Estimates of Intrinsic Growth Rates and Basic Reproduction Number (R₀) for the First Historical Zika Outbreak in Salta, Argentina

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Authors' contributions

This work was carried out in collaboration among all authors. Author JCR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. JCR, NAA and CH managed the analyses of the study. Author CH managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

Abstract

Scopes and Objectives: After entering South America in May 2015 through northeast Brazil, the Zika virus spread to Argentina between April and June 2016 and reached Salta province the following year. We analyzed some aspects of the first historical outbreak of Zika that occurred in Salta, Argentina, in the year 2017. We obtained elementary estimates, such as the intrinsic growth rate of the cases accumulated in the first weeks of the outbreak, using expressions that relate it to the basic reproduction number thereof.
Study design: Retrospective-descriptive studies and relational analysis.

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Methodology: Descriptive and relational analysis. Estimates of parameters and Simulation tests were also carried out in order to qualitatively describe the first Zika historical outbreak in Salta.

Results: Our study revealed that the Zika virus in the province of Salta mainly affects the localities of the departments of Orán, General San Martín, and Rivadavia, with infection forces $\alpha_{2017} \approx 0.42\ week^{-1}$ (SD 0.05) and $\alpha_{2017} \approx 0.32\ week^{-1}$ (SD 0.02) with the refined exponential model. On the other hand, we obtained estimates of the basic reproduction number $R_0 \approx 1.105\ 95\%\ CI[1.104 - 1.106]$ and $R_0 \approx 1.111\ 95\%\ CI[1.110 - 1.112]$.

Conclusion: Both the values of the estimates of the infection forces and R_0 would seem to indicate that the first outbreak of Zika in Salta was of relatively low intensity and of short duration, coinciding with patterns generally present emerging diseases. We found practically no differences with the estimates provided by the two expressions of basic reproduction number used. Although the estimates slightly exceed the threshold value $R_0 = 1$, with respect to other estimates, we consider them quite reasonable for the first historical outbreak occurred in Salta, since it was short-lived and of little intensity.

1   Introduction

The Zika virus (ZIKV) is an arbovirus (arthropod-borne virus) of the *Flaviviridae* family. Transmission is mainly vector, from infected mosquitoes, mainly of the genus *Aedes*. The first outbreak of ZIKV occurred on islands of the Federated States of Micronesia in 2007. Then the virus spread in the Pacific region and to the Caribbean and South and Central America [1],[2].

Before the pandemic caused by SARS-CoV-2, the latest emerging and devastating threat was ZIKV, an arbovirus that provoked more than 532,000 suspicious cases, including 175,063 confirmed cases in the Americas in 2016 and notable processes of social and medical alarms due to the evidence of a causal link between Zika virus and several congenital injuries, like microcephaly, as well as due to its association with neurological disorders such as Guillain-Barré syndrome in adults [3].

After entering South America in May 2015 through the Northeast of Brazil, the ZIKV enters Argentina between April and June 2016, and in 2017 in its continuous expansion, it has arrived in the province of Salta. In the case of Salta province, the situation of cases Zika is new, the first cases were reported in 2017, and provide research opportunities of vital importance in different epidemiological aspects. For example, the theoretical concept the basic reproduction number, R_0, of infectious diseases, could be related to the initial growth of an epidemic outbreak [4]. Growth rate estimates for exponential and logistic models play a fundamental role and its estimates for a historical outbreak can be used for retrospective, modeling, and simulation studies.

ZIKV has the potential to be transmitted in Argentina throughout the current geographic range of the mosquito vector. Although the transmission would be mainly seasonal [5]. Estimates of parameters related to the ZIKV will allow to make better decisions and optimize the design of plans for the provision and supply of treatments, prevention and control measures, by the Public Health authorities for the affected regions.

1.1 Scope and objectives

This study intends to present regional elemental estimates for the occurrence of Zika cases for the first time in the province of Salta, Argentina, as it continues to expand through South America. These estimates could be used in other retrospective studies, for simulation of scenarios with theoretical models and for analysis in decision-making in prevention and control measures.

We estimate the intrinsic growth rate assuming an exponential growth phase for the number of cumulative Zika cases that occurred in the first weeks of the outbreak. This estimation allows us to have an idea of the force of infection and subsequently using expressions that relate this rate to the basic number of reproduction Ro, we obtain estimates thereof.

2 Materials and Methods

2.1 Brief description of the methodology

Infectious disease outbreaks are often observed in the form of uni-or multivariate time series, e.g. as the number of newly reported cases aggregated over some time period [6], cumulative number of cases over weeks, months o years. In order to estimate the relationship between these variables we study of historical first outbreak of Zika in the province of Salta, Argentina, occurred in the year 2017. The framework we used is within the classical one to investigate spatio-temporal variability applied at the provincial level. Information of Zika cases by localities was georeferenced for Departments General San Martín, Orán and Rivadavia. The spatial modeling was performed by the design a heat map. We try to build an explanatory model of the temporary evolution of the variable, the cumulative cases number of Zika at the beginning of the outbreak, in order to quantify the possible effects of infection force and the basic reproduction number on the population, where effectively cases were registered.

We assume as a hypothesis that the cumulative Zika cases data at the beginning of the epidemic outbreak can be described by the exponential model [7]. Once this is verified, since there are expressions that relate the intrinsic growth rate with the force of infection and the basic reproductive number [4],[8],[9], we will obtain estimates of these parameters.

Some of the methodological aspects used are detailed in the subsections that follow.

2.2 Region under study and data of Zika.

Weekly recorded number of cases of Zika occurred in the Departments of General San Martín, Orán and Rivadavia, located in the northeastern of Province of Salta, Argentina, during the period of the epidemiological weeks 5-22, 2017, are those registered in the Argentinian National Health Surveillance System (SNVS), where each suspected, and eventually confirmed, case of Zika infection is notified and reported in the Integrated Surveillance Bulletin (BIV)[10].

2.3 Sources of information and georeferencing

Fig. 1. shows the geographical location of the region of study in Argentina, and, more specifi-cally, the north and northeastern of the province of Salta. The heat map was designed by the authors with shape files from National Geographic Institute,(IGN)[11]. The localities of the Departments of Orán, General San Martín and Rivadavia are indicated with points red color. The software QGIS, Software Development Team (QGIS 3.12) [12], was used for spatial analysis tools. Through QGIS we indicate the localities of the departments where the occurrence of Zika cases took place,

in addition to showing a delimitation of the region in relation to the entire Province of Salta, with a heat map.
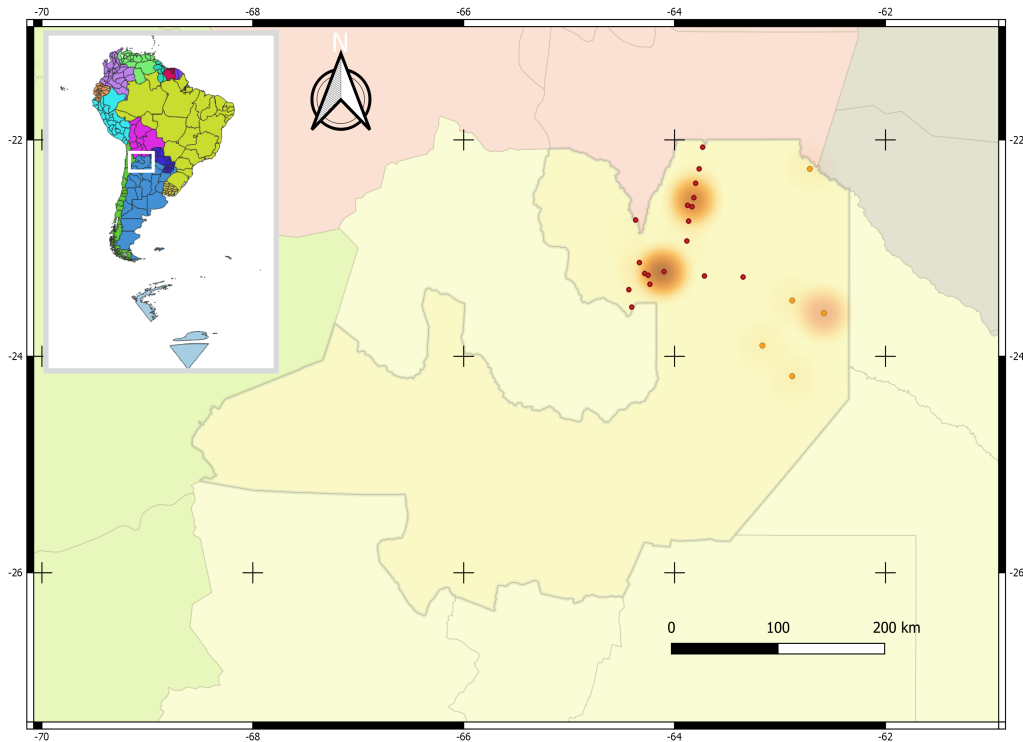

Fig. 1. Indication of the area of study, represented by the white rectangle, located in the Province of Salta, Argentina, and South America. Map of the study area composed of the localities of Orán, General San Martín and Rivadavia. The heat map was designed by the authors with shape files from Instituto Geográfico Nacional Argentino [11] using QGIS Software Development Team (3.12) [12].

2.4 Numerical parameter estimation, intrinsic growth rates

First we will describe the parameters and variables used in this work, see Table 1. Scale changes were made to express the units of time in week.

We estimate the exponential growth rates from the epidemic curve, according to the exponential model (1)[7], where the α and β parameters correspond to the intrinsic growth rate and the intersection to the origin respectively. In order to estimate the weekly exponential rates of the epidemic curve, we considered the number of cumulative cases infected by Zika (N_{Z_c}), we fitted a linear model of the logarithm of cumulative cases adjusted by time, given by the number of epidemiological week (EW) of the early outbreak period, i.e. we used the equation (2).

The basic reproductive number R_0 is a key parameter in mathematical models of transmission of diseases. For new emerging infectious diseases, the value of the basic reproductive number can only be inferred indirectly from the observed exponential epidemic growth rate.

Table 1. Description of parameters and variables used in theoretical development and models

Notation	Description
N_{Z_c}	Number of cumulative cases infected by Zika per week
$N_{Z_{c_t}}$	Number of cumulative cases infected by Zika in a time interval, t
$N_{Z_{c_0}}$	Starting number of cases infected by Zika
EW	Number of epidemiological week
n_{EW}	Number of epidemiological week renumbered from the start of the outbreak
T	Cohort generation time
R	Fundamental net per capita rate of increase
R_0	Basic reproduction number
α	Intrinsic growth rate (force of infection)
β	Intercept of linear regression
λ	Parameter of exponential distribution
λ_h	Infectious period in human
λ_v	Infectious period in vector
a	'Age' of an infection to be the time since infection

$$N_{Z_c}(EW) = \beta \, exp(\alpha \, EW) \tag{1}$$

$$\ln N_{Z_c}(EW) = \ln \beta + \alpha \, EW \tag{2}$$

We take the 5th epidemic week of 2017 as the starting week of the epidemic peak that covered the period from the EW 5 to the EW 22. We use the epidemic time series to calculate the cumulative cases and estimate the corresponding intrinsic rates of exponential growth by linear regression, equation (2).

2.5 Simple estimates of the basic reproduction number, R_0

2.5.1 Expressions used for the basic reproduction number

In this work, we have estimated the basic reproduction number, R_0, using two expressions. We consider the cumulative weekly number of human cases and we apply the R_0 formulation proposed by Begon *et al.* [8] and the formulation proposed by Anderson & May [4] respectively.

Following Begon *et al.*[8], we begin by deriving a general relationship that links population size, the rate of population increase, and time. R_0 is the multiplication factor that converts one population size (in this case the number of cumulative Zika cases) to another population size, one generation later, i.e. t time intervals later.

$$N_{Z_{c_t}} = N_{Z_{c_0}} R_0 \tag{3}$$

we refer to the initial infected size as $N_{Z_{c_0}}$. The deduction follows from an inductive argument,

$$N_{Z_{c_1}} = N_{Z_{c_0}} R \tag{4}$$

where R, is known as the fundamental net reproductive rate or the fundamental net per capita rate of increase. So for time intervals 1, 2, ..., t, $t + 1$, ... and so on. Thus

$$N_{Z_{c_1}} = N_{Z_{c_0}} R, \;\; N_{Z_{c_2}} = N_{Z_{c_1}} R, \;\;\; ..., N_{Z_{c_{t+1}}} = N_{Z_{c_t}} R \tag{5}$$

and

$$N_{Z_{c_t}} = N_{Z_{c_0}} R^t \tag{6}$$

if we considering the cohort generation time, i.e. $t = T$, we have from equations (3) and (6)

$$N_{Z_{c_0}} R_0 = N_{Z_{c_0}} R^T \tag{7}$$

$$\ln R_0 = T \ln R = T\alpha \tag{8}$$

$$R_0 = exp(\alpha\, T) \tag{9}$$

where $\alpha = \ln R$ is the intrinsic growth rate, it is the rate at which the population of infected increases in size. While T is the cohort generation time, a demographic analogue of the epidemiological mean generation interval. So we have an alternative approach to estimation of R_0 is based on observing the outbreak curve in the initial phase of the outbreaks, and using statistical estimation methods. Estimates of R_0, can be derived using a diversity of methods, including the exponential growth and the maximum likelihood methods [13]. Thus an exponential equation (9), was obtained.

We follow the derivation proposed by Wallinga & Lipsitch [9], for the expression of Anderson & May [4], for more details see the indicated reference. We consider as definition of the moment generating function $M(z)$ of the distribution $g(a)$, with $g(a)$ the generation interval distribution, provided that $M(z)$ exists.

$$M(z) = \int_0^\infty e^{za} g(a) da \tag{10}$$

here the variable a the 'age' of an infection to be the time since infection and the distribution $g(a)$

$$g(a) = \frac{n(a)}{\int_0^\infty n(a)da} = \frac{n(a)}{R_0} \tag{11}$$

where $n(a)$ is defined in this case, expected rate of creating secondary cases by an infected person at the 'age' a. Then of the Lotka - Euler equation we have

$$\int_0^\infty e^{-\alpha a} n(a)da = \int_0^\infty e^{-\alpha a} g(a) R_0\, da = 1 \tag{12}$$

from equations (10) and (12), we obtain

$$R_0 = \frac{1}{\int_0^\infty e^{-\alpha a} g(a) da} = \frac{1}{M(-\alpha)} \tag{13}$$

Assuming that the duration of a generation interval is thereby implicitly specified as an exponential distribution, $g(a) = \lambda exp(-\lambda a)$, mean, $\frac{1}{\lambda}$. Thus, the moment generating function for the exponential distribution is $M(z) = \frac{\lambda}{\lambda - z}$, from where, if $z = -\alpha$

$$R_0 = \frac{\lambda + \alpha}{\lambda} = 1 + \alpha\, T \tag{14}$$

where $T = \frac{1}{\lambda}$.

2.5.2 Parameter uncertainty. The main assumption

Zika is a disease transmitted by *Aedes aegypti* vectors. In the expressions presented, the basic reproduction number is estimated from the cohort generation time, T, which is not precisely known. We consider that the time of appearance of a new infected, will involve the necessary time of transmission, human-to-vector and vector-to-human.

We assume exponentially distributed infectious periods both mosquitoes and human, thus $T = \frac{1}{\lambda_h} + \frac{1}{\lambda_v}$, where λ_h is the infectious period in human and λ_v corresponds to the infectious period of vector. Taking into account that, the duration of viraemia, usually 3-5 days after onset of symptoms (possibly over 11 days in some cases). Duration of viraemia prior to disease onset unknown [14]. The extrinsic incubation period of the virus in mosquitoes is around 10 days (similar at 8 to 12 days required by Dengue virus). In *Aedes aegypti*, high levels of virus in mosquitoes 20 to 60 days after infection, although the average life span of the adult female *Aedes aegypti* is shorter in the tropical regions [15].

2.5.3 Simulations

Implementations of algorithms for the simulations, Monte Carlo type, were similar to those developed by Rosales *et al.* [16], in order to get estimates of the cohort generation times, T, and were used for to obtain the approximate values of R_0. We simulate 100 runs with 50 random generations of cohort generation time, T considering infectious period in humans and mosquitoes and we evaluated R_0 with the proposed expressions. Finally we calculate the corresponding averages for the approximation of basic reproduction number, R_0.

2.6 Statistical analysis

The statistical program used was Statgraphics Centurion (version 16.1.03) [17] and the statistical analysis was performed in this software. The selection criteria of the models were based on the coefficient of determination (R^2), adjusted coefficient of determination (adjusted R^2), standard deviation of the differences between the values observed and those predicted by the model (RMS), mean absolute error (MAE), Akaike Information Criterion (AIC). For all tests, the significance level was 0.05. Thus the appropriate model was determined, based on the response variable, cumulative cases of Zika (N_{Z_c}) and the explanatory variable time, in the categories epidemiological weeks (EW).
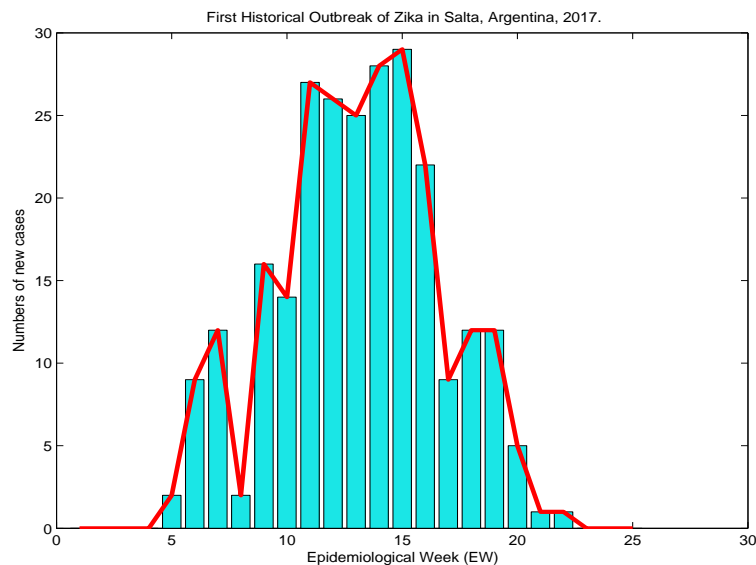
3 Results

Fig. 2. First historical outbreak of Zika in Salta, Argentina 2017. Developed between the epidemiological weeks EW 5 - EW 22, of year 2017, with a total of 252 cases distributed in localities in the northern and northeastern Departments of the Province of Salta, specifically in the Departments of Orán, General San Martín and Rivadavia. Source: BIV [10].

Fig. 2. shows the first historical outbreak of Zika that occurred in the province of Salta, Argentina, in 2017, after entering South America in May 2015 through Northeast Brazil. This historical

outbreak of Zika developed between the epidemiological weeks EW 5 - EW 22, with a total of 252 cases distributed in localities of the Departments of the northern and northeastern of the Province of Salta, specifically in the Departments of Orán, General San Martín and Rivadavia, (see Fig. 1). The province of Salta confirmed the circulation of Zika virus in 3 localities in the Department General San Martín for the first time in 2017. The localities Embarcación with 80 cases, General Mosconi with 22 cases and Tartagal with 50 cases, are the localities with the highest number of registered cases, (see heat map in Fig. 1).

Table 2. shows the statistical summary of each variable recorded in for Zika cases number (weekly cases), natural logarithm of cumulative Zika cases from EW 5 to EW 15. The statistical summary includes parameters of central tendency, variability, and form. Of particular interest are the form statistics (standardized skewness coefficient and kurtosis) which can be used to determine whether the sample comes from a normal distribution. Values of these statistics outside the range of -2 to +2 indicate significant deviations from normality, which would tend to invalidate many of the statistical procedures that are commonly applied to these data. In this case, all the variables are within the range, so that the measured variables can be said to follow a normal distribution. It was found that the variables of Zika cases numbers and natural logarithm of cumulative Zika cases fulfilled the condition of being within this range. The average of Zika cases number obtained per week was, 14 (cases week^{-1}), with a 10 (cases week^{-1}) standard deviation.

Table 2. Statistic description of measured variables, weekly Zika cases number, natural logarithm of cumulative Zika cases from EW 5 to EW 15, Salta, Argentina, 2017*

	Zika cases/EW	$\ln(N_{Z_c})$
Average	14.0	3.62
Standard deviation	9.98	1.34
Coefficient of variation	71.26%	36.93%
Minimum	1.0	0.69
Maximum	29.0	5.08
Range	28.0	4.39
Standardized skewness	0.35	-1.51
Standardized kurtosiss	-1,20	-0.92

*: Total number of Zika cases in the first historical outbreak in Salta, $N = 252$.

In Table 3, we show the estimates and the different models obtained by varying the number of epidemiological weeks. Also the best model was obtained when the number of 10 epidemiological weeks was considered, which gave R^2=88.34 indicates that the regression model explains 88.34% of the variability. The adjusted coefficient of determination $R_{adj}^2 = 86.88\%$, which allows models with different numbers of independent variables to be compared. The RMS =0.48 is the standard deviation of the differences between the values observed and those predicted by the model. This value can be used to construct limits for new observations. The mean absolute error MAE =0.33 is the average value of the deviations mentioned.

Table 3. Regression model to determine exponential model that describes the weekly cumulative Zika cases

$n_{EW}*$	Regression model (2)	R^2	R_{adj}^2	RMS	MAE	AIC
10	$\ln N_{Z_c}(n_{EW}) = 1.34 + 0.42 n_{EW}$	88.34	86.88	0.48	0.33	-1.05
9	$\ln N_{Z_c}(n_{EW}) = 1.21 + 0.45 n_{EW}$	88.20	86.52	0.48	0.32	-1.02
8	$\ln N_{Z_c}(n_{EW}) = 1.08 + 0.49 n_{EW}$	87.74	85.70	0.48	0.32	-0.95
7	$\ln N_{Z_c}(n_{EW}) = 0.94 + 0.53 n_{EW}$	86.56	83.87	0.50	0.34	-0.82
6	$\ln N_{Z_c}(n_{EW}) = 0.80 + 0.59 n_{EW}$	84.70	80.87	0.52	0.35	-0.37
5	$\ln N_{Z_c}(n_{EW}) = 0.57 + 0.69 n_{EW}$	84.35	79.14	0.54	0.38	-0.43

*n_{EW}: Numbers of epidemiological weeks considered in the regression model.

By performing ANOVA test, we found that P-value (p=0.001) associated to the model was less than 0.05. Therefore, the relationship between variables $\ln(N_{Z_c})$ and n_{EW}, was statistically significant, with a confidence level of 95.00%.

Based on both goodness-of-fit statistics for a linear model and Akaike Information Criterion (AIC) values, the optimal value for the number of weeks is 10 weeks. The cumulative Zika cases number in this period is consistent with exponential growth, thus we have obtained the following exponential model.

$$N_{Z_c}(n_{EW}) = 3.82 \, e^{0.42 \, n_{EW}} \tag{15}$$

The atypical residues table lists all observations that have 'Studentized' residuals greater than 2, in absolute value. 'Studentized' residuals measure how many standard deviations each observed value of $\ln N_{Z_{ac}}$ deviates from the fitted model, using all data except that observation. In this case, there is a 'Studentized' residual greater than 3, corresponding to the data $\ln N_{Z_{c_1}}$ =0.693 ($n_{EW} = 1$) with residue -8.66. Without considering this observation we obtained the refined model

$$N_{Z_c}(n_{EW}) = 1.98 \, e^{0.32 \, n_{EW}} \tag{16}$$

The improved model is evidenced in the values obtained of: Pearson coefficient $r = 0.98$, $R^2 = 97.56\%$, $R^2_{aj} = 97.21\%$, $RMS = 0.15$, $MAE = 0.11$ and $AIC = -3.33$. The improvement obtained in the qualitative description can be seen in Fig. 3.
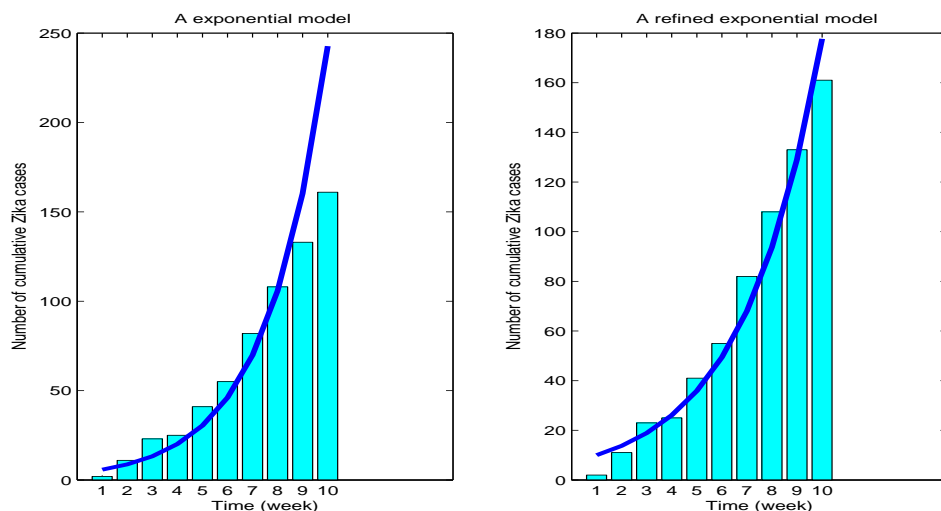

Fig. 3. Exponential models for number of cumulative Zika cases in the first historical outbreak of Zika in Salta, Argentina, 2017 developed between the epidemiological weeks EW 5 - EW 22, of year 2017. Left: Force of infection estimated $\alpha_{2017} \approx 0.42 \, week^{-1}$ and Right: Force of infection estimated with the refined model $\alpha_{2017} \approx 0.32 \, week^{-1}$

Estimated rates provide information on the force of infection of the disease in the first historical outbreak of Zika in Salta, in its first weeks of occurrence. Thus, the estimate of the force of infection was, $\alpha_{2017} \approx 0.42 \, week^{-1}$ (SD 0.05) and for refined model $\alpha_{2017} \approx 0.32 \, week^{-1}$, (SD 0.02). The intrinsic growth rate $\alpha_{2017} \approx 0.32 \, week^{-1}$, found with the refined model was approximately 24% lower than that of the first model obtained. In addition, as seen in Fig. 3, it better describes the cumulative cases of Zika registered in the first historical outbreak that occurred in Salta.

By simulation we generate rough estimates of basic reproduction number, R_0, for the first historical outbreak of Zika in Salta. One 100 runs were made for 50 cohort generation time T stochastically obtained. The results are presented in Table 4. Fig. 4. shows an example of several runs of 50 generation times, T, the respective evaluations of R_0 and the averages values of R_0 obtained for each run applying the model (9).
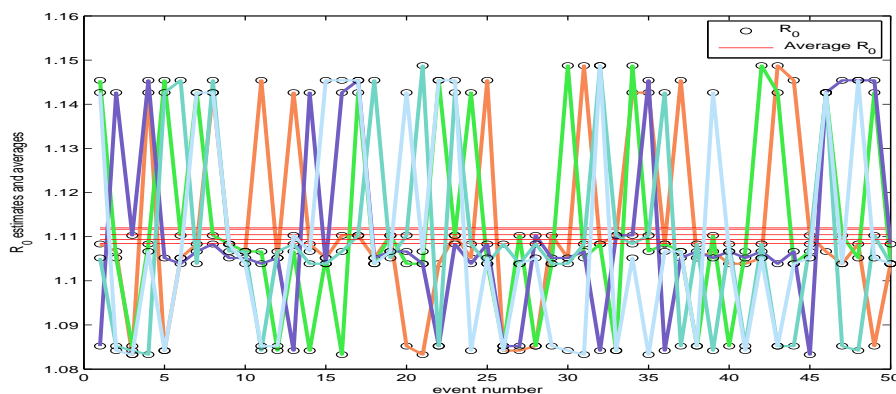

Fig. 4. An example showing several runs and the calculated R_0 values and the corresponding averages of R_0 (horizontal lines) from the cohort generation times, T stochastically obtained

Table 4. Estimates of basic reproduction number, R_0, for the first historical outbreak of Zika occurred in Salta, Argentina, 2017*

Model	Force of infection	$Average\,R_0$	95% CI
$R_0 = 1 + \alpha\,T$	$\alpha \approx 0.32$	1.105	[1.104 - 1.106]
$R_0 = exp(\alpha\,T)$	$\alpha \approx 0.32$	1.111	[1.110 - 1.112]
$R_0 = 1 + \alpha\,T$	$\alpha \approx 0.42$	1.137	[1.136 - 1.138]
$R_0 = exp(\alpha\,T)$	$\alpha \approx 0.42$	1.147	[1.146 - 1.148]

*: Based on simulations of 100 runs for 50 generation times T stochastically obtained.

4 Discussion

In Salta, the outbreak spread between epidemiological weeks 5-22 and then a period of silence followed during the rest of 2017. The affected region was restricted to localities located in the north and northeast departments of the Province of Salta, specifically in the departments of Orán, General San Martín and Rivadavia, (see Fig. 1). Regions characterized by the high level of poverty and the limited capacity of Public Health System, in the province and the country.

The appearance of Zika in Salta for the first time has been presented with the characteristics and general pattern with which emerging diseases begin. In this sense, it coincides with the general description made by Bettancourt *et al.* [18], regarding emerging diseases. For an emerging infectious disease such as Zika in humans, case numbers are small, very stochastic, and alternate short outbreaks with long quiet periods.

Although it is true that different factors such as climate, mosquito density and human living conditions vary widely between regions in South America, and that this would make the estimated values incomparable, we will briefly discuss some aspects related to other estimates.

The first wave of the Zika epidemic in Rio de Janeiro showed exponential growth during 7 weeks, and plateau at around 1500 cases per week during the whole summer of 2015-2016. Based on similar methods applied directly to the number of Zika cases, Villela and collaborators estimated the force of infection as 0.82 $week^{-1}$ based on the first 7 weeks of the epidemic with 25 213 cases registered in Río de Janeiro [19], a doubly higher rate, which shows the difference in the magnitude of the Zika epidemic wave that affected the different regions.

According to the study carried out by Orellano and colleagues [5] the province of Salta have high risk for his geographic location and potential risk of virus transmission evaluated by range of regional temperatures. This study determined the maximum R_0 would be 6.9 using expressions that take into account both the vectorial capacity and duration of infected period, our estimates of R_0, based on cumulative Zika cases reported, do not exceed this maximum value (seen Table 4).

Coinciding with the observation of Muñoz *et al.* [20] in his work of forecasting and modeling, this estimates illustrates why these tools can only be used as a guide for the local and international experts, as these diseases involve complex interactions beyond the presence or not of enhanced environmental conditions suitable for the occurrence and transmission of Aedes-borne epidemics. In this sense, we have knowledge of the region and consider that better estimates for the same could be achieved considering the incorporation of tools related to climatic conditions, however, the values obtained here could explain the low intensity of the first wave of the registered outbreak.

The estimates of R_0 found in this work, $R_0 \approx 1.111$ and $R_0 \approx 1.105$, calculated according to the expressions proposed by Begon *et al.* [8] and Anderson & May [4], seen Table 4, were lower than other estimates for the region. However, they would seem reasonable, observing the low intensity and duration of the first historical outbreak that occurred in Salta in 2017. As Bettencourt *et al.* [18] points out that for an emerging disease this occurs with small numbers of cases and short outbreaks, therefore, the small excess of the threshold value of R_0 would be acceptable.

We found practically no difference between the estimates provided by the two analyzed models Begon *et al.* [8] and Anderson & May [4].

Since this low-intensity outbreak occurred in 2017, it is important not to neglect sustained the awareness of prevention and control measures in the population. As Melo *et al.* study points out [21], the less privileged economic status influences the use of protection measures against the Zika virus, it is important that the Salta Public Health authorities improve prevention and control actions, providing the inhabitants not only with repellents but also insecticides mosquito nets for beds and windows, since most of the population of this region has unsatisfied basic needs.

5 Conclusions

Our study revealed that the ZIKV in the province of Salta mainly affect the localities of departments of Orán, General San Martín, and Rivadavia, with forces of infection estimated from the reported cumulative cases of $\alpha_{2017} \approx 0.42$ $week^{-1}$ (SD 0.05) and $\alpha_{2017} \approx 0.32$ $week^{-1}$ (SD 0.02) with the refined exponential model. These estimates were obtained considering so-called "growth intrinsic coefficient rate" to the cumulative Zika cases occurred in the first historical outbreak in Salta, Argentina in 2017. The intrinsic growth rate $\alpha_{2017} \approx 0.32$ $week^{-1}$, found with the refined model was approximately 24% lower than that of the first model obtained. In addition, it better describes the cumulative cases of Zika registered in the first historical outbreak that occurred in Salta.

On the other hand, with this intrinsic growth rate $\alpha_{2017} \approx 0.32$ $week^{-1}$ we estimate R_0 and obtained $R_0 \approx 1.105 \, 95\% \, CI[1.104 - 1.106]$ and $R_0 \approx 1.111 \, 95\% \, CI[1.110 - 1.112]$ for the models linear (14) and exponential (9) respectively.

We found practically no differences with the estimates provided by the two expressions of R_0 used. Although the estimates slightly exceed the threshold value $R_0 = 1$ with respect to other estimates, we consider them quite reasonable for the first historical outbreak that occurred in Salta, since it was, short-lived and of little intensity.

Although it is true that since 2017 Zika has entered Salta for the first time with a short-lived outbreak, the Salta Public Health authorities must insist on improving preventive actions, not only by providing repellents but also by providing mosquito nets for beds and windows. All this would benefit the control not only of Zika cases, but also Dengue, Chikingunya and Leishmaniasis, neglected diseases that affect these regions with populations with unsatisfied basic needs.

Future studies that consider expressions of R_0, which discriminate best the vector-to-human and human-to-vector transmission times, could provide better regional estimates for the expansion of Zika in these regions of the province of Salta, Argentina.

Acknowledgment

Competing Interests

The authors declare that the research was conducted in the absence of any financial relationships that could be construed as a potential conflict of interest.

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