA).

Title 'Cumulated cases of Zika 2015–2016';
Variables Day, CC;
Parameter gamma =0.02;
Parameter R =20;
Parameter s =100;
Double rho, alpha, phi;
rho=s/R;
*alpha = ((s/rho-1)^2 + 2*s/rho^2)^(1/2);*
*phi =1/2*ln((alpha*rho+s-rho)/(alpha*rho-s+rho));*
Function CC =rho^2/s(s/rho-1-alpha*tanh(-.5*alpha* gamma*Día+phi));*
Plot xvar=Day, xlabel='Time (Day)', ylabel='Cumulated cases';
Plot;
rplot;
ITERATIONS 100;
CONFIDENCE 95;
Data;

Appendix 2 Cumulated cases of Zika by time of onset symptoms relative to index case and estimated parameters values, Antioquia, 2016

Caceres		Nechi		Caucasia		Chigorodo		San Pedro Uraba		Carepa		Turbo		Necocli	
Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8	3	9	2	1	2	5	2	9	2	6	2	1	2	2	3
12	4	10	3	4	3	8	3	11	3	7	4	3	3	3	4
21	5	11	7	7	5	11	4	15	4	10	5	6	5	4	5
29	7	12	8	8	9	15	5	23	5	11	6	7	7	8	6
32	11	13	10	9	13	16	6	25	6	12	7	8	8	11	7
33	12	15	12	10	14	18	7	27	7	14	8	10	9	12	10
34	19	16	13	11	15	19	10	30	8	16	9	11	11	13	11
35	20	17	16	12	16	21	12	31	9	17	11	12	12	14	12
36	24	19	17	13	21	22	14	37	10	18	12	13	16	18	13
37	27	20	19	14	22	23	19	40	11	20	13	14	17	21	14
38	30	21	20	16	25	24	24	44	12	23	15	15	22	22	15
39	32	22	21	17	28	26	26	45	14	24	19	16	26	24	16
40	41	23	23	18	30	28	28	49	15	25	20	17	32	25	18
41	44	25	24	19	31	29	29	50	16	26	21	18	34	26	21
43	45	26	25	20	32	30	34	51	17	27	23	19	39	28	24
		29	26	21	33	31	35	59	18	28	26	20	43	29	26
γ = 0.003		40	27	22	35	32	40	67	19	30	27	21	49	36	30
s = 1975		47	28	26	36	34	42	81	20	31	29	22	59	37	31
		50	29	28	38	35	46	83	21	32	31	23	64	40	34
		γ = 0.17 (CI 95%:		29	39	36	48	84	22	34	35	24	71	52	35
		0.10–0.23)		32	40	37	57	γ = 0.14 (CI 95%:		35	39	25	78	73	36
		s = 54.69 (CI 95%:		34	41	38	65	0.10– .19)		36	46	26	82	γ = 0.49 (CI 95%:	
		51.38–58.00)		37	44	39	68	s = 54.2 (CI 95%:		37	47	27	84	0.29–0.69)	
				40	46	40	73	36.27–72.24)		38	49	28	86	s = 162.99 (CI	
				41	48	41	82			39	50	29	93	95%: 47.13–	
				43	49	42	88			40	52	30	102	278.85)	
				44	50	43	92			41	53	31	107		
				45	51	44	97			42	54	32	116		
				47	53	45	102			43	55	33	124		
				49	54	46	105			45	56	34	128		
				51	55	47	110			47	58	35	135		
				59	56	48	114			48	61	36	144		
				63	57	49	116			49	65	37	154		
				86	58	50	119			50	67	38	161		
				γ = 1.46 (CI 95%:		51	121			51	71	39	167		
				1.21–.71)		52	123			52	74	40	170		
				s = 1133.97 (CI		53	125			53	76	41	171		
				95%: 347.74–		54	126			54	77	42	173		
				1920.20)		55	127			55	79	43	178		
						56	129			56	81	44	180		
						57	130			58	85	45	183		
						58	133			60	87	46	189		
						59	135			66	90	47	191		
						60	138			68	92	50	194		

Table (*Continued*)

Caceres		Nechi		Caucasia		Chigorodo		San Pedro Uraba		Carepa		Turbo		Necocli	
Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec	Time	Cum. Frec
						62	141			70	93	52	198		
						63	143			71	94	53	199		
						64	144			79	96	54	202		
						65	145			80	97	55	205		
						66	146			83	98	57	211		
						67	148			87	99	59	213		
						68	153			88	100	61	214		
						69	154			90	101	62	215		
						72	157			γ = 0.31 (CI 95%: 0.27–0.35)		64	218		
						79	158			s = 316.25 (CI 95%: 274.85–357.66)		65	219		
						83	159					66	221		
						94	160					67	222		
						95	162					71	223		
						γ = 0.15 (CI 95%: 0.12–0.19)						73	224		
						s = 320.21(CI 95%: 303.56–336.87)						75	225		
												76	226		
												81	227		
												91	228		
												γ = 0.71 (CI 95%: 0.64–0.79)			
												s = 940.04 (CI 95%: 833.95–1046.14)			

Apartado		Medellfn		Bello		Remedios		Puerto Berrfo		Sopetran		Puerto Triunfo			
Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.		
1	1	1	1	1	1	1	1	1	1	1	1	1	1	Envigado	
1	2	2	2	1	2	4	2	2	3	7	2	9	2	Time	Cum. Frec
3	3	3	3	10	4	6	3	5	4	14	3	12	3	1	1
4	5	6	4	11	6	16	4	8	7	25	4	14	4	4	2
10	7	7	6	14	7	18	5	9	11	27	5	18	7	9	3
11	9	8	7	20	8	19	7	10	14	30	6	19	8	10	4
12	10	10	9	21	9	21	8	12	15	35	7	20	10	17	6
13	14	12	10	22	10	24	9	13	16	46	8	23	11	23	7
14	16	13	11	26	11	27	11	14	17	47	9	24	12	26	8
15	17	19	12	29	12	30	12	15	23	50	10	25	14	29	9
17	19	27	13	30	13	36	13	16	24	52	11	26	16	34	11
18	20	30	14	31	15	37	14	17	29	54	12	27	17	39	12
19	21	31	15	32	17	41	16	18	38	57	13	28	18	43	13
21	23	32	16	33	18	45	17	22	39	63	14	29	19	50	14
22	27	33	17	35	20	48	18	23	40	70	15	32	21	58	15
23	32	34	18	40	21	γ = 0.26 (CI 95% 0.12–0.41)		28	41	73	16	38	22	60	16
24	33	35	20	41	22			29	42	77	17	45	23	63	18

Table (*Continued*)

Apartado		Medellfn		Bello		Remedios		Puerto Berrfo		Sopetran		Puerto Triunfo			
Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.		
25	36	36	21	45	24	s = 88.33 (CI 95% 72.66–249.32)		30	43			47	24	69	19
26	41	37	22	46	25			31	45	γ = 0.16 (CI 95%: 0.09–0.22)		55	25	93	21
27	47	38	23	50	26			33	46			56	26	γ = 0.35 (CI 95%: 0.27–0.43)	
28	51	41	24	56	27			34	50	s = 229.12 (CI 95%: 33.09–1191.35)		59	30		
29	56	46	25	59	28			36	51			61	31	s = 730.80 (CI 95%: 57.81–3419.42)	
30	59	79	26	61	29			38	52			63	32		
31	67	81	27	68	30			39	53			64	33		
32	69	94	28	69	31			44	54			69	34		
33	79	100	29	81	32			53	55			69	35	Itagui	
34	88	103	30	γ = 0.27 (CI 95%: 0.19–0.35)				57	56			78	36	Time	Cum. Frec
35	98	109	32					61	57			82	37	1	2
36	107	112	35	s = 106.40 (CI 95%: 61.71–151.09)				62	58			86	38	2	3
37	109	113	38					γ = 0.94 (CI 95%: 0.64–1.24)				87	39	8	4
38	117	114	44									γ = 0.46 (CI 95%: 0.33–0.60)		11	5
39	120	115	48					s = 318.73 (CI 95%: 146.13–491.32)						12	6
40	121	116	53									s = 415.66 (CI 95%: 75.77–907.10)		13	8
41	131	117	56											19	11
42	145	118	60											20	12
43	156	119	62											21	13
44	162	120	65											22	14
45	167	121	68											23	15
46	171	122	73											25	16
47	176	123	76											27	17
49	182	124	78											29	18
50	186	125	82											35	19
51	192	126	85											41	20
52	199	127	92											46	21
53	205	128	97											48	23
54	207	129	100											49	24
55	212	130	106											51	25
56	213	131	110											55	27
57	214	132	113											56	28
58	221	133	118											58	29
59	226	134	121											60	31
60	230	135	128											66	32
61	234	136	133											75	34
62	239	137	137											78	35
63	242	138	142											81	37
64	245	139	145											γ = 0.64	
65	250	140	148											s = 1016594.04	
66	256	141	153												
67	260	142	167											Rionegro	
69	264	143	176											Time	Cum. Frec
70	269	144	187											1	1

Table (*Continued*)

Apartado		Medellfn		Bello		Remedios		Puerto Berrfo		Sopetran		Puerto Triunfo			
Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.		
71	273	145	193											5	2
72	277	146	198											8	3
73	281	147	204											12	4
74	284	148	207											13	5
76	287	149	212											17	6
77	289	150	217											18	7
79	290	151	221											27	8
80	292	152	229											28	9
81	293	153	232											36	10
83	294	154	233											39	11
86	296	155	236											40	12
87	300	156	239											44	13
88	301	157	242											54	14
89	303	158	243											56	15
91	305	159	247											75	16
92	306	160	251											98	17
93	307	161	258											γ = 0.37 (CI 95%: 0.30–0.45)	
94	308	162	263											s = 241.44 (CI 95%: 130.69–613.58)	
97	310	163	264												
99	311	164	269												
γ = 0.67 (CI 95%: 0.60–0.75)		165	270												
s = 1658.62 (CI 95%: 1430.19–1887.06)		166	271												
		167	273												
		168	275												
		170	278												
		171	279												
		172	282												
		173	285												
		174	286												
		176	287												
		177	289												
		179	290												
		180	292												
		181	295												
		182	298												
		183	299												
		186	301												
		187	303												
		188	306												
		190	309												
		191	310												
		192	313												
		193	315												
		195	316												
		196	320												

Table (*Continued*)

Apartado		Medellfn		Bello		Remedios		Puerto Berrfo		Sopetran		Puerto Triunfo	
Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.	Time	Cum. Frec.
		197	322										
		198	325										
		199	329										
		200	334										
		201	338										
		202	339										
		203	340										
		204	342										
		206	345										
		207	346										
		210	347										
		$\gamma = 0.002$											
		$s = 3887.26$											

Database of Public Health Surveillance System (SIVIGILA) of Antioquia, Colombia. Estimated parameters: γ per capita recovery rate; s, susceptible.

Corresponding Author Doracelly Hincapie-Palacio, National School of Public Health, 'Héctor Abad Gómez', Epidemiology Group, University of Antioquia, Medellín, Colombia. E-mail: doracely@gmail.com