PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA
DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

http://dx.doi.org/10.17058/reci.v7i2.7685

Revista de Epidemiologia
e Controle de Infecção

Hospital Santa Cruz

ARTIGO ORIGINAL

Cálculo da taxa de reprodutividade (R0) através da simplificação do modelo SIR aplicado à epidemia de influenza A (H1N1) ocorrida em 2009 no Brasil

Calculation of reproductive ratio (R0) by simplifying the SIR model applied to the 2009 influenza A epidemic in Brazil

Cálculo de tasa de reproductividad (R0) simplificando modelo SIR aplicado a epidemia de gripe A (H1N1) de 2009 en Brasil

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Recebido em: 06/06/2016 / Aceito em: 17/01/2017 / Disponível online: 08/04/2017

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RESUMO

Justificativa e Objetivos: A pandemia de influenza A (H1N1) de 2009 atingiu mais de 200 países com graus variados de morbimortalidade, fomentando diversas pesquisas na área, com objetivo de auxiliar futuras estratégias epidemiológicas. O uso de modelos matemáticos de infecções pode propiciar melhor compreensão deste fenômeno e fornecer subsídios para intervenções em saúde pública. O presente estudo teve como objetivos descrever a taxa de reprodutividade R0 através da simplificação de modelo matemático epidemiológico, estimar o valor de R0 na pandemia de influenza de 2009 no Brasil e nos estados brasileiros e comparar R0 com a população infectada. **Métodos:** Trata-se de um estudo ecológico, utilizando um banco de dados público com notificações de influenza pandêmica ocorrida no Brasil em 2009. Foi proposta uma análise simplificada do modelo compartimental (suscetível (S), infectado (I), recuperado (R)) para comparação da taxa de reprodutividade viral nos estados brasileiros. Também foi correlacionado o valor de R0 com o percentual de infectados. **Resultados:** Em 12 estados e no Brasil como um todo foi configurado um surto epidêmico, e em cinco estados além do Distrito Federal ocorreu mais de um surto epidêmico. A correlação entre R0 e o percentual de infectados apresentou-se forte e positiva (r = 0,74), demonstrando que uma maior taxa reprodutiva está associada a maior contágio viral. **Conclusões:** A simplificação matemática realizada neste estudo demonstra outra maneira de identificar epidemias, sendo uma ferramenta básica e de pouca complexidade nas implementações computacionais.

Descritores: *Epidemiologia. Epidemia. Simulação por computador. Influenza humana. Doenças transmissíveis.*

ABSTRACT

Background and Objectives: The influenza A (H1N1) pandemic in 2009 affected over 200 countries with different levels of morbimortality, which stimulated research in the field to help design new epidemiological strategies. The use of mathematical models to describe infections can provide a better understanding of this phenomenon and a basis for public health interventions. The present study aimed to determine the reproductive ratio (R0) by simplifying an epidemiological mathematical model, estimate R0 in the 2009 influenza pandemic in Brazil for the country and states and compare this value with the infected population. **Methods:** The present investigation was ecological and used a public data bank with notifications of the pandemic influenza that occurred in Brazil in 2009. A simplified analysis of the compartmental SIR model (susceptible (S), infected (I) and recovered (R)) for comparison with the viral reproductive ratio in Brazilian states was suggested. The R0 value was correlated to the percentage of infected people. **Results:** An epidemic outbreak was characterized in 12 states and in the country as a whole; more than one epidemic outbreak occurred in five states and the Federal District. The correlation of R0

R Epidemiol Control Infec, Santa Cruz do Sul, 7(2):72-78, 2017. [ISSN 2238-3360]

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to the percentage of the infected population was strong and positive (r = 0.74), showing that a higher reproductive ratio is associated with a higher viral contagion. **Conclusions:** The mathematical simplification developed in the present study reveals a different tool to identify epidemics and has the advantage of being easily implemented in computational simulations.

Descriptors: *Epidemiology. Epidemics. Computer simulation. Human influenza. Transmissible diseases.*

RESUMEN

Antecedentes y objetivos: La pandemia de gripe A (H1N1) de 2009 alcanzó a más de 200 países, con grados variados de morbimortalidad, impulsando diversas investigaciones apuntando a respaldar futuras estrategias epidemiológicas. La utilización de modelos matemáticos de infecciones puede brindar mejor comprensión del fenómeno y ofrecer claves para intervenciones en salud pública. Este estudio tuvo como objetivos describir la tasa de reproductividad (R0) por simplificación de modelo matemático epidemiológico, estimar el valor de R0 en la pandemia de gripe de 2009 en Brasil y en los estados brasileños, y comparar R0 con la población infectada. **Método:** Estudio ecológico, utilizando banco de datos público con notificaciones de gripe pandémica ocurrida en Brasil en 2009. Fue propuesto un análisis simplificado del modelo compartimental: Susceptible (S), Infectado (I), Recuperado (R), para comparación de la tasa de reproductividad (R0) viral en los estados brasileños. También se correlacionó el valor de R0 con el porcentaje de infectados. **Resultados:** En doce estados y en todo Brasil se configuró un brote epidémico, y en cinco estados además del Distrito Federal hubo más de un brote epidémico. La correlación entre R0 y el porcentaje de infectados se mostró fuerte y positiva (r=0,74), demostrando que una mayor tasa reproductiva está asociada a mayor contagio viral. **Conclusión:** La simplificación matemática realizada en este estudio demuestra otra manera de identificar epidemias, siendo una herramienta básica y de baja complejidad en las necesidades de sistematización.

Descriptores: *Epidemiología; Epidemias; Simulación por Computador; Gripe Humana; Enfermedades Transmisibles.*

INTRODUCTION

Influenza A is an acute viral infection in the respiratory system, with global distribution and high transmission rate. Three pandemic caused by subtypes of this virus occurred in the twentieth century, and its variants are still found in birds and swine and in the human beings.[1] The variability of the influenza virus is attributed to the proteins hemagglutinin (H) and neuraminidase (N) present in its surface. Sixteen variations of H protein and nine of N protein are described, however, only three hemagglutinin subtypes (H1, H2 e H3) and four neuraminidase subtypes (N1, N2, N3 e N7) may cause infections in human beings.[2]

The occurrences of these pandemics demonstrate the infectious capacity of the virus. It is estimated that in 1918 the variant A (H1N1) have attacked from 50 to 100 million people worldwide with mortality rates from 2 to 3%.[3] In 1957 and 1968, the subtypes A (H2N2) and A (H3N2) respectively, cause a new epidemic wave, nevertheless, less aggressive than the pandemic in 1918.[4]

Early cases of pandemic influenza virus occurred in Mexico in 2009, posteriorly spreading out to several countries. According to the World Health Organization (WHO), 214 countries notified cases of influenza A (H1N1) in that year.[4] Mortality by respiratory causes was estimated in over 200 thousand, and over 80 thousand by cardiovascular reasons due to the infection by this virus.[5]

After this impact in the global public health, the major concern is related to the effectiveness of prophylactic measures and of early antiviral treatment, beyond the capacity of hospitalization of critical patients. Then, some strategies are essential to the control of these pandemics.[4]

The planning for future epidemics that provides public mechanisms to combat this kind of infection is recommended by the WHO.[6] To corroborate this fact, it is considered that the combination of different strategies may provide higher versatility in the pandemic control.[7,8]

Therefore, the evaluation by mathematic models of dynamics of epidemics is highlighted, which are used to provide simulations about the evolution of diseases and help in the strategies for public health.

In general way, mathematical modeling as a scientific method may stimulate new ideas and experimental techniques, providing information in different features than those initially prevised; being used in interpolations, extrapolations and previsions, suggesting priorities in the use of resources and researches and in decision-making; filling gaps where there is lack of experimental data, being a resource for better understanding of reality; and being asan universal language to the comprehension among researchers in several areas.[6]

The first mathematical model used to describe influenza epidemic was the compartment model of the type SIR (susceptible-infected-recovered) proposed by Kermack and McKendrick in 1927.[9] In this model, the population is divided in three individual classes: the susceptible ones (S), are those who may be infected; the infected ones (I), are those who are sick and may disseminate the disease; and the recovered ones (R), are those who was infected and become immune or go to death. The flow is unidirectional in this model, from class to class: S → I → R and is based on the following additional hypotheses: the variation of susceptible population is proportional to the number of meetings between susceptible and infected populations; the variation of removal population is proportional to the infected population; and the variation of infected population is proportional to the variation of susceptible population, minus the variation of recovered population. It may be described as follows:

Rate of change of susceptible = (- Infection rate)
Rate of change of infected =
= (infection rate-removal rate)
Rate of change of recovered = (removal rate)

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Therefore, in ordinary differential equations, the temporal variation of each class $\left(\frac{dS}{dt}, \frac{dI}{dt}\, e\, \frac{dR}{dt}\right)$ may be presented, where andare constants associated to the rate of infection and to the rate of removal, respectively:

$$\frac{dS}{dt} = -BSI \qquad (1)$$

$$\frac{dI}{dt} = BSI - \mu I \qquad (2)$$

$$\frac{dR}{dt} = \mu I \qquad (3)$$

Where:

$$\frac{dS}{dt} = Temporal\ variation\ of\ susceptible$$

$$\frac{dI}{dt} = Temporal\ variation\ of\ infected$$

$$\frac{dR}{dt} = Temporal\ variation\ of\ recovered$$

Based on this model and through algebraic manipulation, it is possible to achieve the reproducibility rate (R_0), determined as the average of infections caused by one individual. The obtainment of this parameter is extremely important under the view point of public health, because it describes the occurrence of epidemic when $R_0 > 1$.[10]

Within this panorama, the aims of this work were describe the reproducibility rate (R_0) through simplification of SIR model, estimating the value of R_0 in influenza A pandemic occurred in 2009 in Brazil and in the Brazilian states, and also to compare R_0 with infected population.

METHODS

An ecological study was performed using data from the influenza A during the epidemic occurred in 2009 in Brazil. Data were collected from the Brazilian Information System for Notifiable Diseases (SINAN).[11] The data analyzed the notifications from April to December 2009 in Brazil, in the Distrito Federal and in the 26 Brazilian states.

The Brazilian population, the states' and the Distrito Federal's population in 2009, were used in the comparison with the number of infected and were collected from the DATASUS.[12]

For simplification of SIR model, using heuristic hypothesis, the following assumptions were considered:

- The equations (1) and (3) were disregarded;

- Analysis only of variation of infected (2), but rather than infected, it was considered the incidence of infection's rate by month (I_R), dismembered in two differential equations (4) (5):

$$\frac{dI_R}{dt} = BSI_R \qquad (4)$$

$$\frac{dI_R}{dt} = -\mu I_R \qquad (5)$$

Where the solution of equation (4) is $I_R = I_{Ro} e^{BSt}$, and correspond to the interval from the beginning of epidemic until the maximum number of cases.

And the solution of the equation (5) is $I_R = I_{Ro} e^{-\mu t}$, related to the interval from maximum number of cases until the end of epidemic.

Through this simplification, the constants *BS* and *μ* may be analytically obtained by exponential adjustment. According to the SIR model, the reproducibility rate (R_0) is expressed as follows:

$$R_0 = \frac{BS}{\mu} \qquad (6)$$

It was considered epidemic when $R_0 \geq 1$ and absence of epidemic when $R_0 < 1$.

In this model, it will be used as R_0 ', by the difference in its attainment. And it is important to note that the meaning of the constants and differs from the original SIR model.

The value of R_0' was also correlated with the prevalence of infected at the year of 2009. States with more than one epidemic outbreak in 2009 were discarded. A map of Brazil was adapted, identifying the states that had $R_0' \geq 1$, $R_0' < 1$ and more than one outbreak. For all calculations and mathematical modeling was used the software Microsoft Excel®.

RESULTS

Initially, the method of analysis to obtain R_0' was demonstrated for Brazil as a whole (Figure 1). The values of correlation for equations of increase and exponential decrease were higher than 0.9.

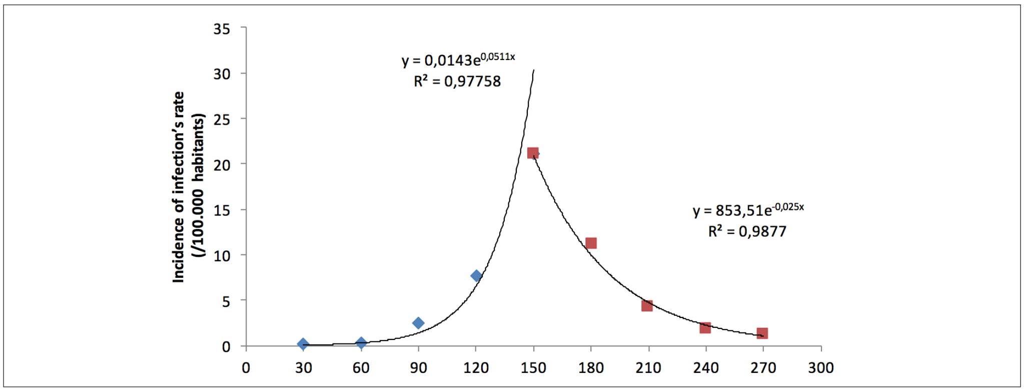

Figure 1. Analysis of reproductibility rate (R0') in Brazil.

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To the beginning of epidemic, the constant was 0.0511. To the decrease of epidemic, the constant was 0.025. In equation, it is obtained:

$$R_0' = \frac{BS}{\mu} = \frac{0.0511}{0.025} = 2.04$$

Other results obtained are described in the table 1 and in the frame 1. All the correlations were higher than 0.9. The first one describes the constants of Brazil and of Brazilian states, with only one outbreak in 2009. The second one highlights these data for each state with more than one outbreak in the same year.

Table 1. Constants BS, μ and R_0 in states which presented one epidemic outbreak.

STATES	BS	μ	R_o'	Prevalence year of 2009 (/100.000 habitants)
Rondônia	0,0302	0,027	1,12	5,0
Acre	0,0279	0,026	1,07	34,6
Roraima	0,041	0,045	0,91	16,6
Pará	0,0448	0,033	1,36	18,5
Amapá	0,0256	0,031	0,83	5,1
Maranhão	0,0409	0,081	0,50	1,7
Piauí	0,0286	0,031	0,92	7,9
Paraíba	0,0387	0,05	0,77	4,0
Pernambuco	0,0443	0,026	1,70	7,1
Sergipe	0,0284	0,021	1,35	3,2
Bahia	0,0377	0,037	1,02	4,4
Minas Gerais	0,044	0,036	1,22	30,6
Espírito Santo	0,0444	0,057	0,78	13,7
Rio de Janeiro	0,0464	0,05	0,93	40,0
São Paulo	0,0477	0,027	1,77	53,7
Paraná	0,0628	0,025	2,51	393,0
Santa Catarina	0,0614	0,043	1,43	82,1
Rio Grande do Sul	0,0499	0,033	1,51	49,2
Mato Grosso do Sul	0,0384	0,043	0,89	14,3
Mato Grosso	0,0319	0,035	0,91	10,3
Goiás	0,0398	0,025	1,59	21,7
BRASIL	0,0511	0,025	2,04	50,2

(*) Não houve crescimento.

Brazil as a whole presented one epidemic outbreak (R_0'= 2.04). Among states from the North region, Rondônia, Acre and Pará presented also one epidemic outbreak. Amazonas presented two outbreaks, and Tocantins, three. Amapá and Roraima did not present epidemic. In the Northeast region, Pernambuco, Sergipe and Bahia presented one outbreak. Ceará, Rio Grande do Norte and Alagoas presented two outbreaks. Maranhão, Piauí and Paraíba did not present epidemic. In the Midwest, Goiás presented one outbreak and Distrito Federal, two. Mato Grosso and Mato Grosso do Sul did not present epidemic. In the Southeast, Minas Gerais and São Paulo presented one outbreak and Rio de Janeiro and Espírito Santo did not present epidemic outbreaks. In the Southern, Rio Grande do Sul, Santa Catarina and Paraná presented one outbreak (Figure 2).

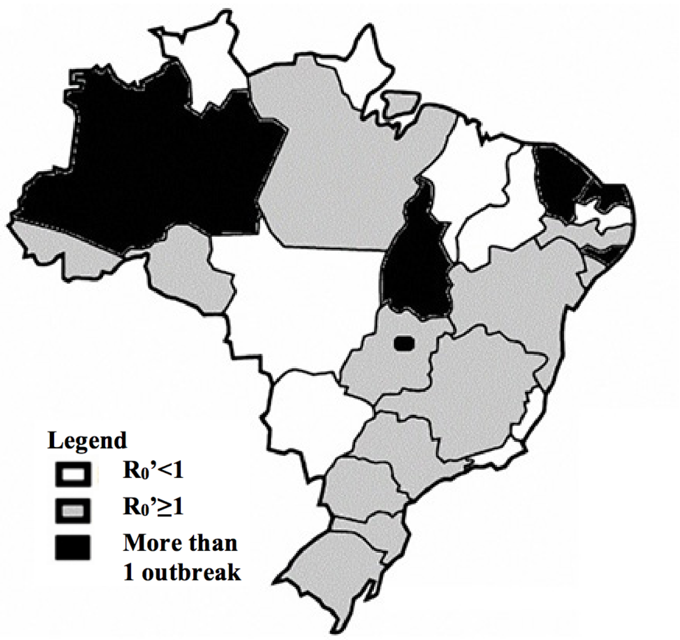

Figure 2. States and Distrito Federal, according to the values of R_0'.

Frame 1. Constants BS, μ and R0 in Distrito Federal and in states which presented more than one epidemic outbreak.

	1st Outbreak		2nd Outbreak		3rd Outbreak		Prevalence year of 2009 (/100.000 habitants)
STATES	BS	μ	BS	μ	BS	μ	
Amazonas	0,0761	0,013	0,0215	0,051			9,5
	Ro' = 5,85		Ro' = 0,42				
Tocantins	0,0347	0,0536	0,0536	0,037	0,0223	0,021	2,4
	Ro' = 0,62		Ro' = 1,45		Ro' = 1,06		
Ceará	0,0368	0,048	0,0183				2,7
	Ro' =0,77						
Rio Grande do Norte	0,0313	0,013	0,0356				7,0
	Ro' = 2,41						
Alagoas	0,0693	0,014	0,0174	0,032			44,4
	Ro' = 4,95		Ro' =0,54				
Distrito Federal	0,0599	0,02	0,0707	0,029			40,9
	Ro' = 3,00		Ro' =2,44				

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From mathematical viewpoint, the value of R_0’ in this model is related to the rise and exponential decrease, as may be seen in the Figure 3 in three different configurations.

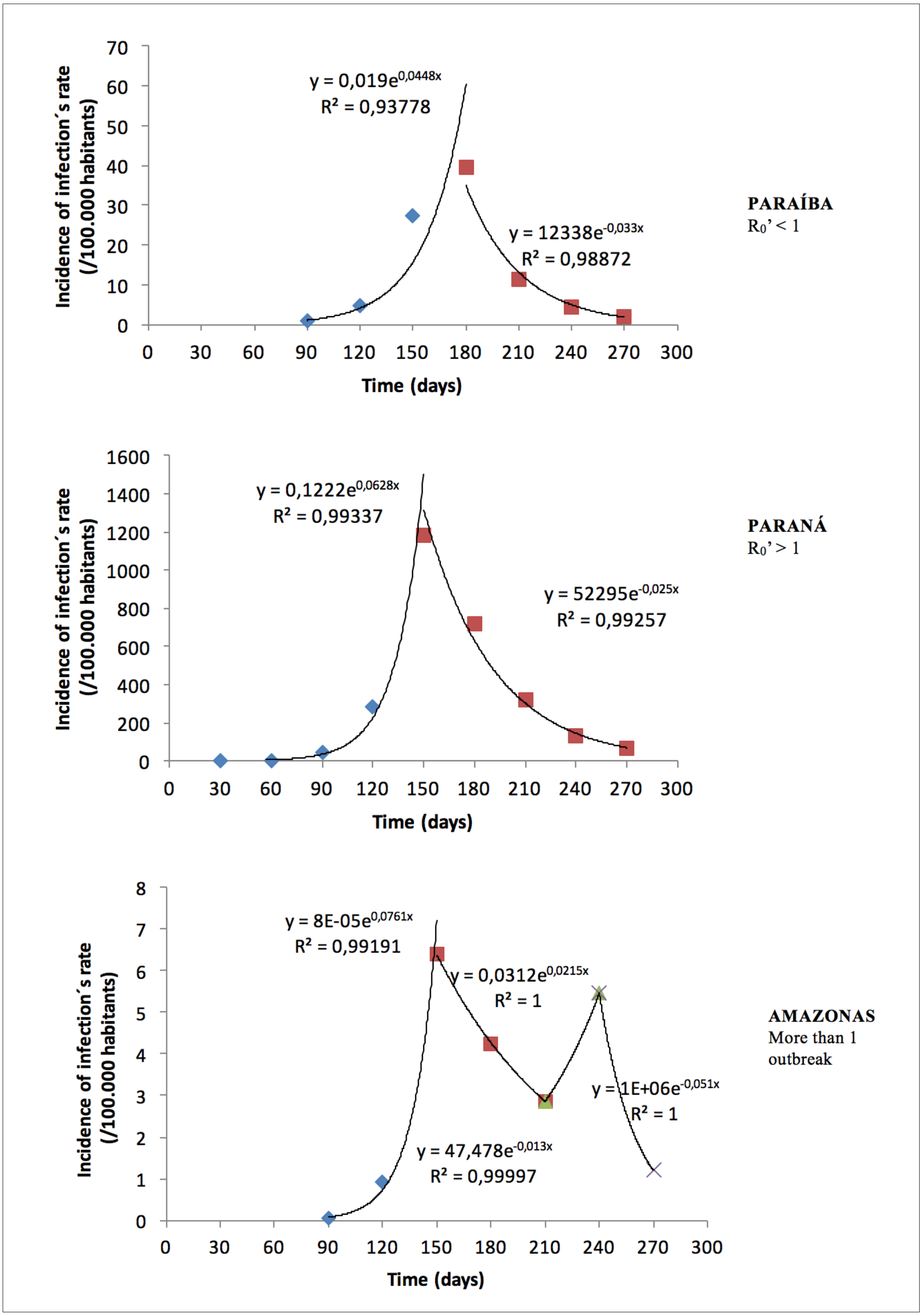

Figure 3. Demonstration of R_0’ < 1. R_0’> 1 and more than one epidemic outbreak.

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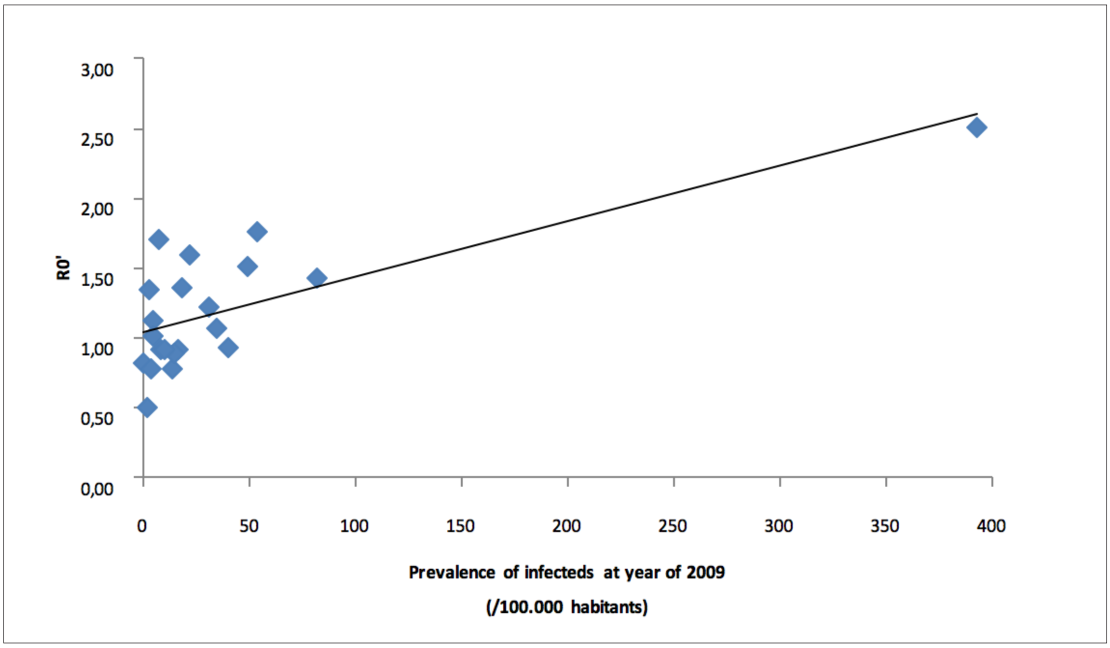

Figure 4. Correlation of prevalence of infected at the year of 2009 with the reproducibility rate (R_0').

When compared the reproducibility rate (R_0') with the prevalence of infected at the year of 2009, it was observed strong and positive correlation (r = 0.74) (Figure 4).

DISCUSSION

The simplification of SIR model, despite its reductionist aspect, seems portray a reasonable analysis of influenza epidemic in Brazil in 2009. Another study performed, using calculus through exponential growth, have pointed to the variable reproducibility rate for Brazil, from 1.31 to 1.78, somewhat smaller than this work, but both confirm the epidemic. In this same work are also mentioned states with higher infected population, Paraná and São Paulo, which are according to the higher values of R_0 obtained in this study.[13]

With similar methodology, was analyzed the influenza epidemic occurred in Mexico in 2009, and demonstrated values of R_0 from 1.2 to 1.6 in the first outbreak, and R_0 from 2.2 to 3.1 in the second outbreak, observing that in most states occurred epidemic.[14]

In this study, it was observed that states which presented more than one outbreak, in general, the value of R_0 was very high in the first outbreak, and possibly representing a trend for new waves of epidemic.

R_0 is widely presented in the literature; however, its value is subject to variations due to the different ways of analysis, what generates uncertainty in projections of new epidemics. In a systematic review, 18 articles were included and have simulated the initial reproducibility rate ($R_{0\text{-initial}}$), in other words, they have performed a projection of their values; in 36 were calculated the effective reproductive rate ($R_{0\text{-effective}}$), namely with real data. It was found a variation of simulated value $R_{0\text{-initial}}$ from 0.3 to 3.4, and of $R_{0\text{-effective}}$ with values from 0.5 and 3.1.[4] In general way, researches have demonstrated value of $R_{0\text{-effective}}$ from 1 and 2, only six works pointed to this parameter higher than 2. The value of $R_{0\text{-effeticve}}$ is presented generally less than$R_{0\text{-initial}}$.

However, it is important point to some distinctions in the models for calculus of reproducibility rate. There are those which perform predictions or projections, and infer situations that might occur, using fictional data. On the other hand, there are models with real data, complexes to perform, because they need differential mathematic implementations, and the analysis by exponential growth is more common.[15]

Besides, mathematic models with real data may describe the initial reproducibility rate (R_0), or even demonstrate the time-dependent reproducibility rate, in other words, in any point of the curve. These features are described several ways to calculate this parameter using the attack rate, the exponential growth, and estimate the maximum likelihood reason through the Bayesian sequential method and estimate the time-dependent reproductive number.[16-21]

Despite the different methods of analysis, the reproducibility rate is used as a parameter for evaluation of strategies during epidemics, like quarantine, vaccination, antiviral drugs, prevention policies in schools and closed areas, restriction to travels, at long last, measures which may reduce viral transmission. In this way, it is possible to compare the reproducibility rate and the effectiveness of these mechanism of control.[7]

From mathematical and epidemiological view point, the meaning of epidemic ($R_0' \geq 1$) in the model analyzed in this study is related to the rapid rise and to the slow exponential decay. Unlike, the absence of epidemic is connected to the slow rise and rapid exponential decay. This aspect makes sense, since it translates the

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Páginas 06 de 07
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viral reproductive capacity or incapacity, associated to the epidemic dissemination.[4]

This hypothesis is corroborated by the association between R_0' and prevalence of infecteds, what demonstrate that a higher reproducibility rate may transmit more viruses and infect more individuals.

It is possible to conclude that the mathematical simplification performed in this study points to another way to identify epidemic, because it is a basic analytical tool, and there is no complexity in computational implementations. Through the use of this tool, epidemic was identified in Brazil as a whole, and in 17 states and Distrito Federal. It was also observed correlation between R_0' with the prevalence of infecteds of each Brazilian state.

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Please cite this article in press as: *KOCK, Kelser de Souza et al. Cálculo da taxa de reprodutividade (R0) através da simplificação do modelo SIR aplicado à epidemia de Influenza A (H1N1) ocorrida em 2009 no Brasil. Revista de Epidemiologia e Controle de Infecção, Santa Cruz do Sul, v. 7, n. 2, maio 2017. ISSN 2238-3360. Disponível em: <https://online.unisc.br/seer/index.php/epidemiologia/article/view/7685/5965>. Acesso em: 27 out. 2017. doi:http://dx.doi.org/10.17058/reci.v7i2.7685.*