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Influenza a Virus (H1N1)

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Abstract

Influenza is a contagious respiratory disease and its main etiological agent is the Influenza A virus, which is responsible for several pandemics. Viruses belonging to this genus are constantly mutable beyond being difficult to control and eradicate. The H1N1 flu is one of the most frequent types and in this year it has already killed about 70 people. Currently Brazil produces a vaccine and distributes it in annual campaigns to avoid epidemic outbreaks of this disease. This vaccine presents in its formulation mercury-based excipients, generating several debates around the theme. For this reason this study aims to present a recent content of H1N1 history.

Keywords: Vaccine; Influenza A virus; H1N1; Thimerosal

Introduction

Influenza is a contagious respiratory disease caused by the influenza virus. Characterized by irregular inflammatory changes in the lungs it is largely confined to the alveolar septa and pulmonary interstices. However, in some cases it may be a severe infection of the lower and upper respiratory tract [1]. The Influenza virus belongs to the family *Orthomyxoviridae*, which presents five inserted genera: *Influenza virus* A, B, C, *Thogotovirus* and *Isa virus* (International Committee of Taxonomy of Virus, 2010). Among them, genus A is responsible for major pandemic events and seasonal epidemics. The viruses of this lineage are conceptualized and promoted by the great variety of hosts, ranging from mammals to birds [2]. The others, B and C are restricted in human infections and are less frequent (World Health Organization, 2014). Influenza A virus, due to its existing mutations, it is subdivided according to antigenic properties of two glycoproteins present on its viral surface, which are Hemagglutinin (HA) and Neuraminidase (NA). Currently 18 varieties of HA (H1 - H18) are known and 11 from NA (N1-N11) [3]. Most of this variety is not viable in nature, therefore three HA subtypes has been predominant (H1, H2 and H3); Nevertheless, other subtypes occasionally affect humans (World Health Organization, 2014), for example H7N9 avian origin. The H7N9 subtype, until March 2013, had not been detected in another animal or infected humans when the first cases of human infection in China were detected (Ministry of Health, 2015).

According to the known viral structure, the genome of Influenza A is single stranded ribonucleic acid (RNA) of negative polarity, presenting from 890 to 2341 nucleotides in length that can encode up to 13 proteins [2]. Among these 13 proteins, the glycoproteins HA and NA are said to be the main antigens and because of this they are part of the vaccine composition against Influenza A, which in Brazil is made available by Butantan Institute [4]. When speaking of the composition of the vaccine, it is

obligatorily modified annually due to the great variety of mutations that this virus presents. This explain why it is necessary the annual campaigns.

Even before annual campaigns, vaccination is the best cost-benefit and it has been responsible for controlling the spread of various diseases such as measles, polio, diphtheria, pertussis, tetanus and tuberculosis, although viral infections such as those caused by Influenza A are difficult to control. This occurs because of the constant mutations of the virus and also by social, cultural, economic and occupational conditions [5]. Other factors that affect vaccination campaigns are the side effects reported by some individuals, and also the use of excipients that may present toxicity and anaphylaxis, which frighten the population [6]. Therefore, obtaining knowledge about virus spreading, history of epidemics, diagnosis, symptoms, vaccination and possible side effects, as well as the use of excipients in vaccine formulations is very important for the knowledge to be passed in a correct, informed and accurate way. Thus, the objective of this work is to present a recent literature review on the H1N1 flu.

Virus History

Viruses generally have a wide mutant capacity and the viruses of the genus Influenza A as stated above are the main cause of the pandemics, which underwent several mutations that ensured the adaptation of this microorganism as well as its dissemination. The first record of the H1N1 virus was in 1907, when it was isolated from a frozen man in Alaska. However, the first record of pandemics associated with the virus was in 1918, when it became known as the Spanish Flu reaching 50% of the world population due to high virus spread and virulence. In 1919 the end of the pandemic was determined; despite of the virus has remained for 38 years undergoing several mutations without causing damage to health. In 1957 the Asian flu occurred and in about six months led to one million deaths [7]. When the virus was isolated, it presented three more genes than those present in the 1918 H1N1, obtained from an avian virus, which contained Neuraminidase, Hemagglutinin and a PB1 viral polymerase, making it highly virulent again, being called H2N2. These new constituents have increased the potential for immune system evasion, leading to influenza outbreaks for the next eleven years [8].

In 1966, the virus resurfaced with two new genes, being called H3N2, because it had another Hemagglutinin and another PB1 viral polymerase, causing a new pandemic, that of Hong Kong. As early as 1977, the H1N1 virus resurfaced and caused the Russian Influenza pandemic, which in turn is the virus identical to that of 1918 without gene acquisition. Since then the viruses that most frequently cause infections are H1N1 and H3N2.

In March 2009, the epidemic of influenza A H1N1 began in Mexico. Then the World Health Organization, on April 24 of the same year expanded the alert about the risk of a pandemic, for already presenting more than ten thousand cases called Swine flu [7,9,10].

Influenza A(H1N1) in Brazil

Epidemiology

Disease surveillance is done through two sentinel groups, the Gripal Syndrome (GS), which reports cases of individuals with fever, accompanied by cough or pain relief with onset of symptoms around seven days, and the Severe Acute Respiratory Syndrome (SARS), which are individuals hospitalized in an Intensive Care Unit (ICU) with fever, cough or sore throat, dyspnea and respiratory distress. Sentinel groups collect five weekly samples per unit. So far, 13,775 samples were collected by GS sentinels, of which 74.3% were processed and 11.8% positive for influenza, of which 79.2% were predominantly influenza A (H1N1), 12.2% were positive for influenza B, 7% were non-sub typed influenza A and 1.5% were influenza A (H3N2). The regions most affected by H1N1 are the South and Southeast and the most affected age group corresponds to individuals from 10 years of age.

The SRAG Sentinel Group has at the moment collected 2,366 samples, of which 82.1% have been processed and updated, 18.16% have been positive for influenza, 85% of which correspond to influenza A (H1N1), 10.7% for influenza A Non-sub typed, 3.2% for influenza B and 1.2% presented positive for influenza A (H3N2). However, the epidemiology through compulsory notifications in Brazil presents about 47,500 cases of SARS, where 78.2% of the samples collected in hospitals were processed. From the samples processed, 29.8% were positive for influenza, presenting 89.6% of cases positive for influenza A (H1N1), 6.4% for non-sub typed influenza A, 3.6% for influenza B and 0.4% of cases related to influenza A (H3N2). In these cases the median age was 40 years, presenting a Southeast region with the highest number of cases of SARS caused by Influenza virus. These data correspond to the five weekly samples obtained since the first week of 2016.

The beginning of the pandemic observed by the Ministry of Health in Brazil was on June 15, 2009, when there was a virus contamination abroad or through direct contact with a host. The World Health Organization (WHO) has created a national preventive program for vaccination against the virus. Virus prevention is divided into two phases, the containment phase, where there are surveillance actions at airports, border crossing points and a phase of mitigation or promotion of products with the aim of reducing the intensity of the disease [7].

The Ministry of Health has developed a course of preparation of professionals, with the purpose of making them multipliers in knowledge in their territories, knowledge about the disease [7]. The year 2016 was an atypical year due to an anticipation of viral infections caused by the H1N1 virus. Therefore, vaccination campaigns occurred at the end of May, obeying the immunological window of 15 days until the immunized individuals actually presented defense against the pathogen, although there were no cases of claims and emerging nations.

The Oswaldo Cruz Institute - FIOCRUZ is currently responsible for the diagnosis of H1N1. It receives biological samples from all over the country and continues to provide support to society on strategies of combat and prevention, course on clinical management of the disease, symptoms and recent data of the anticipated outbreak of 2016.

Brazil has been on alert for a possible influenza A (H1N1) epidemic. According to the Ministry of Health, only in these first months of 2016 were registered 444 cases of severe acute respiratory syndrome (SARS) caused by Influenza A (H1N1). Of the 76 deaths recorded, three were children under the age of two. Oseltamivir phosphate is the most suitable for treating the disease [11].

Diagnosis and Symptoms

The Ministry of Health in 2009 found that influenza A virus is transmitted from person to person through coughing, sneezing and by contact with respiratory secretions by infected patients. It is noteworthy that the most susceptible groups are the elderly, children, immunosuppressed, and pregnant women, cardiac and pneumatic patients [7].

In the United States, a report of 642 confirmed cases reported fever (94%), coughs (92%), sore throat (66%), diarrhea (25%), vomiting (25%) and 2 patient's death. The Ministry of Health reported other symptoms such as: headache, muscle pain, joint pain and breathing difficulties. The figure 1 describes the symptoms of H1N1 and those of the common flu [10].

Tests for confirmation of infection with influenza A (H1N1) virus may be by means of Real Time-PCR (Q-PCR), or by viral culture, which is virus isolation. Nevertheless in Brazil suspicious cases are submitted to collection of clinical samples such as: respiratory secretions, these must be collected within the first seven days at the onset of symptoms. Blood collection is also used to monitor the clinical evolution of the patient [12].

Both adult and pediatric treatments are with the use of oseltamivir phosphate granted by the National Agency of Sanitary Surveillance (ANVISA) and produced by the Institute of Drug Technology, beyond hygienic care and adequate food. However, prevention is the best cost-benefit (Table 1).

Symptoms	Common Influenza	H1N1
Fever	Under 39°	Start up at 39°
Headache	Lower intensity	Intense
Chill	Sporadic	Frequent
Tiredness	Moderate	Extreme
Sore throat	Elevated	Light
Cough	Less intense	Dry and continuous
Mucus	Strong and with nasal congestion	Rare
Body pain	Moderate	Intense
Eyes burning	Light	Intense

Table 1: Symptoms of H1N1 influenza compared to common influenza.
Source: www.pandemiah1n1.com, accessed in 06/09/2016.

Current Vaccine and the Excipient Thimerosal

The vaccine is produced every six months, starting with the selection of the circulating strains until the final product for distribution. Campaigns take place in the spring, so that the immune system is activated with the vaccine formulation. Then, in the winter, the society would be protected due to increased dissemination in rainy times [13].

The work realized by the global influenza surveillance network updates the composition of the seasonal vaccines each year. The effect of vaccination on reducing the

occurrence of influenza depends on the composition of the viral subtypes contained in the vaccine and the circulating viruses of the population in the coinciding period. Seasonal influenza vaccines, both live attenuated and inactive virus, make up the trivalent vaccines, as they present both influenza B, A (H1N1) and A (H3N2) viruses [14].

The vaccine contraindications are evident for those who are allergic to eggs, because the virus is incubated in proteins of chicken eggs. Care is also taken of patients who have already presented Guillain-Barré syndrome, since they must be vaccinated with the medical consent [13]. The commercial name of the vaccine in Brazil is influenza A (H1N1) and it is manufactured in the laboratory Sanofi Pasteur, where the Butantan Institute has affiliation for the production of the vaccine in the country, since [15]. The side effects, through the killed virus are basically tolerated, with only pain and inflammation at the site injected [13].

In vaccines with the authorized use in Brazil, ANVISA allows the addition of excipients such as Thimerosal, which is not allowed in other countries because it contains in its organic composition mercury, called ethyl mercury (EtHg). Ethyl mercury in small amounts does not present health risks according to the Food and Drug Administration (FDA). However, as well as those obtained in formulations of vaccines associated with food, especially fish containing methyl mercury (MeHg), this in turn neurotoxic, the body becomes a reservoir of mercury and this combination, are associated with negative responses in neurological development, especially in early childhood [16,17]. Marques, et al. studied 1,139 children (6-24 months of age plus prenatal period) from the Western Amazon based on combined exposure (low, intermediate and high) for chronic MeHg through fish and acute consumption through vaccines containing Thimerosal (EtHg) [18]. Several parameters in the development of children with analysis and the outcome of the study reported several neurological problems and delays in the development of these children, which were dosed through the hair and breast milk. Children with low exposure had a more positive score on the Mental Development Index (MDI).

Another study developed by Geier DA, et al. in the United States of America assessed through medical records between 1991-1994 of Safety Data link Vaccine (VSD) the relationship between exposures to EtHg of Thimerosal present in hepatitis B vaccines administered at specific intervals in the first 6 months of life and specific delays in development [19]. Several studies have shown that Thimerosal interferes with the neurological development of children. In 2001, the use of this excipient in vaccine formulations was banned in the USA. However, in Brazil the use is allowed and assured by the World Health Organization, the Ministry of Health and ANVISA.

Final Considerations

The virus of Influenza A is very diverse and has two lines that have great spread among humans, H1N1 and H2N3. The virus has been distributed worldwide and since 1918 has been causing countless deaths. In Brazil, in 2009 we had the onset of the H1N1 outbreak and since then preventive measures have been taken to avoid further deaths.

Sentinels distributed throughout Brazil make collections to verify the frequency of H1N1 in cases of virus. The symptoms of H1N1 are different from the common flu and it is important to pass on the information to the greater knowledge of the population. Butantan Institute produces the vaccine against the virus specifically in the spring, with the vaccination campaign in the fall. Its purpose is to guarantee protection for society, which will be susceptible in the winter. The Brazilian government has doses for the groups of risks and the other groups can acquire in private companies.

Further studies in Brazil are needed on the excipient used in question, Thimerosal. However, several studies already report their relation with low development in early childhood, an important point to be considered by ANVISA. In this context, it can be concluded that due to constant mutations in the Influenza A virus, annual vaccinations are of great importance for the protection of the population and the dissemination of relevant information about the symptoms; diagnoses are highly considerable for a society to be conscious about a Pathology [20,21].

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