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Evolutionary Pattern of Reemerging Influenza B/Victoria Lineage Viruses in São Paulo, Brazil, 1996–2012: Implications for Vaccine Composition Strategy

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Since the 1980s, 2 antigenically distinct influenza B lineages have cocirculated in the world: B/Victoria/2/87 (first appeared in the 1980s) and B/Yamagata/16/88 (became predominant in the 1990s). B/Victoria/2/87 isolates were geographically restricted to eastern Asia during 1991–2000. During 2000–2001 and 2001–2002, B/Victoria/2/87 isolates reemerged in North America, Europe, and South America, and then spread globally. During influenza virus surveillance, season 2002, an outbreak of acute respiratory illness, which quickly spread among the population, has been notified by public health authorities living in Araraquara, São Paulo, Brazil. Instituto Adolfo Lutz and Secretariat of Health of São Paulo state teams initiate an investigation towards to describe the pattern of infection in this population temporally and by age and to characterize the strains by virus isolation and hemagglutination inhibition assay. The outbreak lasted approximately 10 weeks; many cases occurred between mid-August and mid-September. Children younger than 13 years were the most affected; the elderly were mostly immune to infection. Analysis of the clinical respiratory samples helped in identifying the B/Hong Kong/330/2001 and B/Brisbane/32/2002 subtypes—recent variants of B/Victoria/02/88, a lineage restricted to Southeast Asia until 2001. The Araraquara outbreak confirms the reemergence of the B/Victoria viruses in South America and highlights the importance of monitoring local circulating strains, especially in light of the absence of cross-protection between antigenically distinct influenza lineages. Based on influenza virus surveillance, public health authorities worldwide should decide whether trivalent vaccines or quadrivalent vaccines (containing both influenza virus B lineages) are to be used in each country. ***J. Med. Virol. 85:1983–1989, 2013.***

KEY WORDS: Araraquara; B/Victoria lineage; outbreak; surveillance; evolution; vaccine composition

INTRODUCTION

Influenza is a highly contagious acute respiratory viral infection transmitted by RNA viruses of the family *Orthomyxoviridae*. Incubation usually lasts from 1 to 4 days, with human-to-human transmission typically occurring through airborne aerosols produced by infected individuals who cough or sneeze, or by direct contact with nasal secretions or contaminated surfaces [Cox and Bender, 1995]. Viral shedding generally starts 1 day prior to the onset of symptoms, which commonly include fever associated with chills, sore throat, headache, muscular aches, and coughs,

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although asymptomatic individuals may also be contagious.

Although morbidity is high among children and young adults, serious influenza-related complications such as pneumonia, and higher hospitalization and mortality rates have been reported more frequently among children younger than 1 year and the elderly (over 65 years) [Ellis and Zambon, 2002]. However, influenza morbidity and mortality can vary widely from year to year, depending on the strains that are circulating and the corresponding immunity of the population. For example, of the three main influenza virus types (A–C), influenza A viruses have been associated with higher rates of influenza-related complications and mortality. Both influenza A and B viruses undergo antigenic drift, and influenza A virus also presents antigenic shifts resulting from genetic reassortment between different subtypes [Cox and Bender, 1995]. With much slower rates of antigenic change and predominantly only two antigenically distinct virus lineages circulating since the 1980s, influenza B viruses have been, in turn, associated with milder epidemic seasons. On the other hand, reassortment of influenza B viruses has been observed between cocirculating influenza B virus strains of different lineages [Yamashita et al., 1988; Rota et al., 1992; Lindstrom et al., 1999; McCullers et al., 1999; Shaw et al., 2002; Chi et al., 2003; Xu et al., 2004; Tsai et al., 2006].

In August 2002, the Division of Infectious Respiratory Diseases of the epidemiological surveillance centre "Professor Alexandre Uranjac," located in São Paulo (Brazil) was informed by the regional health authorities of an increase in the number of medical consultations in the basic health and first-aid units in Araraquara district. Patients complained of fever and gastrointestinal and respiratory symptoms, which were described by local physicians as resembling a mild-to-moderate influenza-like viral infection. The disease quickly spread among the population in schools, working facilities, and homes, but there was no increase either in hospitalization or death rates. The aim of the present study was to investigate the occurrence of the outbreak to confirm the increased morbidity rates reported by the local health authorities and to describe the pattern of infection in this population temporally and by age. Additionally, the isolation and characterization of the infecting viral pathogen were also carried out towards to contribute with possible control measures.

MATERIALS AND METHODS

The study was conducted in the city of Araraquara (South-eastern Brazil), located 273 km from the capital of the state, São Paulo. Araraquara is characterized by a subtropical climate with mild winters. In 2002, it had a population of 174,380 inhabitants and a demographic density of approximately 172 habitants per square km. Facing significant concern by local health authorities, 1 researcher from the Respiratory Virus Laboratory and 3 nurses working in the Epidemic Surveillance Center of the State Secretariat of Health, São Paulo, SP went to Araraquara city in order to investigate the epidemiologic scenarios in loco. Based on physician clinical data analysis by the Special Health Service team, children and young adults were found to be the most affected age groups. The medical records from the following health and first-aid units in the city were inspected for the identification of cases: 3 hospitals, 1 municipal first-aid unit, 4 units of the Family Health Program, 13 Municipal Health Centres, and 1 Special Health Service, which was in charge of the epidemiological vigilance in the city and actively examined virological specimens on a daily basis in private hospitals and municipal first aid centers. Suspected cases were monitored by active case finding from medical records, establishment of case definition by collecting oropharyngeal wash samples from those individuals in the acute phase of infection (maximum 3 days after the onset of symptoms), and weekly monitoring of visits taking into account the definition of suspected cases. Cases were defined as those seeking medical evaluation with the following symptoms: high fever, cough, migraine, and sore throat, with or without gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal pain). No individuals were excluded based on age or vaccination status (namely, whether or not they had been previously vaccinated against influenza). In 1 case, a paired serum sample corresponding to the acute and convalescent disease period was collected in addition to the oropharyngeal wash. Respiratory samples were collected under verbal parental consent. This investigation followed the Adolfo Lutz Institute mission towards influenza virus surveillance coordinated by Ministry of Health of Brazil and the World Health Organization. All samples were sent to the Respiratory Virus Laboratory of the Adolfo Lutz Institute for processing and diagnosis.

Viral Isolation

The respiratory specimens were inoculated into MDCK (dog kidney), Vero (African green monkey kidney), and Hep-2 (human larynx carcinoma) cell cultures as previously described [Takimoto et al., 1991]. Isolated viruses were then identified with indirect immunofluorescence assays by using monoclonal antibodies from Panel 1 Viral Screening and Identification Kit (Light Diagnostics, Chemicon, Temecula, CA) [Paiva et al., 2000]. Subtype characterization was carried out by hemagglutination-inhibition test as described in the kit manual using the WHO Influenza reagent kit for identification of influenza isolates, produced and distributed by WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza in the American Continent (CDC, USA).

Hemagglutination Inhibition Test

Sera were inactivated by heating at 56°C for 30 min, and the nonspecific inhibitors of hemagglutination were destroyed with receptor-destroying enzyme just prior to titration. Paired serum samples were tested by hemagglutination/inhibition for antibodies against influenza virus A (H1N1) and (H3N2) subtypes and influenza virus B/Victoria/2/87, B/Victoria/504/2000, B/Victoria/330/2001 strain reference antigens provided by the World Health Organization (WHO) kit. Titration of hemagglutination/inhibition antibodies was performed in U-shaped, 96-well microplates by a standard method with four units of virus and 0.5% red blood cells [Palmer et al., 1975; Paiva et al., 2001].

RESULTS

A total of 3,783 cases were identified by the Municipal Epidemic Surveillance from July to September 2002, with an average of 50 daily cases during this period. As shown in Figure 1, the outbreak lasted approximately 10 weeks, with more number of cases observed between mid-August and mid-September, and the major epidemic peak occurring in the first week of September (September 6, 2002). Figure 2 shows the age distribution of patients. Young children (aged 1–12 years) were the most affected, with incidence gradually decreasing with age.

Influenza B virus was isolated in 5 oropharyngeal samples from a total of 14 investigated samples. Of these, 4 were antigenically characterized as belonging to the B/Hong Kong/330/2001 lineage, and 1 sample was characterized with a Victoria lineage that was first identified in Australia and named B/Brisbane/32/2002. From those cases, it was possible to collected paired serum samples, in addition to the oropharyngeal washes, whereby the seroconversion to B/Victoria lineage was demonstrated.

DISCUSSION

According to the Epidemic Surveillance Center of Araraquara (São Paulo), an influenza outbreak such as the one presently described, had not been observed in this city since 1991. The 2002 outbreak led to social disruption, including school and work absenteeism, and a high number of medical appointments. The results of the virus detection assays conducted on the paired serum samples confirmed the occurrence of influenza B infections. Since the 1980s, two antigenically distinct lineages of influenza B viruses have cocirculated in the world: the B/Victoria/2/87 lineage (which first appeared in the 1980s) and the B/Yamagata/16/88 lineage (which became the predominant lineage in the 1990s) [Higgins and Sharp, 1989; Shaw et al., 2002]. The B/Victoria/2/87 isolates were geographically restricted to eastern Asia from 1991 to 2000. However, during the 2000–2001 and 2001–2002 seasons, B/Victoria/2/87 isolates reemerged in North America, Europe, and South America, and then spread globally [Hampson, 2002; Paget et al., 2002; Paiva et al., 2002; Shaw et al., 2002;

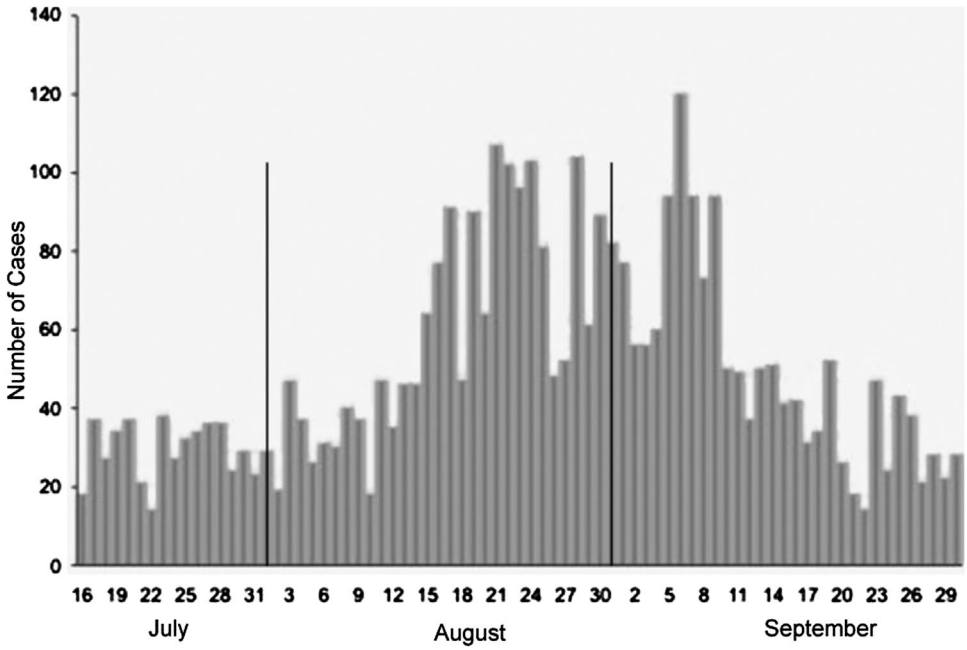


Figure 1. Temporal distribution of the number of influenza cases (as based on corresponding medical appointment dates) in the first-aid clinic of Araraquara (Sao Paulo, Brazil) in the period from July 16 to September 30, 2002.

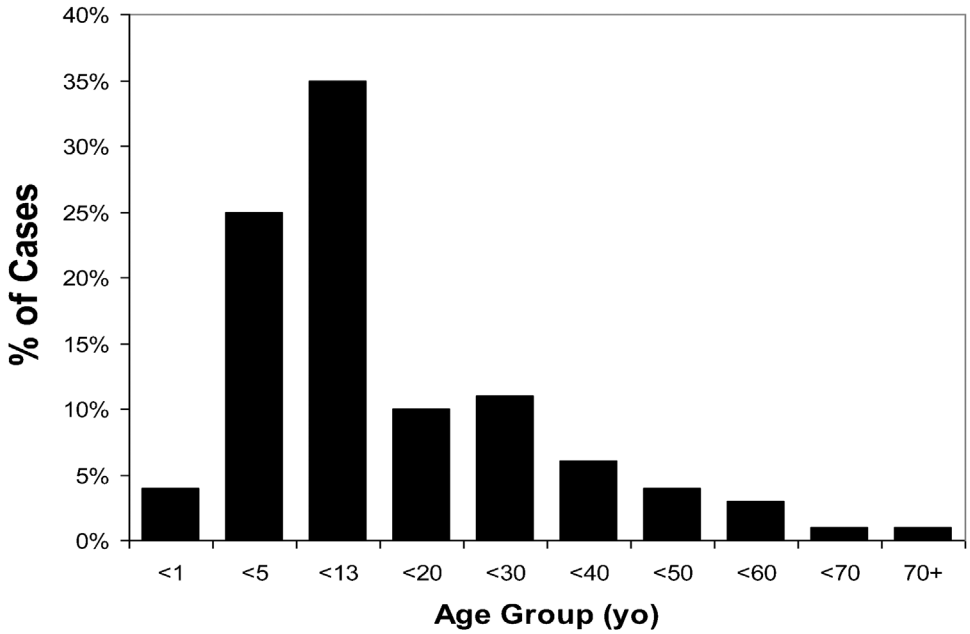


Figure 2. Distribution of patients in Araraquara by age from July to September 2002.

Ansaldi et al., 2003; Motta et al., 2006]. The cocirculation of both the Victoria and Yamagata lineages was reported during the 2001–2002 season [Ellis and Zambon, 2002; Ansaldi et al., 2003], with the influenza B reassortants presenting the Victoria lineage of hemagglutinin and the Yamagata lineage of neuraminidase, observed since February 2002 [Yamashita et al., 1988; Ellis and Zambon, 2002; Paget et al., 2002]. In the clinical respiratory samples from Araraquara, the B/Hong Kong/330/2001 lineage—a recent variant of B/Victoria/02/88—was identified. This variant was first detected outside Asia (Hawaii) in May 2001, from where it was believed to have spread to other continents (Fig. 3). Another influenza B variant, known as B/Brisbane/32/2002, and previously detected in Oceania and in the Brazilian Federal District, was also detected in the Araraquara outbreak. In Brazil, B/Hong Kong/330/2001 isolates have been detected in the southern, southeastern, central eastern, and northern regions, whereas the variants B/Hong Kong/1351/2002, B/Sichuan/379/99, B/Shizuoka/5/2001, and A/Panama/2007/99-like were

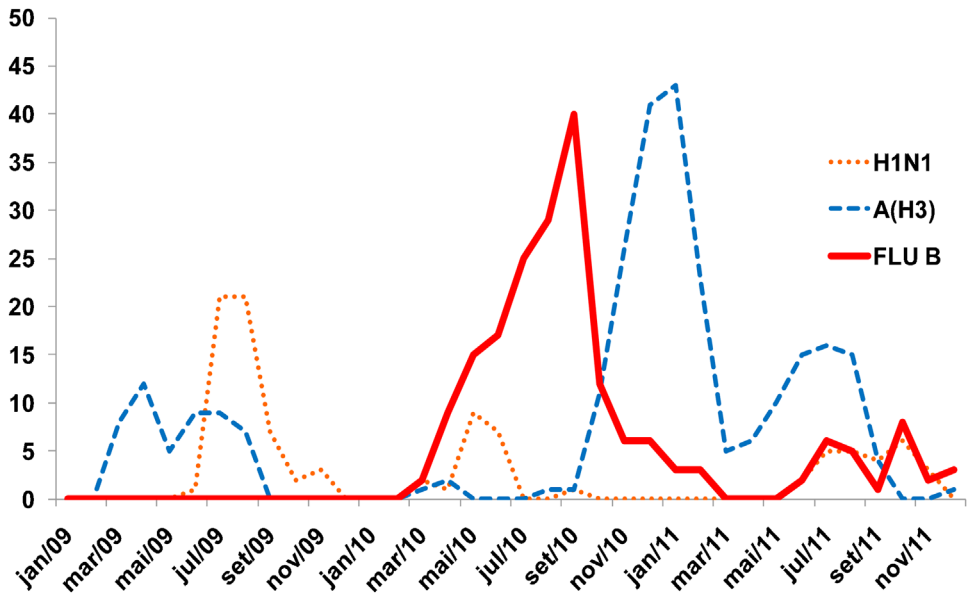


Figure 3. Influenza virus seasonality post-pandemic period in São Paulo. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jmv]

identified in the southeastern and central eastern regions of the country [Paiva et al., 2003].

The analysis of cases by age (Fig. 2) revealed that the elderly were mostly immune to infection, possibly as a result of the presence of antibodies against the B/Victoria/02/88 lineage, as this strain was reported to have circulated globally in 1991 [Nakagawa et al., 2000]. Influenza outbreaks were also identified in neighbouring cities (Iacanga and Américo Brasiliense) that were close to the Araraquara district in September 2002. The outbreak was confirmed by serological tests performed in seven paired serum samples sent to the Respiratory Virus Laboratory, with the first sample collection on September 13, in order to investigate an outbreak of respiratory disease. During July 2002, Iacanga hosted a music festival. From the seven paired serum samples investigated, five demonstrated B/Victoria lineage seroconversion, one was identified as H3N2 influenza strain, and one was identified as H1N1 influenza strain. Similarly, seven paired serum samples, collected from patients living in Américo Brasiliense, with the first sample collection on September 25, were sent to the laboratory in order to investigate an outbreak of respiratory disease. Of these, six seroconverted to the B/Victoria lineage. Clinical specimens obtained by oropharyngeal washes from patients living in Araraquara, in order to perform virus isolation, were collected on October 3, 2002.

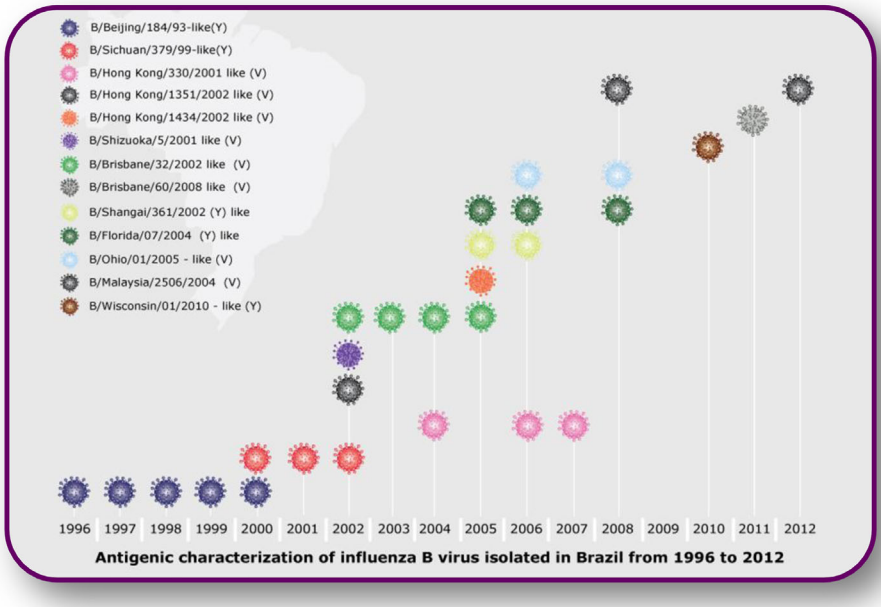
In contrast to the influenza season of 2002, influenza B isolates decreased significantly in the center east, northeast, and northern regions of Brazil during the influenza virus surveillance season in 2003, with the identification of influenza virus B/Brisbane/32/2002-like, a minor variant of B/Hong Kong/330/2001 (CDC communication), in the São Paulo state. This may have occurred as a result of the immunity against the B variants acquired in the 2002 outbreak, and the updated vaccine composition by the new influenza B/Victoria lineage, as well as the immunity of the elderly against the B/Victoria/02/87 lineage [Paiva et al., 2002]. The 2002 outbreak in Araraquara further confirmed the reemergence of the B/Victoria viruses in South America, and stressed the importance of continuous monitoring of suspected influenza cases. Monitoring and reporting measures were, therefore, recommended to the regional health authorities as a means to prevent and control the potential spread of new outbreaks. Continuous viral surveillance is also necessary in light of the antigenic differences in the influenza B virus lineages, as antibodies produced against these two lineages showed no cross-protection [Lindstrom et al., 1999; Rota et al., 1990], and only 1 influenza B component is included in the influenza vaccine. In fact, B/Victoria group strains were not detected in the conventional hemagglutination/inhibition test with ferret serum for the B/Yamagata group strains [World Health Organization, 2002]. The B/Victoria lineage reemergence globally in the 2001–2002 season lead to the World Health Organization recommending B/Hong Kong/330/01 (a representative B/Victoria lineage) for the vaccine strain for both the Northern and Southern Hemispheres in the 2002–2003 seasons [World Health Organization, 2002]. As influenza B/Victoria lineage detection is undertaken by the surveillance activities of the National Influenza Network, sponsored by the Brazilian Ministry of Health, it was possible to monitor influenza virus type B lineages. The cocirculation of the two influenza B virus lineages has been unpredictable serves to highlight the important task of the Global Influenza Surveillance Network towards preventable disease strategies.

A period of 12 years of influenza B virus surveillance demonstrates the pattern of circulation of the 2 influenza B/lineages; influenza B/Victoria lineage reemerged during influenza season 2002 and predominated in Brazil during the 2003, 2004, 2007, 2010, 2011, and early 2012 influenza seasons. In contrast, the cocirculation of the two influenza B/lineages was demonstrated during the 2002, 2005, 2006, and 2008 influenza seasons, as shown in Table I. This study highlights the importance of monitoring local circulating strains, especially in light of the absence of cross-protection between antigenically distinct B influenza lineages (Fig. 3). The follow up of the Influenza B/Victoria strain lineage evolution since its

TABLE I. Mismatch Between Influenza B/Yamagata Circulation, in Brazil, and Vaccine Composition, B/Victoria lineage, to Be Used in the South Hemisphere Influenza Season 2010

Year	Influenza B lineages	South hemisphere vaccine composition
1996	Yamagata	B/Beijing/184/93-like (Y)
2001		B/Sichuan/379/99-like (Y)
2002	Victoria/Yamagata	B/Sichuan/379/99-like (Y)
2003	Victoria	B/Hong Kong/330/2001 like (V)
2004	Victoria	B/Hong Kong/330/2001 like (V)
2005	Victoria/Yamagata	B/Shangai/361/2002 like (Y)
2006	Victoria/Yamagata	B/Malaysia/2506/2004 (V)
2007	Victoria	B/Malaysia/2506/2004 (V)
2008	Victoria/Yamagata	B/Florida/4/2006-like (Y)
2010	Yamagata	B/Brisbane/60/2008-like (V)
2011	Victoria	B/Brisbane/60/2008-like (V)
2012	Victoria	B/Brisbane/60/2008-like (V)

TABLE II. Influenza B Lineages Circulating in Brazil, 1996–2012



reemergence in 2001 contributes to public health authority discussions regarding quadrivalent vaccine composition. A single lineage of influenza B predominated globally between 1990 and 1997 (Yamagata lineage). Now, there is an alternating dominance of two B lineages (Yamagata and Victoria lineages; Table II). This new pattern of influenza B virus circulation worldwide highlights the difficulty in predicting the global dominance pattern in recent years. The present study provides information about influenza B/Victoria lineage evolution for Brazil in the Southern Hemisphere, and clarifies why vaccine match proportion decreased unexpectedly for influenza B viruses from 100% to 54%, concomitant with the implementation of Southern Hemisphere recommendations, a decrease that appears to be a coincidence related to changes in virus dynamics. The present study clearly demonstrates the mismatch between influenza B/Yamagata lineage circulating in Brazil and the vaccine composition containing influenza B/Victoria lineage during influenza virus season 2010 (Table II). Aiming to resolve this new influenza B virus evolution scenario, it has been suggested that the annual vaccine be updated to include representative antigens for both B lineages, as the development of quadrivalent influenza vaccines is an important step in reducing the burden of influenza on the population. Another strategy would create an annual vaccine by systematically alternating inclusion of the two lineages (Yamagata in the first year and Victoria in the next) in order to provide some residual protection against both lineages of B viruses [Roos, 2009; Richard et al., 2010]. Finally, this study emphasizes the importance of the global influenza virus surveillance.

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