

ORIGINAL ARTICLE

A DESCRIPTIVE STUDY OF PANDEMIC INFLUENZA A(H1N1)PDM09 IN BRAZIL, 2009 – 2010

Erika Valeska ROSSETTO & Expedito José de Albuquerque LUNA

SUMMARY

Influenza A viruses undergo frequent antigenic mutations and may thus cause seasonal epidemics and pandemics. The aim of this study was to recover the epidemiological history of the pandemic influenza A(H1N1)pdm09 in Brazil. A descriptive study was conducted in 2009-2010. The Brazilian Information System for reportable diseases (SINAN) was the data source. A total of 105,054 suspected cases of influenza A(H1N1)pdm09 were reported to SINAN. Of these, 53,797 (51.2%) were classified as the new influenza virus subtype. Among the confirmed cases, 56.7% were female, the mean age was 26.31 (SD ± 18.1) years. Fever was the most common sign among the confirmed cases (99.7%) and the presence of comorbidities was reported in 32.5% of cases. In 2009 there were confirmed cases in all 26 Brazilian States and the Federal District. The incidence (per 100,000 inhabitants) of severe influenza in the population was 28.0 in 2009 and 0.5 in 2010. The states of *Paraná* (301.3), *Santa Catarina* (36.0) and *Rio Grande do Sul* (27.4) presented the highest incidence; 46.4% of the confirmed cases were hospitalized and 47,643 were cured (93.8%). The case-fatality rate was 3.9% in 2009. The pandemic virus A(H1N1)pdm09 hit Brazil between April/2009 and December/2010 with an important difference in the geographic pattern distribution of the cases from the northeast to the south of the country. Children and young adults were the most affected. The limitations of the study were data quality and inconsistencies in the final classification of cases in SINAN. This study highlights the urgent need for improvements in the surveillance of emerging diseases in Brazil.

KEYWORDS: Influenza; Epidemiological surveillance; Information system; Disease outbreaks; Brazil.

INTRODUCTION

Influenza or flu is an acute disease of the respiratory system and is present worldwide. The antigenic mutation capacity of the influenza A virus can cause pandemics with great social and economic repercussions¹.

The signs and symptoms of influenza are nonspecific: sudden fever, cough, headache, muscle pain, joint pain and coryza¹ with clinical characteristics that vary from asymptomatic cases to severe cases leading to death, making it a challenge to the surveillance system.

Due to the dissemination of the new influenza A virus subtype with the occurrence of cases in humans since March 18, 2009, in Mexico and the United States of America², the World Health Organization (WHO) declared, on April 25, a Public Health Emergency of International Concern. On the same day, the Brazilian Ministry of Health (MoH) instituted the Permanent Cabinet for Public Health Emergencies^{3,4}.

The Brazilian MoH divided the pandemic into two phases for a better handling: containment and mitigation phases⁵. In Brazil, the cases

of the first phase were attributed to international trips or contact with sick people who had traveled abroad. This period occurred between April 19 (identification of the first suspected cases) and July 18, 2009 (declaration of sustained transmission), epidemiological weeks (EW) 16 to 28/2009. The mitigation phase corresponds to the period in which the MoH acknowledged the occurrence of sustained transmission, from one person to another, in the country. That acknowledgement was belated, as even cases of death had already occurred, which were not related to the transmission chain involving travelers⁵. The mitigation phase started on July 19, 2009 (EW 29) and lasted until August 10, 2010; EW 32, when the post-pandemic phase was declared by the WHO^{6,7}. Since the beginning of the epidemic, the Brazilian MoH has routinely published epidemiological bulletins and notices, as well as technical notes⁸.

Considering the historical precedents and the studies that have been already published, it is possible to identify the limitations of the information on influenza in tropical countries that are even less effective in epidemics. Specifically regarding this pandemic in Brazil, there are partial, unconsolidated data of information by person, time and place and the morbimortality. It was not found, neither in governmental nor in

academic publications, a descriptive study regarding the whole pandemic period. The aim of this study was to recover the epidemiological history of the pandemic influenza A(H1N1)pdm09 in Brazil, focusing on the set of characterization, morbidity and mortality of cases under the national surveillance system.

METHODS

A descriptive study was conducted by using 2009 and 2010 secondary data, considering cases reported to the Brazilian Information System on Notifiable Diseases (SINAN), module pandemic influenza.

The definitions of confirmed and discharged cases of severe acute respiratory syndrome caused by influenza as per the directives of the MoH were taken into consideration^{1,6}.

During the containment phase, Brazil adopted the following case definition for surveillance purposes: fever, cough, and close contact with an infected person or a history of traveling to countries with documented cases within the 10 previous days. In the sustained transmission phase in the country, as of the EW 28/2009, the case definition was changed, and only severe cases, presenting fever, cough, respiratory distress or death were reported. Laboratory investigations were restricted to cases of severe influenza⁹.

A copy of the databases was requested to the MoH. Subsequently, the databases were submitted to the duplicity verification process by using the software RecLink III® (<http://reclink.sourceforge.net/>). When the duplicities were identified, the registrations with the oldest notification dates were kept¹⁰. It was decided that, if the notification dates were the same, the registration with the most recent closing date would be kept, considering that the case had a greater chance of having a better investigation for its closing.

The registrations that did not have the required data filled were excluded from the proportions calculation. Frequencies and proportional distributions of reported cases were presented. When appropriate, the odds ratio of exposure and the 95% confidence interval were calculated.

The population data were provided by the 2000-2012 estimates used in the publication “*Saúde no Brasil* [Health in Brazil] - 2012”, according

to the age group and gender. This information was made available by DATASUS, and was taken into consideration for the cumulative incidence calculation¹¹. For the cumulative incidence in pregnant women, the estimate of the number of pregnant women at the time, calculated as the number of live births in the previous year plus 10%, was considered in the denominator^{12,13}.

Ethical considerations

The project was submitted to the Scientific Research Ethics Committee of the Medical School of *Universidade de São Paulo* and was approved in June 06, 2012, under the resolution n°. 34710. The database requirement was conducted according to the directives of the MoH under the Access to Information Act^{14,15}.

RESULTS

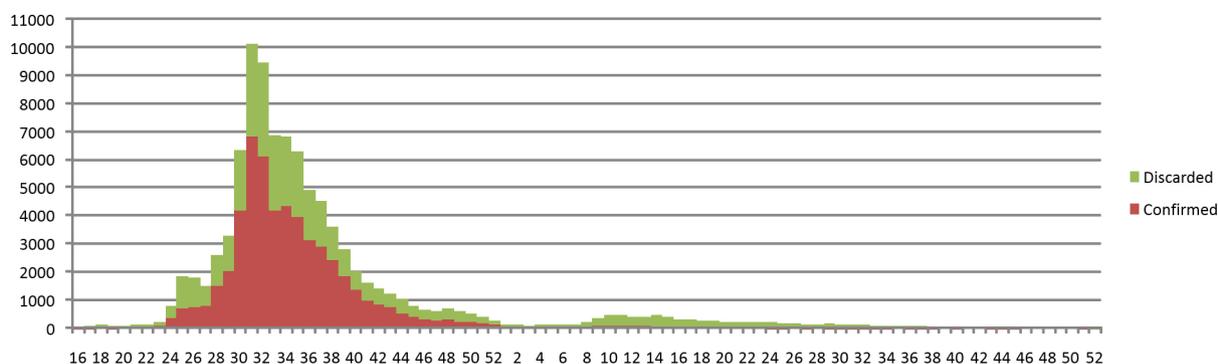
One hundred seventy-three (0.16%) duplicities were identified and excluded. Taking into consideration the registrations kept, 105,054 suspect cases of severe acute respiratory syndrome caused by influenza have been notified. Out of this total, 95,485 (90.9%) were notified in the year of 2009, and 9,569 (9.1%) were notified in 2010.

For the final classification, 53,797 (51.2%) of the notified cases were classified as influenza by the new viral subtype, 40,926 (39.0%) were discarded, 3,297 (3.1%) were caused by another infectious agent and 7,034 (6.70) were not categorized. The distribution frequency by epidemiological week can be observed in Graphic 1.

Out of the confirmed cases, 52,827 (98.2%) were notified in the year 2009 and 970 (1.8%) in 2010.

Among the confirmed cases, 65.8% were classified by a clinical-epidemiological criterion and 34.2% by the laboratory criterion. The diagnosis method recommended by the WHO for laboratory confirmation was the reverse-transcription polymerase chain reaction (RT-PCR)^{1,6}.

The cumulative incidence of influenza in the year 2009 was 28.0/100,000 inhabitants and, in 2010, 0.5/100,000 inhabitants. In the incidence distribution per age group, the group of people younger than one year had a greater incidence (84.2), followed by the 1- 4 years group



Graphic 1 - Distribution of the notified cases of influenza by the new viral subtype according to the epidemiological week of symptoms onset, and the final diagnostic classification. Brazil, 2009-2010.

(40.6) and the 20- 29 years group (38.5) in 2009. The age groups with the lowest incidence were the 60- 69 years group (13.7), the 70- 79 years group (12.4) and the group > 80 years old (11.4).

Regarding the epidemiological characteristics, 56.7% were female among the confirmed cases. The average age in the confirmed cases was 26.3 (SD ± 18.1) years old and the median age was 24 (range: 0- 98) years old.

It was possible to observe in Table 1 the distribution, according to the age group, of the number of cases classified as pandemic influenza, the proportion and incidence per 100,000 inhabitants, in the year 2009.

Table 1

Distribution of the number of cases classified as pandemic influenza according to the age group, proportion and incidence per 100,000 inhabitants. Brazil, 2009

Age Group (years)	Confirmed cases of pandemic influenza		
	N	%	Incidence/ 100,000 inhabitants
< 1	2,322	4.4	84.2
1 - 4	4,578	8.7	40.6
5 - 9	3,425	6.5	22.6
10 - 14	4,435	8.4	25.8
15 - 19	5,211	9.9	30.5
20 - 29	13,065	24.7	38.5
30 - 39	8,045	15.2	27.5
40 - 49	5,428	10.3	22.4
50 - 59	3,737	7.1	21.1
60 - 69	1,506	2.8	13.7
70 - 79	756	1.4	12.4
≥80	319	0.6	11.4
Total	52,827	100.00	28.0

According to the ethnic group/skin color, 38,111 (79.2%) of the confirmed cases were white. Regarding the educational level, 9,748 (21.0%) confirmed cases had this information ignored. Among the cases that had this category filled, the most frequent educational level category was high school graduate (21.8%). Regarding the area of residence, 93.8% of the confirmed cases lived in urban or peri-urban areas.

Among the confirmed cases, 31,507 (58.6%) resided in *Paraná (PR)* State and 8,139 (15.1%) in *São Paulo (SP)* State. In 2009, cases were confirmed in the 26 states, as well as in the Federal District (DF). The states of *Paraná* (301.3), *Santa Catarina (SC)*(36.0), *Rio Grande do Sul (RS)* (27.4), *Rio de Janeiro (RJ)* (20.1) and *São Paulo* (19.7) had the highest incidence per 100,000 inhabitants (Fig. 1).

Considering the epidemiological antecedents, the proportion among the confirmed cases of people who were vaccinated against flu was

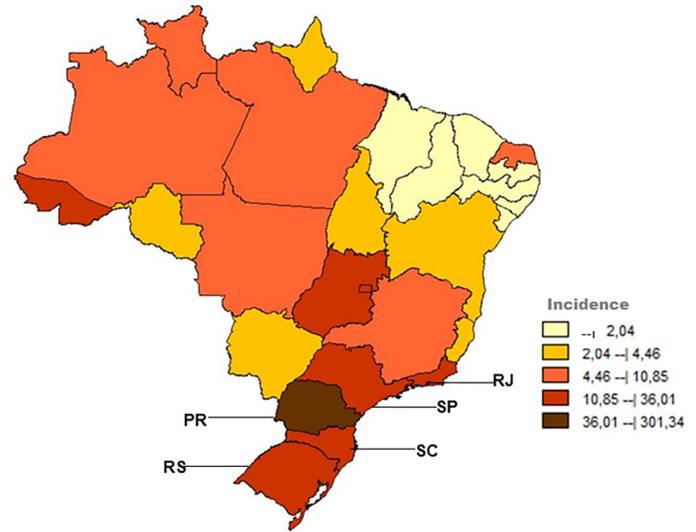


Fig. 1 - Incidence of influenza by the new viral subtype per 100,000 inhabitants, according to state of residence. Brazil, 2009.

9.7% (n = 4,356). A lower proportion was found when the use of anti-pneumococcal vaccines was evaluated, 2.1% received the vaccine and 97.9% did not.

Fever was the most frequent sign, registered in 99.7% of the cases. Cough (99.6%) and dyspnea (95.1%) were the other most frequent symptoms reported by the confirmed cases.

The presence of comorbidities was notified in 32.5% of the cases. The most frequent comorbidities were: chronic pneumopathy (26.35%), smoking (23.96%) and chronic cardiopathy (13.09%). On the progression evaluation, 46.4% of the confirmed cases involved hospitalizations.

The collection of 51,837 biological samples was performed from the notified cases, whereas 19,979 (35.5%) were from the cases classified as confirmed. Among these cases, 19,068 (95.4%) nasopharyngeal secretion samples were collected as well as 911 (4.6%) bronchoalveolar lavage samples (n = 67), feces (n = 1), post-mortem tissues (n = 138), serum samples (n = 123) and other non-specified samples (n = 582).

Among the 26,390 samples from the notified cases processed by RT-PCR, the results were positive for influenza by the new viral subtype (pandemic) in 18,603 (70.5%) samples. Among the cases classified as confirmed, 99.50% were classified as influenza by the new viral subtype, 0.24% by the seasonal influenza A, 0.02% by the seasonal influenza B, 0.05% by the avian influenza and 0.19% had other infectious agents. However, among the cases classified as discarded, 3.93% were classified as influenza by the new viral subtype, 17.66% by the seasonal influenza A, 0.55% by the seasonal influenza B, 0.06% by the avian influenza and 77.79% had other infectious agents.

A laboratory diagnosis was performed by culture in 676 samples. Among these, 283 were from cases classified as confirmed: 223 (78.8%) were positive and 60 (21.2%) were negative. In the 393 cultures performed in the cases classified as discarded, 15 (3.8%) were positive and 378 (96.2%) were negative.

Three hundred and seventy-eight samples were processed by both, RT-PCR and culture. Out of the 142 positive cultures, 132 (92.96%) were also positive by RT-PCR, eight (5.63%) were negative and two (1.41%) were inconclusive. Out of the 236 negative cultures, 30 (12.71%) were positive by RT-PCR, 205 (86.86%) were negative both in culture and RT-PCR, and one sample (0.42%) of a negative culture was inconclusive by RT-PCR.

Thoracic X-ray exams showed, more frequently, an interstitial infiltrate in 57.4% of the confirmed cases, followed by results considered normal in 23.3%. The solidification of the lung tissue that refers to non-specific air-space opacification (pulmonary consolidation), was presented in 3,968 (9.9%) of the notified cases, whereas 1,533 were confirmed.

In the case progression analysis 47,643 (93.8%) of the confirmed cases of influenza caused by the new viral subtype evolved to cure. The case-fatality rate was 3.9% (2,056/ 52,827) in 2009 and 12.4% (120/ 970) in 2010.

Pregnant women

Among pregnant women, 3,267 (53.6%) of the notified cases were classified as influenza by the new viral subtype and 2,820 (46.4%) were discarded. Among the confirmed cases, 1,839 (56.3%) were classified by laboratory criteria and 1,428 (43.7%) by clinical-epidemiological connections.

The incidence of influenza by the new viral subtype in pregnant women in 2009 was 97.0/ 100,000 and, in 2010, 4.3/ 100,000.

Upon evaluation of the gestational age, in most cases of confirmed pregnancy 1,288 (39.42%) women were in the second trimester of pregnancy, followed by 1,249 (38.23%) in the third trimester of pregnancy.

Among the confirmed cases, the presence of comorbidities was notified in 35.5%. When pregnant women (yes/no) and the presence of comorbidities (yes/no) were compared, the OR was 1.15 (95% CI -1.06-1.23). Regarding the evolution assessment, 74.5% of the confirmed cases were hospitalized.

In the case progression analysis, 2,730 of the confirmed cases of influenza by the new viral subtype progressed to cure. The case-fatality rate (225/3,267) was 6.9%.

DISCUSSION

Historically, due to the need to improve and expand the monitoring of the influenza virus activity in Brazil, the MoH started, in 2000, the implementation of an Influenza Surveillance System throughout the national territory based on sentinel units and on indirect morbidity and mortality data associated with this disease in susceptible and vaccinated populations¹⁶. The surveillance system is comprised of healthcare units distributed throughout all Brazilian States, and uses an online information system, the Sivep *Gripe*¹⁷. Reporting of seasonal influenza cases is not mandatory in Brazil^{6,9}. Regardless of the inclusion in the sentinel net, all suspected cases of seasonal influenza or human influenza by new subtype outbreaks must be notified to the Brazilian Information System

on Notifiable Diseases (SINAN) and be submitted to the International Health Regulation decision algorithm^{4,18,19}.

Description by time, place and individual

The behavior of the epidemic curve followed the seasonal influenza pattern of sustained and self-limiting transmission.

Regarding the spatial distribution of the cases, large differences were observed in the incidence according to the geographic regions of the national territory and among the Brazilian States, both in our study and in the literature. The incidence rates are difficult to compare, as there are some variation between the periods, locations and populations analyzed by us and the ones presented in other studies. In the published studies, an incidence/ 100,000 inhabitants of 241.9 in *Santa Catarina* State²⁰, 20 in people under the age of two, and approximately 10 in the 20-29 years age group *São Paulo* State²¹ were found. In *Ceará* State, during the containment phase, the number of cases varied between zero in people under two years of age and 0.54 in people between 20-29 years. In the mitigation phase, that variation was 0.51 (40 - 49 years) and 2.68 (10 - 19 years)²².

The climate conditions in Brazil are essentially the inverse of the European and United States seasons, and 90% of the country is located in the tropical zone, with considerable climate variation between the north (equatorial region) and the south (below the tropic of Capricorn). The national tendency is that the influenza virus spreads in the south and southeast regions during winter (June-August) and in the north and northeast regions, during rainy periods. However, in tropical and subtropical countries, there may be peaks during the year in the dynamics of the seasonal influenza A; some authors suggest that this behavior is associated with climate aspects (temperature, humidity), solar radiation, possibly with levels of vitamin D, the host immunity and the virulence of the viral strain²³.

As such, it can be questioned whether the pandemic influenza virus did not spread to the north and northeast regions of the country. This would also suggest the confirmation of the difference on the transmission pattern, whereas the territorial extension of the country would allow the pandemic to follow both the north and the south hemispheres transmission patterns. Studies performed by other authors presented a concentration of cases in the large cities, showing that the pandemic had a very low spread level in the countryside. The underreporting is a plausible explanation to both situations.

As a result of our study, among the total of reported cases, the highest frequency occurred in females, children and young adults who are white, with an educational level of completed high school and residents in urban areas were the most frequently notified, as well as confirmed cases of influenza A(H1N1)pdm09 were found. Such findings are supported by results of other authors^{20,21,23-28}.

Thus, we interpret that these results reflect the configuration of the Brazilian population. The result of the demographic census performed by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE) in 2010 accounted for the proportion of 50.8% of females, 47.7% of people defining themselves as white, and 81.2% of the population in the country were registered as residents of

urban areas. According to the 2010 Census, 84.30% of the population above the age of five was literate²⁹.

In the cases classified as confirmed during the pandemic influenza, we have noted a slight increase in the proportion of pregnant women who present comorbidities when compared with the general population, and in the case-fatality rate in pregnant women and also in the general population (4.04%). The severity of infection by the the influenza virus in pregnant women may be related to alterations that the gestational process triggers in women, such as the overburden of the circulation, as well as of the respiratory and immunologic systems. This group is submitted to additional care, as they routinely present better adherence to the services, including the prenatal care. As a consequence, the greater attention of health professionals regarding pregnant women may contribute to a better detection of suspected and confirmed cases leading to lower complication rates, hospitalizations and mortality in this group.

Epidemiological precedents

We have found out in our study that a minority of the cases was vaccinated against influenza or had received the anti-pneumococcal vaccine. This vaccination could not be evaluated as a protective factor for influenza virus infection as the strain responsible for the pandemic was not in the vaccine used in the national 2009 campaign³⁰. Brazil was hit by the pandemic before vaccines for the A(H1N1)pdm09 virus became available.

The national vaccination strategy against pandemic influenza virus was organized to occur in five stages, between March 8 and May 21, 2010, simultaneously in all the 5,565 municipalities in the country, with the acquisition of 112.9 million doses of monovalent pandemic influenza (H1N1) 2009 vaccine³⁰. The National Immunization Program registered 89,580,203 doses used in this campaign. The applied doses and immunization coverage for the target population in the 2010 campaign were: health workers (2,985,774; 120.33%), indigenous people (507,851; 90.62%), pregnant women 10- 49 years old (2,324,666; 77.14%), patients with chronic diseases \geq 60 years old (8,511,628; 219.05%) and children < 2 years old (5,580,671; 127.52%) (31). As in 2010, an important reduction in the number of cases of flu, in morbidity and mortality rates was observed probably due to this extensive vaccination campaign.

We have found a minimal proportion between cases that had being in contact with dead or sick birds within 10 days before the signs and symptoms onset. Despite the genetic rearrangement of the influenza A(H1N1)pdm09 virus³² and reports of infection by the variant of the swine influenza virus in humans after contact with sick pigs³³, the analysis of this kind of exposure did not contribute to the investigation of epidemiological antecedents of H1N1 virus infection in Brazil.

Clinical Information

The clinical manifestations caused by the pandemic influenza virus were, in general slightly more severe than the infection caused by the seasonal virus. In the case definition updates performed by the MoH, a condition of severe influenza characterized by the triad fever, cough and dyspnea, was kept^{1,6,34,35} and was the most frequent clinical manifestation in our study, as well as in others.

Regarding the presence of comorbidities, in our study population, we have found proportions that are approximately similar to those of other studies. The higher proportion of comorbidities registered suggests that the population was informed on the characteristics of the symptomatology of the infection by the pandemic virus, was alert for the risk conditions and advised to search for help of healthcare services. Another hypothesis for the high proportion of individuals reported with comorbidities may be an increased susceptibility to infection in this group and possibly, more severe symptoms, leading to a greater demand for health services, and hence to a greater reporting.

Other authors have demonstrated that the hospitalization was more frequent in children, the elderly, pregnant women and bearers of comorbidities³⁶⁻⁴⁴. The studies available in the literature have shown that the already known comorbidities and risk factors, as well as a severe clinical condition, require hospital care. In our findings, signs, symptoms and comorbidities rates are similar to those found in the literature. Patients with the characteristic severe influenza triad, age < 2 years or > 60 years, those in use of immunosuppressants, bearers of chronic diseases and pregnant women are the most vulnerable groups for the worsening of the infection caused by the pandemic influenza H1N1 virus⁴⁵.

Diagnosis and complementary exams

As the pandemic progressed, more cases were classified as confirmed according to clinical-epidemiological criteria, which is an expected situation in the case of a pandemic involving a respiratory disease transmission profile.

As determined in the protocols, the preferred specimen for laboratory diagnosis and detection of the influenza virus is the nasopharyngeal secretion. The diagnosis method preconized by the WHO for laboratory confirmation is the RT-PCR^{1,6}.

We emphasize the 3.9% of cases classified as discarded and that had samples processed by RT-PCR that were positive for influenza by the new viral subtype. We also emphasize the 21.2% of the negative cultures in the cases classified as confirmed and the 3.8% of positive cultures in the cases classified as discarded. We postulate herein the hypothesis of misclassification of the cases. We have decided not to reclassify the cases and analyze a new scenario, as this situation reflects the reality of the information system and reinforces the discussion regarding data quality.

Clinical manifestations and radiological results in the influenza virus infection are not specific⁴⁶. As previously mentioned, the clinical setting is similar to that of other respiratory infections and can be worsened by the characteristics of the infectious agent or by the host condition, but up to now, parameters such as the viral load were not associated with the severity of symptoms. The interstitial infiltrate found in the thoracic x-ray is not deemed in the differential diagnosis as it is seen in several diseases, usually referring to inflammatory processes or, yet, in cases of infection by the pandemic influenza virus suggesting an exacerbated immunological response⁴⁷.

Deaths

In the comparison of the mortality rate between our results and the results of other studies we have found in the literature, we had the same

difficulty reported concerning the incidence rate. The case-fatality rate was calculated by using different populations, times and places, creating biases in possible comparisons^{9,48,49}.

Limitations

We had the same limitations described by several authors that conducted studies using secondary data related to: data quality, difficulty and heterogeneity when filling the disease reporting form, underreporting and inaccuracy of the data collected, registration priority of severe cases or cases of people that belong to risk groups.

This kind of limitation (data quality) has already been made clear to the reader of our study, as well as the inconsistencies in the classification of closed cases in SINAN. We have mentioned a second limiting factor, which is the administrative and time difficulty of accessing databases with nominal registrations made available by the MoH.

CONCLUSION

This study aimed at describing the epidemiological history of the pandemic influenza A in Brazil, followed by MoH, but one of the highlights of the study was the inconsistency of the SINAN data, which makes a consistent criticism of the system for this disease necessary and evident.

The analyses comprised the period formally acknowledged as the pandemic period, but it should be mentioned that the virus kept disseminating in both the global and the Brazilian population as of this day⁵⁰.

We have concluded that the epidemiological profile of the cases classified as confirmed for pandemic influenza found in our study represents the Brazilian population profile, not adding characteristics that could call attention to specific groups in the epidemic profile. Regarding the spatial distribution of the cases, the tropical-equatorial region had a low number of notified cases during the peak period (winter). This is an important situation that must be investigated by the Influenza Surveillance Services in order to understand the geographic distribution pattern of the pandemic in Brazil, aiming at monitoring the disease.

During the course of the pandemic, the investigation on the status regarding trips or contacts lost importance, with the clinical severity of new cases becoming the focus. Considering the triad composed of fever, cough and dyspnea, although it can be a traditional clinical condition of acute severe viral respiratory infections, infected people must be monitored in order to avoid worsening of the condition, hospitalization and death. Asymptomatic cases must be considered, as they are important in the transmission of infection and they contribute to maintaining the pandemic.

We suggest a reduction of the number of the variables in the SINAN influenza notification form due to the complexity to collect and register all the data currently required.

Optional completion variables rarely bring good quality data for usage, as there is no standardization to perform collection. We, therefore, recommend the exclusion of the variables: information regarding transportation, contact with sick or dead birds within 10 days before the

signs and symptoms onset, other signs and symptoms, other comorbidities and data regarding the thoracic X-ray exam whose result is interesting for the clinical management and not for the epidemiological surveillance.

Human influenza by new viral subtypes is of mandatory notification for public health surveillance purposes¹⁸. Due to this fact, it is necessary to stimulate and capacitate professionals so that the local levels of surveillance will use the information system data in a comprehensive manner, identifying data weaknesses and inconsistencies, improving their quality and making the systems effective for their purpose.

We have also taken this opportunity to demonstrate the necessity of urgent improvements in the surveillance of emergent and re-emergent diseases.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Guia de vigilância epidemiológica. 7. ed. Brasília: Ministério da Saúde; 2009. (Caderno 1. Influenza).
2. Carvalho M. Um susto revelador. *RADIS*. 2009;82:8-9.
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Influenza Pandêmica (H1N1) 2009: análise da situação epidemiológica e da resposta no ano de 2009. *Bol Eletr Epid*. 2010;10(1):1-21.
4. Brasil. Congresso Nacional. Decreto Legislativo nº 395, de 2009. Aprova o texto revisado do Regulamento Sanitário Internacional, acordado na 58ª Assembléia Geral da Organização Mundial de Saúde, em 23 de maio de 2005. [cited 2016 May 24]. Available from: <http://www2.camara.leg.br/legin/fed/decleg/2009/decretolegislativo-395-9-julho-2009-589324-publicacaooriginal-114307-pl.html>
5. Marques D, Figueira GC, Moreno ES, Almeida CL, Cordero R, Campos K, et al. Investigação de óbito relacionado à influenza pandêmica H1N1 2009 no município de Osasco, SP, junho e julho de 2009. *Bol Epidemiol Paulista*. 2011;8:4-14.
6. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Protocolo de vigilância epidemiológica da influenza pandêmica (H1N1) 2009 : notificação, investigação e monitoramento. Brasília: Ministério da Saúde; 2010.
7. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Coordenação Geral de Doenças Transmissíveis. Coordenação de Vigilância das Doenças de Transmissão Respiratórias e Imunopreveníveis. A Organização Mundial da Saúde (OMS) decreta em 10/08/2010 o início da fase pós-pandêmica do vírus Influenza Pandêmica (H1N1) 2009. [cited 2016 May 24]. Available from: file:///C:/Users/biblioteca/Downloads/nt_pos_pandemica_h1n1_10_08_2010.pdf
8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Gabinete Permanente de Emergências em Saúde Pública. Ocorrências de casos humanos de infecção por Influenza A (H1N1). Brasília: Ministério da Saúde; 2009.
9. Oliveira WK, Carmo EH, Penna GO, Kuchenbecker RS, Santos HB, Araujo WN, et al. Pandemic H1N1 influenza in Brazil: analysis of the first 34,506 notified cases of influenza-like illness with severe acute respiratory infection (SARI). *Eurosurveillance*. 2009;14:1-6.
10. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Coordenação Geral de Doenças Transmissíveis. Gerência Técnica do Sinan. Roteiro para uso do Sinan NET, análise da qualidade da base de dados e cálculo de indicadores epidemiológicos e operacionais: caderno geral. Brasília: Ministério da Saúde; 2008.

11. Brasil. Ministério da Saúde. Informações de saúde (TABNET): demográficas e socioeconômicas. [cited 2016 May 24]. Available from: <http://www2.datasus.gov.br/DATASUS/index.php?area=0206&VOBJ=http://tabnet.datasus.gov.br/cgi/defohtm.exe?poestim/cnv/pop>
12. Brasil. Ministério da Saúde. Secretaria de Assistência a Saúde. Portaria SAS/MS nº 650, de 5 de outubro de 2011. Dispõe sobre os planos de ação regional e municipal da Rede Cegonha, que são os documentos orientadores para a execução das fases de implementação da Rede, assim como para o repasse dos recursos, o monitora. [cited 2016 May 24]. Available from: http://bvsm.sau.gov.br/bvs/sau/legis/sas/2011/prt0650_05_10_2011.html
13. Brasil. Ministério da Saúde. Nascidos vivos: Brasil. [cited 2016 May 24]. Available from: <http://tabnet.datasus.gov.br/cgi/defohtm.exe?sinasc/cnv/nvuf.def>
14. Brasil. Presidência da República. Casa Civil. Lei nº 12.527, de 18 de novembro de 2011. Regula o acesso a informações previsto no inciso XXXIII do art. 5º, no inciso II do § 3º do art. 37 e no § 2º do art. 216 da Constituição Federal; altera a Lei no 8.112, de 11 de dezembro de 1990; revoga a Lei no. 11.111, de 5 de maio de 2005, e dispositivos da Lei no 8.159, de 8 de janeiro de 1991; e dá outras providências. [cited 2016 May 24]. Available from: http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2011/lei/l12527.htm
15. Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria nº 1.583, de 19 de julho 2012. Dispõe, no âmbito do Ministério da Saúde e entidades a ele vinculadas, sobre a execução da Lei nº 12.527, de 18 de novembro de 2011, que versa sobre a Lei de Acesso à Informação, e do Decreto nº 7.724, de 16 de maio, que a regulamenta. [cited 2016 May 24]. Available from: http://bvsm.sau.gov.br/bvs/sau/legis/gm/2012/prt1583_19_07_2012.html
16. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. O desafio da influenza: epidemiologia e organização da vigilância no Brasil. *Bol Eletr Epid*. [cited 2015 Mar 4]. Available from: http://bvsm.sau.gov.br/bvs/periodicos/boletim_eletronico_epi_ano04_n01.pdf
17. Brasil. Ministério da Saúde. Vademecum ampliado : Influenza: aprender e cuidar. Brasília: Ministério da Saúde; 2010.
18. Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria nº 104, de 25 de janeiro de 2011. Define as terminologias adotadas em legislação nacional, conforme o disposto no Regulamento Sanitário Internacional 2005 (RSI 2005), a relação de doenças, agravos e eventos em saúde pública de notificação compulsória em todo o território nacional e estabelece fluxo, critérios, responsabilidades e atribuições aos profissionais e serviços de saúde. [cited 2016 May 24]. Available from: http://bvsm.sau.gov.br/bvs/sau/legis/gm/2011/prt0104_25_01_2011.html
19. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Notificação de Influenza no SINAN. [cited 2016 May 24]. Available from: ftp://ftp.cve.sau.gov.br/doc_tec/resp/nt309_notinflusan.pdf
20. Schuelter-Trevisol F, Dutra MC, Uliano EJ, Zandomênicó J, Trevisol DJ. Perfil epidemiológico dos casos de gripe A na região sul de Santa Catarina, Brasil, na epidemia de 2009. *Rev Panam Salud Publica*. 2012;32:82-6.
21. São Paulo (Estado). Coordenadoria de Controle de Doenças. Centro de Vigilância Epidemiológica “Prof. Alexandre Vranjac”. Divisão de Doenças de Transmissão Respiratória. Características dos casos notificados de Influenza A/H1N1. *Rev Saúde Pública*. 2009;43:900-4.
22. Pires Neto RJ, Lemos DR, Cavalcanti LP, Ramos Jr AN, Alencar CH, Façanha MC, et al. Pandemic influenza A (H1N1) 2009: epidemiological analysis of cases in a tropical/semi-arid region of Brazil. *Rev Soc Bras Med Trop*. 2013;46:141-6.
23. Silva RC, Siqueira MA, Netto EM, Bastos JS, Nascimento-Carvalho CM, Vilas-Boas AL, et al. Epidemiological aspects of influenza A related to climatic conditions during and after a pandemic period in the city of Salvador, northeastern Brazil. *Mem Inst Oswaldo Cruz*. 2014;109:229-35.
24. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Investigação de casos de Síndrome Respiratória Aguda Grave por Influenza pandêmica (H1N1) 2009 no estado do Rio Grande do Sul, Junho-Agosto/2009. *Bol Eletr Epid*. 2010;10(12):1-4.
25. Lenzi L, Wiens A, Grochocki MH, Pontarolo R. Study of the relationship between socio-demographic characteristics and new influenza A (H1N1). *Braz J Infect Dis*. 2011;15:457-61.
26. Lobo RD, Oliveira MS, Garcia CP, Caiaffa Filho HH, Levin AS. Pandemic 2009 H1N1 influenza among health care workers. *Am J Infect Control*. 2013;41:645-7.
27. Lenzi L, Mello AM, Silva LR, Grochocki MH, Pontarolo R. Manifestações clínicas, desfechos e fatores prognósticos da influenza pandêmica A (H1N1) de 2009 em crianças. *Rev Paul Pediatr*. 2012;30:346-52.
28. Guatura SB, Watanabe AS, Camargo CN, Passos AM, Parmezan SN, Tomazella TKC, et al. Surveillance of influenza A H1N1 2009 among school children during 2009 and 2010 in São Paulo, Brazil. *Rev Soc Bras Med Trop*. 2012;45:563-6.
29. Instituto Brasileiro de Geografia e Estatística. Censo demográfico 2010: características gerais da população, religião e pessoas com deficiência. [cited 2016 May 25]. Available from: http://www.ibge.gov.br/home/estatistica/populacao/censo2010/caracteristicas_religiao_deficiencia/default_caracteristicas_religiao_deficiencia.shtm
30. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Programa Nacional de Imunizações. Estratégia nacional de vacinação contra o vírus Influenza Pandêmico (H1N1) 2009: 8 de março a 21 de maio de 2010: informe técnico operacional. Brasília: Ministério da Saúde; 2010.
31. Brasil. Ministério da Saúde. Sistema de Informação do Programa Nacional de Imunizações. Estratégia da vacinação contra a Influenza Pandêmica (H1N1). [cited 2016 May 25]. Available from: http://pni.datasus.gov.br/consulta_h1n1_10_selecao.asp
32. Temporão JG. Carta aberta do Ministro da Saúde: o enfrentamento do Brasil diante do risco de uma pandemia de influenza pelo vírus A (H1N1). *Epidemiol Serv Saúde*. 2009;18:201-4.
33. Centers for Disease Control and Prevention. Variant (swine origin) influenza viruses in humans [cited 2016 May 25]. Available from: <http://www.cdc.gov/flu/swineflu/variant.htm>
34. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Doenças infecciosas e parasitárias: guia de bolso. 8. ed. ver. Brasília: Ministério da Saúde; 2010. p.41-64.
35. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Gabinete Permanente de Emergências em Saúde Pública. Protocolo de manejo clínico epidemiológica da Influenza: versão II. Brasília: Ministério da Saúde; 2009.
36. Lenzi L, Wiens A, Pontarolo R. The characteristics, clinical manifestations and outcomes of pandemic influenza A (H1N1) 2009 in the elderly. *Rev Soc Bras Med Trop*. 2013;46:135-40.
37. Melchior TB, Guatura SB, Camargo CN, Watanabe AS, Granato C, Bellei N. Occurrence of influenza among patients hospitalized for suspicion of influenza A (H1N1) infection in 2010 at a sentinel hospital in São Paulo, Brazil. *J Bras Pneumol*. 2011;37:655-8.
38. Schout D, Hajjar LA, Galas FR, Uip DE, Levin AS, Caiaffa Filho HH, et al. Epidemiology of human infection with the novel virus influenza A (H1N1) in the Hospital das Clínicas, São Paulo, Brazil: June-September 2009. *Clinics*. 2009;64:1025-30.
39. Duarte PA, Venazzi A, Youssef NC, Oliveira MC, Tannous LA, Duarte CB, et al. Outcome of influenza A (H1N1) patients admitted to intensive care units in the Paraná state, Brazil. *Rev Bras Ter Intensiva*. 2009;21:231-6.

40. Nassar Junior AP, Mocelin AO, Nunes AL, Brauer L. Influenza A (H1N1) patients admitted to intensive care units during the 2009 pandemics: clinical features and outcomes. *Rev Bras Ter Intensiva.* 2010;22:333-8.
41. Jiménez MF, El Beitune P, Salcedo MP, Von Ameln AV, Mastalir FP, Braun LD. Outcomes for pregnant women infected with the influenza A (H1N1) virus during the 2009 pandemic in Porto Alegre, Brazil. *Int J Gynaecol Obstet.* 2010;111:217-9.
42. Camargo C, Guatura SB, Bellei N. Respiratory viral coinfection among hospitalized patients with H1N1 2009 during the first pandemic wave in Brazil. *Braz J Infect Dis.* 2012;16:180-3.
43. Watanabe AS, Carraro E, Moreira L, Camargo C, Sinohara J, Puerari D, et al. Respiratory virus infections among hospitalized patients with suspected influenza A H1N1 2009 virus during the first pandemic wave in Brazil. *Braz J Infect Dis.* 2011;15:220-4.
44. Figueiró-Filho EA, Oliveira ML, Pompilio MA, Uehara SN, Coelho LR, De Souza BA, et al. Obstetric, clinical, and perinatal implications of H1N1 viral infection during pregnancy. *Int J Gynaecol Obstet.* 2012;116:214-8.
45. Yokota RT, Skalinski LM, Igansi CN, de Souza LR, Iser BP, Reis PO, et al. Risk factors for death from pandemic (H1N1) 2009, southern Brazil. *Emerg Infect Dis.* 2011;17:1467-71.
46. Ribeiro SA, Brasileiro GS, Soleiman LN, Silva CC, Kavaguti CS. Severe acute respiratory syndrome caused by the influenza A (H1N1) virus. *J Bras Pneumol.* 2010;36:386-9.
47. Carmona F, Carlotti AP, Ramalho LN, Costa RS, Ramalho FS. Evidence of renal infection in fatal cases of 2009 pandemic influenza A (H1N1). *Am J Clin Pathol.* 2011;136:416-23.
48. de Souza MF, Widdowson MA, Alencar AP, Gawryszewski VP, Aziz-Baumgartner E, Palekar R, et al. Trends in mortality from respiratory disease in Latin America since 1998 and the impact of the 2009 influenza pandemic. *Bull World Health Organ.* 2013;91:525-32.
49. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Investigação de óbito por influenza pandêmica (H1N1) 2009 no estado do Rio Grande do Norte/RN, agosto-novembro de 2009. *Bol Eletr Epid.* 2010;10(13):1-5.
50. World Health Organization. Pan American Health Organization. Actualización epidemiológica: inicio de mayor actividad de influenza en América del Norte, 2 de enero de 2014. [cited 2016 May 25]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=23912&Itemid=

Received: 09 September 2015

Accepted: 30 May 2016