THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Regional Review

Influenza in Brazil: surveillance pathways

Ligia Cantarino[1], Edgar Merchan-Hamann[2]

[1] *Faculty of Agronomy and Veterinary Medicine, University of Brasília, Brasília, DF, Brazil*
[2] *Faculty of Health Sciences, University of Brasília, Brasília, DF, Brazil*

Abstract
Influenza is a viral disease of global concern that has demanded the attention of health authorities. Since 1947, as a preventive measure, the World Health Organization monitors viral circulation to define the annual vaccine through a worldwide network of laboratories. This article presents the structuring of influenza surveillance in Brazil and highlights virological surveillance and the role of diagnostic laboratories as well as the expansion of actions to improve detection and expedite responses. The model set corresponds to sentinel surveillance complemented by the universal notification of severe acute respiratory syndrome investigating outbreaks, deaths, and unusual events and monitoring hospitalization and mortality in an expanded surveillance. In this review, we address aspects of influenza surveillance in animals, the need for interagency integration, and the sharing of information in many surveillance systems.

Key words: influenza; epidemiological surveillance; public health.

J Infect Dev Ctries 2016; 10(1):013-023. doi:10.3855/jidc.7135

(Received 13 May 2015 – Accepted 03 August 2015)

Introduction

Influenza ("flu") is a respiratory disease of worldwide distribution that is caused by the influenza virus *Myxovirus influenzae*, which belongs to the *Orthomyxoviridae* family and includes viruses A, B, and C. The antigenic variations of the virus comprise an important immunological escape mechanism that favors the infection of new susceptible hosts. These factors, along with high transmissibility and zoonotic and pandemic potential, make the challenge of its prevention and control an increasing problem with a recognized importance in public health [1,2].

This viral infection has been considered as a multifaceted disease throughout history. Flu is a common disease with a benign clinical course and known seasonality that may lead to severe and fatal medical conditions. Pandemics such as those that occurred in the past – the Spanish flu (1918–20), Asian flu (1957–60), and Hong Kong flu (1968–72) – caused millions of deaths. In the pandemic episode of 2009, the H1N1 virus rapidly spread among humans and had high morbidity rates [3,4,5].

Depending on the pandemic potential and clinical manifestation severity, influenza presents different problems from the public health perspective that require specific surveillance and control [6]. In fact, the worldwide surveillance of this disease is recommended [7].

Given the threats of pandemic flu, the importance of this disease has motivated this narrative review in which we present the structure of surveillance of human influenza in Brazil as well as a brief overview of surveillance aspects in animals.

Global Surveillance

Since 1947, the World Health Organization (WHO) has been monitoring the activity of the influenza virus through a network of laboratories for viral identification, which was initially named as Global Influenza Surveillance Network (GISN). In 2011, the name of this network was changed to Global Influenza Surveillance and Response System (GISRS). Its objective is to follow the evolution of influenza viruses and provide information to support the WHO's recommendations for laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment, in addition to establish a mechanism of global alert of the emergence of viruses with pandemic potential [2,8].

The objectives of influenza virological surveillance are to: identify viral circulation – types and subtypes – as well as its correlation with regional and global patterns; describe antigenic and genetic features; monitor antiviral sensibility; understand the correlation between a viral strain and its severity; and provide information and samples for the selection of virus candidates for the production of vaccines [7].

The GISRS is composed of six Collaborating Centers (CCs) of the WHO and 141 institutions of viral disease diagnosis in 111 member states of the WHO. The diagnosis laboratories are known as National Influenza Centers (NICs) [8]. The organization of this laboratory system assigns the NICs of each country as responsible for collecting clinical specimens, isolating, and sending viral samples of interest to the CCs. In addition to the antigenic and genetic characterization of the viruses, the CCs have the purpose of providing training and developing guidelines for laboratory techniques, quality control, and assessment of standardized procedures throughout the network. For technique standardization and unification, the protocols and common reagents are provided by the WHO through the Centers for Disease Control (CDC) to the NICs [2].

Brazil, part of the GISRS, has three WHO-accredited NIC laboratories: the Virology Laboratory of the Evandro Chagas Institute in Pará (IEC/PA); the Respiratory Virus Laboratory of the Adolfo Lutz Institute in São Paulo (IAL/SP); and the Respiratory Virus and Measles Laboratory of the Oswaldo Cruz Foundation in Rio de Janeiro (Fiocruz/RJ). The first two laboratories are recognized by the National System of Public Health Laboratories (Sislab) as regional references, while the latter is considered a national reference for influenza in Brazil [9,10].

In addition to viral surveillance, since 1950 a global standardized system has been improving the monitoring activities of influenza virus with the following specific objectives: describing the seasonality of influenza in each country; signaling the start of the influenza season; establishing and monitoring the trends of influenza-like illness (ILI) and severe acute respiratory syndrome (SARS). This information is important since it provides data on the disease burden and the impact of influenza compared to other diseases; it assists in the identification and monitoring of high-risk groups and annual changes in severity, and factors in specify priorities for the utilization of resources [7].

Surveillance of human influenza in Brazil

In Brazil, the surveillance of influenza started in the 1990s with the identification of the circulating viruses in some parts of the country and in outbreak situations [11]. Based on the sentinel surveillance system of virus circulation developed in Paris, France, and started in October 1984 by the Groupe Regional d'Observation de la Grippe (GROG) [12], in 1995 the GROG Flu Monitoring Group was created in Brazil by some public and private health services from the southern and southeastern regions. The goal was to systematize information about the circulation of respiratory viruses in Brazil, the influenza virus in particular. In 2000, the Brazilian GROG was renamed the VigiGripe Project, part of the VigiVirus Project. This group was associated with the Federal University of São Paulo in a joint effort with the Enteric and Respiratory Virus Department of the IAL/SP [11,13,14]. The epidemiological surveillance of influenza was nationally implemented in 2000 based in Sentinel Units (SUs) and the use of indirect morbidity and mortality associated data [9]. At this time, the epidemiological surveillance was performed by the National Centre of Epidemiology (Cenepi) of Ministry of Health, which structured the technical team in coordination with the state offices of health and the laboratories of respiratory viruses of the IAL/SP, IEC/PA, and Fiocruz/RJ, which were accredited as reference centers by the WHO [11]. Therefore, a set of specific and ongoing actions was introduced to elucidate the behavior of influenza and allow the introduction of appropriate, timely, and effective preventive measures [9,10].

The implemented surveillance system aimed to: monitor the circulation of influenza virus strains and morbidity trends; evaluate the impact of vaccination; respond to unusual situations; and produce information about the disease. To select at least one SU per state, the following specific criteria were adopted: the real interest of the unit in participating in the epidemiological surveillance work; its situation as a care center regarding consultation demands for general practice or pediatrics; the minimum requirements for staff and structural resources; preferable close location to the laboratory; and good managerial performance. Each SU should record the proportion of consultations due to ILI compared to the total number of consultations and send five biological samples of respiratory secretions each week to one of the 27 Central Laboratories of Public Health (Lacen) [9].

The surveillance of influenza has been able to identify the circulating respiratory viruses as well as their seasonality and high-risk populations. In a study of the Brazilian surveillance of influenza performed in 2000–2010 [10], a total of 29,318,698 patient consultations were recorded in the SUs, of which 3,291,949 (11%) were due to ILI. Of these, 37,120

(1%) had samples of nasopharyngeal secretions collected for respiratory virus detection. Of the 6,421 (17%) positive results, 1,690 (26%) were positive for influenza A, 567 (9%) for influenza B, 277 (4%) for parainfluenza 1,571 (9%) for parainfluenza 2,589 (9%) for parainfluenza 3,742 (12%) for adenovirus, and 1,985 (31%) for respiratory syncytial virus.

In 2003, strengthening of the influenza surveillance was driven by the outbreaks in the Asian region and some European countries of an avian influenza (AI) virus with high pathogenicity (A/H5N1), which led to episodes of severe disease and mortality [1,2,15]. This situation generated worldwide concern and, in Brazil, several organizations were mobilized to discuss strategies that led to Brazil's Contingency Plan to Confront an Influenza Pandemic, which was presented and discussed in an international seminar in Rio de Janeiro in November 2005. This collective effort placed influenza on the agenda of the national policy of public health [11].

With the approval of the review of the International Health Regulations (IHR) by the World Health Assembly in 2005, the signatory countries also reviewed their monitoring structures and processes, surveillance, and responses to Public Health Emergencies of International Concern (PHEIC), and committed to developing the capability to respond to those emergencies [2,14].

With regard to the notification of outbreaks or death, *human influenza* became part of the list of the national mandatory notifiable diseases in July 2005 [16]. *Human influenza by new subtype (pandemic)* was included in February 2006 [17]. The ordinance GM/MS No. 104, January 25, 2011, in addition to defining the terminologies according to the IHR 2005, changed the nomenclature of *human influenza by new subtype* as mandatory and immediate notification, and classified *human influenza* as a mandatory notifiable disease in SUs [18]. According to the current regulations, Ordinance GM/MS No. 1271 created on June 6, 2014, it is registered as *human influenza provided by a new viral subtype* [19].

The regulation of the Operational directives of the Pacts for Life and Management, by Ordinance GM/MS No. 699 created March 30, 2006 also contributed to the strengthening of influenza surveillance. Prerogatives of the transfer of federal funds were agreed to strengthen the capacity to respond to influenza among other emerging and endemic diseases. The national goal for 2006 established the implementation of SUs and the Information System of Epidemiological Surveillance of Influenza Virus in Brazil (Sivep-Gripe) in 100% of the capitals. The defined indicator for monitoring and evaluation was the system participation rate: number of epidemiological weeks reported divided by the total of epidemiological weeks during that period multiplied by 100. Having the financial investments targeting qualification, training, and supervision and the acquisition of supplies and laboratory and computer equipment, the surveillance of influenza was gradually implemented and expanded throughout the country [20].

Surveillance in 2009: pandemic year

When the pandemic of 2009 was announced, in April, the national surveillance of influenza had a structured program in 60 SUs, which facilitated the monitoring of the recommended measures, which, even with shortcomings – problems with the system and dissemination of information – showed an increase in infection by the A/H1N1 2009 virus among other respiratory viruses [21].

During the pandemic, with a sustained transmission in the country declared on August 16, 2009, only cases of SARS were placed under surveillance with notification, hospitalization, and laboratory research according to WHO recommendations. There were changes in the undertaken surveillance that went from a universal notification to a notification of death and SARS cases with laboratory confirmation of pandemic influenza infections [6]. This strategy contributed to the subsequent addition of SARS sentinel surveillance.

The end of the pandemic was declared on August 10, 2010 by the WHO. The worldwide disease activity returned to seasonal levels. In Brazil, the Southern and Southeastern regions were the most affected (66.2 and 9.7 cases/100,000 habitants, respectively), while the incidence of SARS per pandemic influenza was 14.5 cases/100,000 habitants. Children of less than 2 years old (22 cases/100,000 habitants) and young people 20–29 years old (16 cases/100,000 habitants) were the most affected age groups [6]. After stabilizing the epidemiological occurrence of influenza, the management experience acquired through the pandemic event, public awareness for health issues, and WHO recommendations led to governmental understanding of the need to review and adjust the surveillance strategy.

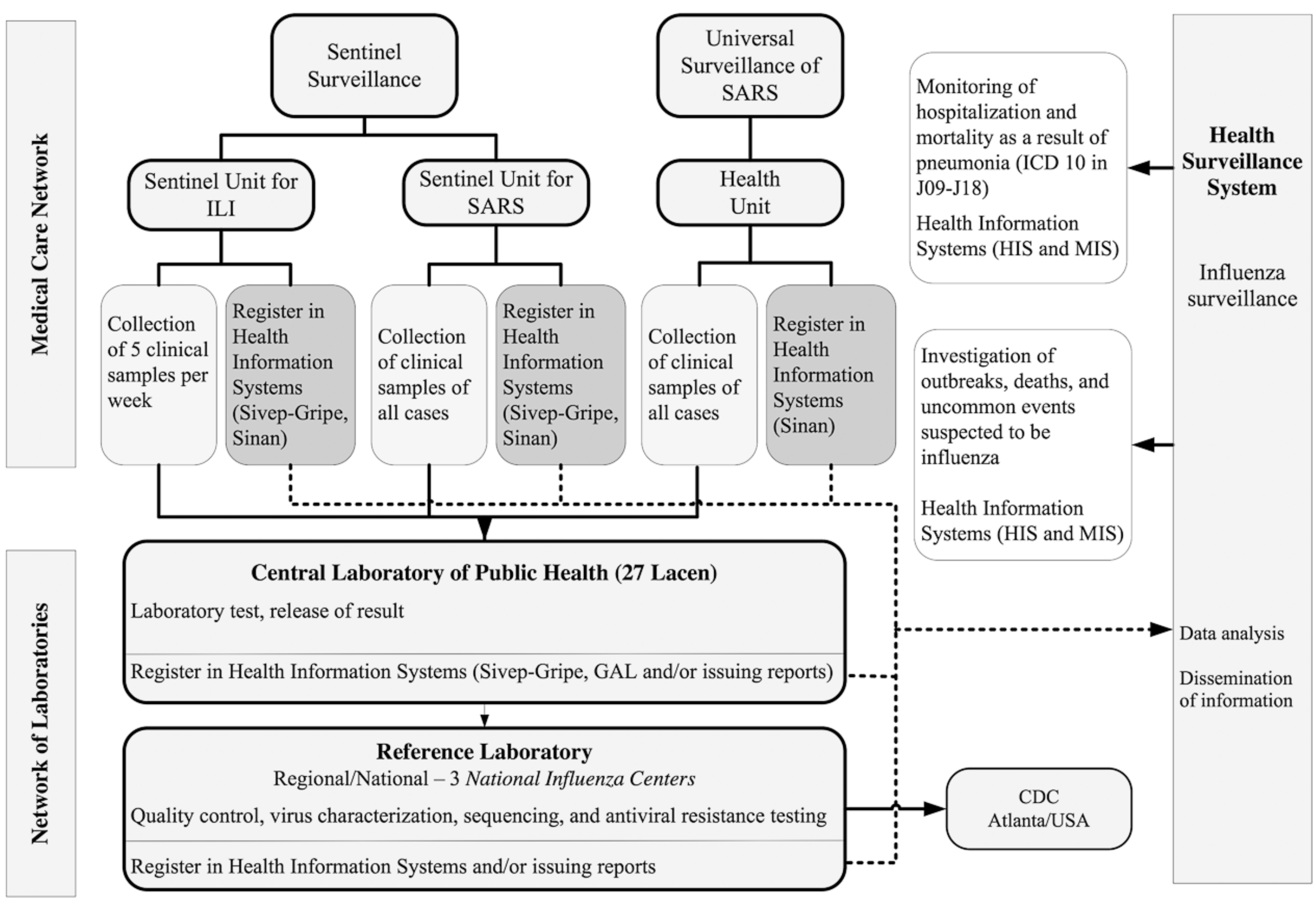
Current surveillance of influenza in Brazil

To improve and expand the surveillance of influenza, a mechanism of financial transfer was established by opt-in from the Brazil's National Health Fund to the Health Fund of the Federal District and Municipalities by GM/MS Ordinance No. 2693 on November 17, 2011 [22]. In this provision, while seeking the minimum representativeness of viral circulation in all Brazilian states, for both severe and mild cases, the capitals and larger municipalities of the metropolitan regions were defined as sentinels, while the SU selection criteria were reviewed. This financial funding incentive for implementation and maintenance measures and strategic public health surveillance services was regulated by Ordinance GM/MS No. 183 on January 30, 2014 [23], which also established the financing, monitoring, and evaluation criteria.

Different strategies are employed in an expanded surveillance of influenza: sentinel surveillance of ILI and SARS; universal surveillance of SARS complemented by the monitoring of hospitalization and death by pneumonia according to the International Classification of Diseases and Related Health Problems (ICD-10) from J9 to J18; and the investigation of outbreaks, deaths, and unusual events of suspected influenza (Figure 1). The case definitions considered were: for ILI, individual with fever (including reported fever) accompanied by cough or sore throat and symptom onset within the last 7 days; and for SARS, individual hospitalized with fever, including reported fever, accompanied by cough, sore throat, and dyspnea as well as the signs of oxygen saturation < 95%, respiratory distress, or increased respiratory rate [6].

The SUs record ILI consultations and aggregate data by epidemiological week (proportion of suspected ILI cases of the total number of consultations) and are committed to collecting five clinical samples per week to reach the minimum of 80% of the weekly goal for material collection. In due course, they register the weekly aggregate in the Sivep-Gripe by gender and age of the ILI consultations and the total number of consultations in the SU in at least 90% of the epidemiological weeks of the year. The GM/MS Ordinance No. 2693, created November 17, 2011, recommends this protocol and that the sentinel surveillance of SARS should be performed in the

Figure1. Flowchart of influenza surveillance in Brazil



intensive care unit with monitoring of the aggregate surveillance for each epidemiological week by the ICD-10 of J09–J18. The aggregated Sivep-Gripe data about the hospitalization registered weekly are from at least 90% of the year's epidemiological weeks. Samples of at least 80% of the notified SARS cases are collected and sent to the Lacen. The registration of the universal (and immediate) notification of SARS is performed in the Influenza module of the of Notifiable Diseases Information System (Sinan), with records of outbreak investigation, deaths, and uncommon events suspected for influenza in the outbreak-specific component (Sinan-NET) and the monitoring of the hospitalization and mortality by the ICD-10 in J09–J18 in the Hospitalization Information System (HIS) and Mortality Information System (MIS), respectively [22].

The SU number increased across the country with the financial transfer strategy adopted in 2011. In 2009, there were 60 active SUs; in March 2014, there were 221. Despite the increase in number, these were not equally distributed across the country: the Northern region had 22 for ILI and 11 for SARS; the Northeastern region had 28 for ILI and 17 for SARS; the Southeastern region had 36 for ILI and 10 for SARS; the Southern region had 40 for ILI and 41 for SARS; and the Midwestern region had 11 for ILI and five for SARS [24].

Laboratorial diagnosis in surveillance

The diagnosis of influenza in Brazil follows the recommended WHO methodology with clinical specimens being tested for influenza A and B by indirect immunofluorescence (IIF) or by classical molecular techniques in real time. Positive samples are selected for virus isolation and genetic and antigenic characterization according to the standardized protocol from the CDC. Isolation of the influenza virus (in eggs or cells derived from the epithelium of the canine kidney – MDCK – Madin-Darby canine kidney cells) is also performed [6].

Diagnosis depends on collected clinical sample quality, appropriate transportation and storage, and following of the biosafety guidelines. The clinical specimens can be obtained by nasal, nasopharyngeal, oral, or combined nasal plus oral swabs, nasopharyngeal aspirate, or a nasal, bronchial, or tracheal wash. The samples should be collected preferably between the third and fifth days after symptom onset (acute disease stage) [9,25] being currently accepted, until the seventh day [6].

Laboratory network

To structure the surveillance of influenza, it was necessary to organize a laboratory diagnosis network, a mandatory infrastructure for the surveillance's efficiency. The National Influenza Diagnostic Network, one of the specific sub-networks that compose the National Epidemiological Surveillance Network, is part of the Sislab and acts under the scope of the Lacen and the three WHO-accredited NIC laboratories.

Clinical samples belonging to ILI and SARS cases are directed to the Lacens of each state for analysis of the detection of respiratory viruses: influenza A and B; parainfluenza 1, 2, and 3; adenovirus; and syncytial virus. All of the samples with inconclusive results, all that are positive for influenza A and 10% of the negative are sent to one of the three NICs for quality control testing. In addition, the positive samples are also subjected to virus characterization, sequencing, and antiviral resistance testing [10].

Current laboratory analyses use molecular biology methodologies such as real-time reverse transcription polymerase chain reaction (RT-PCR). The laboratories that use this methodology direct 100% of samples that are positive for influenza A with no sub-type identification or inconclusive (regardless of the cycle threshold [Ct]) and the positive samples with a Ct ≤ 30 according to seasonality to Reference Laboratories (RL) for complementary analysis. For ILI, 20% of the positive samples from poultry and swine workers and from outbreaks are sent. For SARS, 20% of the positive samples during the seasonal period as well as all of the positive samples from outside that period should be sent. Samples from patients with SARS who are 2–65 years old or have been hospitalized for more than 10 days while taking oseltamivir phosphate should be referred to the RLs. Samples from patients who are 2–65 years old who died of SARS, had a recent history of flu vaccination, or used oseltamivir phosphate up until 2 days after symptom onset should also be sent to the RLs. In the Lacens that do not make a molecular diagnosis, the clinical material should be processed by IIF and the laboratory should send 100% of both the positive samples and the inconclusive ones [6].

Results and virus strains are periodically sent to the CDC for complementary analysis of the circulating viruses in Brazil, these are also forwarded to the WHO's Expert Meetings to support the formulation of a vaccine for the Southern Hemisphere [10].

Vaccination as a preventive measure

Immunization against influenza is recognized as an important control strategy. Used worldwide since 1945, the vaccine composition changes periodically as a result of viral monitoring. Since 1977, the trivalent vaccine has included strains from influenza viruses A/H3N2, A/H1N1 and B. In 2004, with the co-circulation of the Victoria and Yamagata lineages of the influenza B virus, a study was initiated to develop a tetravalent composition [26]. In November 2014, in Brazil, the registration of the tetravalent influenza vaccine (fragmented, inactivated) [27], which consists of two strains of the virus influenza B in addition to the influenza A strains, was approved by ANVISA, the Brazilian Health Surveillance Agency.

Global influenza virological surveillance was an important factor in the WHO's adoption of specific recommendations for the composition of the annual influenza vaccine for the Southern Hemisphere in September 1998. Since then, the vaccine composition recommendation is performed twice yearly, in February for the Northern Hemisphere (from November to April) and in September for the Southern Hemisphere (from May to October). For the equatorial regions, the epidemiological data are considered to indicate the most appropriate composition – that from February or that from September [28].

In Brazil, the implementation of vaccination against influenza preceded the measures of epidemiologic surveillance [11]; in 1999, it was included in the National Immunization Program with annual national campaigns aimed at people who are 65 years old or more [11,13] to protect high-risk groups such as the elderly and chronically ill from influenza complications.

In 2000, the age was reduced to people 60 years old and more. Gradually, other priority groups were also included; for the campaign in 2014, with a target group of 49.6 million people, the indication was for people aged 60 years of age or more, health workers, native indigenous people, children 6 months to 5 years old, pregnant women, women up to 45 days after giving birth, people with chronic non-communicable diseases and other special clinical conditions, and inmates and employees of the prison system. The vaccine is available for people with special clinical conditions with a medical prescription at the Special Immunobiological Reference Centers [29].

Information systems

To follow the surveillance strategies for this disease, online information is used in different HIS: the Sivep-Gripe uses sentinel surveillance data, while the Sinan uses SARS universal surveillance data of aggravated morbidity, mortality, and case fatality [6] in addition to the HIS and MIS. The system Laboratory Environment Manager is also a tool for monitoring and controlling laboratory tests that are essential to the management and monitoring of the programs [30]. FluNet is also relevant since it is the international web-based platform of GISRS for the sharing of data and communication since 1996 [8].

Aspects of flu surveillance in animals

In 1963, WHO developed an informal program to coordinate studies on the relevance of animal influenza to humans that have contributed to the evidence of transmission between species. The importance of these investigations led to the designation of a specific CC for research on the ecology of animal influenza, in Memphis, TN, USA, that remains active today [8].

In 2005, the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) established the OFFLU (OIE/FAO Network of Expertise on Animal Influenza), a global network of information about animal influenza that is available at http://www.offlu.net. OFFLU promotes cooperation between experts in animal and human health in addition to providing support and coordination of worldwide efforts to prevent, detect, and control animal influenza [31,32].

Studies on the human–animal interface have been important both to understanding the role of the animals in the virus transmission chain and surveillance activities, especially those regarding highly pathogenic AI. The influenza A virus is present in many mammalian and avian species. Phylogenetic studies have demonstrated species-specific viral lineages that cause highly contagious infections in animals with a significant economic impact. From the perspective of human health, the highest risk comes from swine and poultry for their role as a source of new flu viruses that are able to cause pandemics. Swine can be infected with viruses of both avian and human origin; therefore, they have a higher capability to promote viral rearrangements [33].

The influenza in poultry produces evident clinical signs (neurological and respiratory problems, limited mobility, edema on the chest and legs, and depression) and high mortality rates [33]. In swine, however, the disease manifests as clinical symptoms that tend to be mild or subclinical with high transmissibility, high morbidity, and low mortality. This may favor the viral circulation without detection; therefore, control measures cannot be implemented to interrupt transmission and dissemination. This may contribute to the maintenance of the circulation of different viral strains and, therefore, rearrangement opportunities [34].

In equine, the disease is caused by two viral subtypes – H7N7 and H3N8 – that can also cross the species barrier and have already been identified in respiratory diseases in dogs, swine, and people due to occupational exposure [33].

The pandemic influenza virus of 2009 was described in both domestic and non-domestic animals, such as in giant pandas in China [35] and swine in Brazil [36,37] and in other countries such as Australia, India, Sri Lanka, Colombia, and Cameroon [38]. Many studies emphasize the importance of knowledge about animal influenza to the disease in humans. However, despite the extensive scientific literature on the ecological and molecular properties of the influenza virus in animals, there is no comprehensive international surveillance system [32,39].

The surveillance of influenza in farm animals is crucial; in Brazil, it is performed by the Ministry of Agriculture, Livestock, and Food Supply (MAPA). Most of the attention is given to the AI because, in addition to the issues regarding its transmission to humans with severe and deadly cases, poultry production is economically relevant and Brazil is a major worldwide producer and exporter of poultry meat. This poultry profile was consolidated in the early 2000s [40], a period of highly pathogenic AI outbreaks [1,2,15,41].

MAPA instituted a national passive surveillance program that supported all suspected AI cases and actively monitored migratory bird sites, as well as commercial and subsistence poultry flocks, and sent material for laboratory diagnosis. This diagnosis follows the OIE regulations, both for the collection and transport (blood, tracheal swab, and cloacal swab) and the employed methodologies, and is performed in the official MAPA network with the National Agricultural Laboratory (Lanagro), Campinas, São Paulo, as the reference laboratory for poultry diseases [42]. To date, no highly pathogenic AI virus has been identified in Brazil; however, several lowly pathogenic virus strains were described by Mota *et al.* (2013) [40], Rajão *et al.* (2013) [36] Araujo *et al.* (2014) [43], among others.

The OIE maintains a list with the mandatory notifiable diseases updated annually. This list includes both AI and equine influenza, but not swine influenza [44]. In addition to the AI, confirmed cases of equine influenza (horses, donkeys and mules) and swine influenza are to be mandatorily notified to MAPA, with registration in the monthly reports, according to the Normative Instruction MAPA No. 50, September 24, 2013 [45].

The use of avian influenza vaccine for poultry is prohibited in Brazil [42]. There is no recommended vaccination for swine according to the National Swine Health Program, instituted by the Normative Instruction MAPA No. 47 on June 18, 2004 [46], although a commercial vaccine is available. The National Equine Health Program instituted by Normative Instruction MAPA No. 17 on May 8, 2008 does not refer vaccination [47]. However, the Service Instruction MAPA No. 17, November 16, 2001 [48] refers to vaccination as a health measure in the occurrence of an equine influenza outbreak. The indication is for primary vaccination with two doses at a 4–6-week interval and a booster every 6 months after that. Foals should be vaccinated after 4 months of age, while competition animals should be vaccinated every 3–4 months [49].

Veterinary surveillance information is registered in the National Animal Health Information System (SIZ), which belongs to the Brazilian System for Surveillance and Veterinary Emergencies (SisBraVet). The MAPA's Department of Animal Health is responsible for the maintenance and management of the SIZ based on the list of the notifiable diseases in Brazil and of the OIE. Data of the World Animal Health Information System (WAHIS) is available on the OIE website via the World Animal Health Information Database (WAHID). The Continental Epidemiological Surveillance System (SivCont), another monitoring tool, was developed in 2004 by the Pan American Foot-and-Mouth Disease Center (Panaftosa), for the logging and analysis of data and information on syndrome surveillance events in which, by the end of 2010, included avian respiratory and neurological syndrome [50].

MAPA monitors the epidemiological situation of avian influenza worldwide and has improved the health measures and requirements in the country's entry points to protect and preserve the health status of the Brazilian poultry flocks [51]. However, there is little knowledge on the circulating influenza viruses in animals in Brazil, especially in swine, and a single infection seems to have become endemic in livestock throughout the country after introduction of the pandemic virus [37].

Considerations

Despite the intention of approaching the structuring of the Brazilian surveillance of influenza, effectiveness studies, system performance, information systems qualification, and integration of surveillance from the aspects of human and animal are issues that require further and deeper analysis. This description has focused on interventions of the official influenza surveillance network – human or animal – through continued and systematic measures as required by epidemiological surveillance while avoiding encompassing the valuable research work conducted by research teams from educational and research institutions on this subject. The approach to the official influenza surveillance network, although brief, does not ignore the importance of the sectors involved in it.

The investment in the improvement of the surveillance of human and animal influenza in Brazil is worth mentioning. Strategic differences should be considered since the surveillance is passive in animals, while the base of epidemiological surveillance of human influenza follows the sentinel model.

Since 2000, the structure has been chiseled according to the epidemiological and political settings, and the system is able to demonstrate the presence and circulation of viruses, even with limitations. The number of SUs and collected samples is small compared to the composition of the Brazilian population as well as its geographical distribution. The positive results of 17% may be due to the patient selection (case definition), adequate collection procedures, storage and transport to the laboratory, and diagnostic technique. These elements are configured as critical points for surveillance and should be improved through supervision and public health service evaluations. It is necessary to improve surveillance, mainly with regard to the representativeness, opportunity, and test positivity, to refine knowledge of the impact of the viruses and increase response capacity of the public health services.

Nelson & Vincent [38] emphasize the biases – of the sample, time, and space – in the surveillance of influenza in humans and swine given that the imbalance of the surveillance activities affects the understanding of viral ecology. The authors state the necessity of intensifying the surveillance of influenza in swine, especially in countries that have large populations of these animals, and with reduced surveillance such as in Brazil, Vietnam, and Russia. The bias issue can be extrapolated to other animal species.

Brazil, a major producer of swine and poultry, needs to improve surveillance and communication among the involved governmental organizations. Due to the characteristics of the disease in swine and to confer a greater representation of the research of circulating viruses, both healthy and unhealthy animals should be considered for sample collections as suggested by Henningson *et al* [34].

It is important to emphasize the necessary investment in the laboratory diagnostic network since the provision of supplies, professional and technical staff, and adequate and appropriate infrastructure are critical to the establishment of new sensitive and effective methodologies. Investing in human resources at different levels of participation is an indisputable factor in the undeniable improvement that it provides to the health services.

Given its high infectivity and dissemination, influenza is a complex health problem that demands exceptional emergency measures even in the event of low lethality. The prevention and control of influenza are impossible without a permanent monitoring of the human and animal influenza viruses. The circulation of the virus in animals can represent a risk for both public health and animal health.

It is necessary to promote studies and surveillance in animals; therefore, the legal instruments of human and animal health should be more objective and consistent within a single health approach. It is essential to improve the interface and the sharing of information as well as to optimize resources among government agencies, to establish information flows, and build friendly platforms and technological ambience (merging, layers of geographic information systems) to provide subsidies for joint decision making.

To maintain the alert regarding influenza, it is also essential to invest in health education – a major task of the public health organizations – as well as the production of disease-related information to provide continuous education to the public as well as to health professionals. Influenza is a permanent worldwide challenge for veterinary and public health authorities.

Acknowledgements

We wish to thank Dr. Wildo Navegantes de Araújo, Professor at University of Brasilia, and Denise Mancini, Technical Analyst of Social Policies at Brazil's Ministry of Health, for their critical reviews.

References

1 Zambon M (2014) Influenza and other emerging respiratory viruses. Medicine 42: 45-51.

2 Jerigan DB, Cox NJ (2013) Human influenza: one health, one world. In: Webster RG, Monto As, Braciale TJ, Lamb RA, editors. Textbook of influenza. 2th edition. Oxford: Wiley Blackwell. 3-19.

3 Cox NJ, Subbarao K (2000) Global epidemiology of influenza: past and present. Annu Rev Med 51: 407-421.

4 Monto AS, Webster RG (2013) Human pandemic: history and lessons learned. In: Webster RG, Monto AS, Braciale TJ, Lamb RA, editors. Textbook of influenza. 2th edititon. Oxford: Wiley Blackwell. 20-33.

5 Potter CW (2001) A history of influenza. J Appl Microbiol 91: 572-579.

6 Brasil. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica (2014) Influenza. In: Guia de Vigilância em Saúde. 1th edition. Brasília: Ministério da Saúde. 13-39.

7 World Health Organization (WHO) (2013) Global epidemiological surveillance standards for influenza. Switzerland: WHO Press 84p.

8 World Health Organization (WHO). Global Influenza Surveillance and Response System (GISRS). Available: http://www.who.int/influenza/gisrs_laboratory/en. Accessed 5 November 2014.

9 Barros FR, Daufenbach LZ, Vicente MG, Soares MS, Siqueira M, Carmo EH (2004) O desafio da influenza: epidemiologia e organização da vigilância no Brasil. Boletim Eletrônico Epidemiológico da Secretaria de Vigilância em Saúde, 19: 197-225.

10 Freitas FTM (2013) Sentinel surveillance of influenza and other respiratory viruses, Brazil, 2000-2010. Braz J Infect Dis 17: 62-68.

11 Luna EJ (2011) Vigilância epidemiológica da influenza no Brasil - onde estamos? In: Kfouri RÁ, Berezin EN, editors. Atualização em vírus respiratórios. 1th edition. São Paulo: Guinom Propaganda & Comunicação. 15-20.

12 Dab W Quenel P, Cohen JM, Hannoun C (1991) A new influenza surveillance system in France - TheIle-de-France GROG.2. Validity of indicators (1984-1989). Eur J Epidemiol 7: 579-587.

13 Forleo-Neto E, Halker E, Santos VJ, Paiva TM, Toniolo-Neto J (2003) Influenza. Rev Soc Bras Med Trop 36: 267-274.

14 Carmo EH. O regulamento sanitário internacional e as oportunidades para fortalecimento do sistema de vigilância em saúde. Recife: Portal DSS Nordeste; 30 abr. 2013. Available:<http://dssbr.org/site/opinioes/o-regulamento-sanitario-internacional-e-as-oportunidades-para-fortalecimento-do-sistema-de-vigilancia-em-saude>. Accessed 29 November 2014.

15 Perdue ML, Swayne DE (2005) Public health risk from avian influenza viruses. Avian Dis 49: 317-327.

16 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Portaria n 33, de 14 de julho de 2005. Inclui doenças à relação de notificação compulsória, define agravos de notificação imediata e a relação dos resultados laboratoriais que devem ser notificados pelos Laboratórios de Referência Nacional ou Regional. Available: http://bvsms.saude.gov.br/bvs/saudelegis/svs/2005/prt0033_14_07_2005.html. Accessed 5 February 2015.

17 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Portaria n 5, de 21 de fevereiro de 2006. Inclui doenças na relação nacional de notificação compulsória, define doenças de notificação imediata, relação dos resultados laboratoriais que devem ser notificados pelos Laboratórios de Referência Nacional ou Regional e normas para notificação de casos. Available: http://bvsms.saude.gov.br/bvs/saudelegis/svs/2006/prt0005_21_02_2006_comp.html. Accessed 5 February 2015.

18 Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria n 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. Available: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2011/prt0104_25_01_2011.html. Accessed 5 February 2015

19 Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria n 1.271, de 6 de junho de 2014. Define a Lista Nacional de Notificação Compulsória de doenças, agravos e eventos de saúde pública nos serviços de saúde públicos e privados em todo o território nacional, nos termos do anexo, e dá outras providências. Available: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt1271_06_06_2014.html. Accessed 5 February 2015.

20 Brasil. Ministério da Saúde (2006) Portaria n 699, de 30 de março de 2006. Regulamenta as Diretrizes Operacionais dos Pactos Pela Vida e de Gestão. Diário Oficial da União, Brasília, 3 abr. p. 49-67. Seção 1. Available: http://www.saude.pr.gov.br/arquivos/File/CIB/LEGIS/PortGM_699_30marco_2006.pdf. Accessed 13 March 2015.

21 Oliveira WK, Carmo EH, Penna GO, Kuchenbecker RS, Santos HB, Araujo WN Malaguti R, Duncan B, Schmidt M; Surveillance Team for the pandemic influenza A (2009) Pandemic H1N1 influenza in Brazil: Analysis of the first 34,506 notified cases of influenza-like illness with severe acute respiratory infection (SARI). Euro Surveill 14: 19382.

22 Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria n 2.693, de 17 de novembro de 2011. Estabelece mecanismo de repasse financeiro do Fundo Nacional de Saúde aos Fundos de Saúde do Distrito Federal e Municípios, por meio do Piso Variável de Vigilância e Promoção da Saúde, para implantação, implementação e fortalecimento da Vigilância Epidemiológica da Influenza. Diário Oficial da União, Brasília, p.81-82, 18 nov. 2011. Seção 1. Republicada no DOU. Brasília, 26 abr 2012. p.37-38. Seção 1.

23 Brasil. Ministério da Saúde. Gabinete do Ministro. Portaria n 183, de 30 de janeiro de 2014. Regulamenta o incentivo financeiro de custeio para implantação e manutenção de ações e serviços públicos estratégicos de vigilância em saúde, previsto no art. 18, inciso I, da Portaria n 1.378/GM/MS, de 9 de julho de 2013, com a definição dos critérios de financiamento, monitoramento e avaliação**.** Diário Oficial da União**,** Brasília, 31 jan 2014. p.59, Seção 1.

24 Brasil.Ministério da Saúde. Secretaria de Vigilância em Saúde. Influenza: monitoramento até a semana epidemiológica 5 de 2014. Boletim epidemiológico. Brasília, DF: Ministério da Saúde, 2014. Available: http://portalsaude.saude.gov.br/images/pdf/2014/maio/28/2boletim-influenza-se05-2014.pdf. Acessed 5 February 2015.

25 WHO (2011) World Health Organization. WHO global influenza surveillance network: manual for the laboratory

diagnosis and virological surveillance of influenza. Geneva: WHO Press 137p.
26 Keitel WA, Neuzil KM, Treanor J (2013) Immunogenicity, efficacy of inactivated/live virus seasonal and pandemic vaccines. In: Webster RG, Monto As, Braciale TJ, Lamb RA, editors. Textbook of influenza. 2th edition. Oxford: Wiley Blackwell. 313-326.
27 Brasil. Agência Nacional de Vigilância Sanitária. Resolução-RE n 4319 de 31 de outubro de 2014.Brasília, DF: Diário Oficial da União de 3 nov 2014.
28 WHO (1998) World Health Organization. Recommendation for the composition of influenza virus vaccines for use in 1999. Wkly Epidemiol Rec 73: 305-308.
29 Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Coordenação-Geral do Programa Nacional de Imunizações.Campanha Nacional de Vacinação Contra a influenza 2014. Informe Técnico. Brasília: Ministério da Saúde, 2014.Available: http://www.sbim.org.br/wp-content/uploads/2014/04/Informe_Campanha_Influenza-_-25_03_2014.pdf. Accessed 13 March 2015.
30 Jesus R, Guimarães RP, Bergamo R, Santos LCF, Matta ASD, Paula-Júnior FJ (2013) Sistema Gerenciador de Ambiente Laboratorial: relato de experiência de uma ferramenta transformadora para a gestão laboratorial e vigilância em saúde. Epidemiol Serv Saúde 22: 525-529.
31 Edwards S (2006) OFFLU network on avian influenza. Emerg Infect Diseases 12: 1287-1288.
32 Vincent A, Awada L, Brown I, Chen H, Claes F, Dauphin G, Donis R, Culhane M, Hamilton K, LewisN, Mumford E, Nguyen T, Parchariyanon S, Pasick J, Pavade G, Pereda A, Peiris M, Saito T, Swenson S, Van Reeth K, Webby R, Wong F, Ciacci-Zanella J (2014) Review of influenza A virus in swine worldwide: a call for increased surveillance and research. Zoonoses Public Health 61: 4-17.
33 Alexander DJ, Brown IH (2000) Recent zoonoses caused by influenza A viruses. Rev Sci Tech OIE 19: 197-225.
34 Henningson JN, Rajão DS, Kitikoon P, Lorussoc A, Culhaned MR, Lewise NS, Anderson TK, Vincent AL (2015) Comparative virulence of wild-type H1N1pdm09 influenza A isolates in swine. Vet Microbiol 176: 40-49.
35 Li D, Zhu L, Cui H, Ling S, Fan S, Yu Z, Zhou Y, Wang T, Qian J, Xia X, Xu Z, Gao Y, Wang C (2014) Influenza A (H1N1)pdm09 virus infection in giant pandas, China. Emerg Infect Dis 20: 480-483.
36 Rajão DS, Costa AT, Brasil BS, Del Puerto HL, Oliveira FG, Alves F, Braz GF, Reis JK, Guedes RM, Lobato ZI, Leite RC (2013) Genetic characterization of influenza virus circulating in Brazilian pigs during 2009 and 2010 reveals a high prevalence of the pandemic H1N1 subtype**.** Influenza Other Respir Viruses 7: 783-790.
37 Schaefer R, Zanella JRC, Brentano L, Vincent AL, Ritterbusch GA, Silveira S, Caron, L, Mores N (2011) Isolation and characterization of a pandemic H1N1 influenza virus in pigs in Brazil. Pesqui Vet Bras 31: 761-767.
38 Nelson MI, Vincent AL (2015) Reverse zoonosis of influenza to swine: new perspectives on the human-animal interface. Trends Microbiol 23: 142-153.
39 Webster RG (2002) The importance of animal influenza for human disease. Vaccine 20: S16-S20.
40 Mota MA, Lima FA, Oliveira PFN, Guimarães MP (2013) Ações de vigilância para influenza aviária desenvolvida no Brasil, no período de 2004 e 2007. Arq Bras Med Vet Zootec 65: 1265-1273.
41 WHO (2005) World Health Organization. Evolution of H5N1 Avian Influenza Viruses in Asia. Emerg Infect Diseases 11: 1515-1521.
42 Brasil. Ministério da Agricultura, Pecuária e Abastecimento. Secretaria de Defesa Agropecuária. Departamento de Saúde Animal. Plano de contingência para influenza aviária e doença de Newcastle. 2013 a. 59p. Available: <http://www.agricultura.gov.br/arq_editor/file/PNSA/Plano%20de%20Conting%C3%AAncia%20-%20Vers%C3%A3o%201_4.pdf>. Accessed 11 October 2014.
43 Araujo J, Azevedo-Júnior SM, Gaidet N, Hurtado RF, Walker D, Thomazelli LM, Ometto T, Seixas MMM, Rodrigues R, Galindo DB, Silva ACS, Rodrigues AMM, Bomfim LL, Mota MA, Larrazábal ME, Branco JO, Serafini P, Neto IS, Franks J, Webby RJ, Webster RG, Durigon EL (2014) Avian Influenza Virus (H11N9) in Migratory Shorebirds Wintering in the Amazon Region, Brazil. Plos One 9: e110141.
44 World Organization for Animal Health (OIE). OIE listed disease, 2014. Available: <http://www.oie.int/animal-health-in-the-world/oie-listed-diseases-2014>. Accessed 15 December 2014.
45 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Instrução Normativa n 50, de 24 de Setembro de 2013. Estabelece a relação das doenças de notificação obrigatória ao serviço veterinário oficial. Brasília, DF: Diário Oficial da União 25 Set 2013, p47. Seção 1.
46 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Secretaria de Defesa Agropecuária. Instrução Normativa n 47, de 18 de junho de 2004. Aprova o Regulamento Técnico de Programa Nacional de Sanidade Suídea - PNSS, na forma do anexo a esta Instrução Normativa. Brasília, DF: Diário Oficial da União de 23 jun 2004, p64. Seção 1. Available: http://extranet.agricultura.gov.br/sislegis-consulta/consultarLegislacao.do?operacao=visualizar&id=7938. Accessed 15 December 2014.
47 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Secretaria de Defesa Agropecuária. Instrução Normativa n 17, de 8 de maio de 2008. Institui o Programa Nacional de Sanidade dos Eqüídeos **-** PNSE, no âmbito do Ministério da Agricultura, Pecuária e Abastecimento. Brasília, DF:Diário Oficial da União de 9 mai 2008, p27.Seção 1. Available at: http://extranet.agricultura.gov.br/sislegis-consulta/consultarLegislacao.do?operacao=visualizar&id=18609. Accessed 15 December 2014.
48 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Secretaria de Defesa Agropecuária. Departamento de Defesa Animal. Instrução de Serviço n 17, de 16 de novembro de 2001. Brasília, 2001.
49 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Sanidade Animal. Calendário de vacinação. 2014. Available: <http://www.agricultura.gov.br/animal/sanidade-animal/calendario-de-vacinacao>. Accessed 11 October 2014.
50 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Secretaria de Defesa Agropecuária. Manual do Sistema Nacional de Informação Zoossanitária – SIZ. 2nd edition. Brasília: Ministério da Agricultura 2013. 40p. Available:<http://www.agricultura.gov.br/arq_editor/file/Manual%20SIZ/Manual_SIZ_09_12_2013.pdf>. Accessed 11 October 2014.
51 Brasil.Ministério da Agricultura, Pecuária e Abastecimento. Mapa monitora situação da gripe aviária pelo mundo. Assessoria de Comunicação Social. Notícias, 11 fev 2015.

Gripe Aviária. Available:http://www.agricultura.gov.br/comunicacao/noticias/2015/02/mapa-monitora-situacao-da-gripe-aviaria-pelo-mundo. Accessed 4 de March 2015.

Corresponding author
Ligia Cantarino
Faculdade de Agronomia e Medicina Veterinária
Universidade de Brasília – UnB
Campus Darcy Ribeiro, Instituto Central de Ciências, Caixa Postal 4508, 70.910-900 - Brasília - DF - Brasil
Phone: + 55 61 31077565
Fax: + 55 61 31077118
Email: ligiacantarino@unb.br

Conflict of interests: No conflict of interests is declared.