INFLUENZA A (H1N1) AND THE RESISTANCE TO OSELTAMIVIR

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ABSTRACT

Influenza is an acute infection of the respiratory system usually self-limiting, evolving towards complete cure due to the immunological response of the infected organism, but that can have serious complications, such as pneumonia and death. It is a disease widely distributed around the world, associated with several pandemics for over a century. The most recent pandemic occurred in 2009, when a new strain of influenza A (H1N1) virus caused an outbreak in Veracruz, Mexico, and rapidly spread though all the continents, causing over 12 thousand deaths in less than a year. Considering that this new strain of the virus is only sensitive to neuraminidase inhibitors (oseltamivir and zanamivir) and that the protocol of the World Health Organization recommends the use of oseltamivir as a single drug therapy, this study was performed with the intention of collecting and compiling data about the occurrence of resistance to this medication, in particular due to a H274Y substitution. In addition to mapping the occurrence of resistant virus, data was also collect about the person-to-person transmission of the virus with the mutation H274Y, as well as about the association of the appearance of resistance with the use of the drug.

Keywords: Influenza A (H1N1); oseltamivir; drug resistance; H274Y substitution.

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Influenza, commonly known as flu, is an acute infection of the respiratory system caused by the virus of the same name, which can affect both birds and mammals, including humans. Initially, it is characterized by high fever, muscle pain, sore throat, headache, dry cough, chills, prostration, sneezing and runny nose, and the symptoms tend to become more evident with the progression of the disease, which generally lasts for 3–4 days. It is a self-limiting disease, usually evolving to full healing due to the immune response of the infected organism. However, the disease can lead to complications, especially in high-risk groups such as the elderly, pregnant women, newborns, children, immunocompromised people and persons with chronic diseases such as diabetes mellitus, cancer, heart, lung and kidney disease. Pneumonia is the most common complication, being responsible for the large number of hospitalizations in Brazil (MS, 2009).

It is a very common disease worldwide, and the number of cases is estimated to be between 3 and 5 million yearly, associated with up to 250,000 to 500,000 deaths (Shankaran e Bearman, 2012). It can affect the same individual several times in the course of his life and the diagnosis can only be confirmed by specific laboratory tests, since the symptoms are common to other diseases, like common cold and allergic rhinitis. These are diseases of the upper airways, the same as influenza, but are caused by different agents and show slightly different symptoms. Colds can be caused by a variety of infectious agents (rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, enterovirus or adenovirus) and it is generally milder than influenza; the symptoms include nasal congestion, rhinorrhea, coughing, hoarseness, malaise, myalgia and headache; fever is less common and of low intensity when present. In turn, allergic rhinitis has environmental causes and is characterized by sneezing, nasal congestion and rhinorrhea; usually is not accompanied by fever, but it can occur when rhinitis is associated with an infection (MS, 2009).

The transmission of influenza can occur either directly or indirectly. In a direct way, the contaminated secretions released by an infected person while talking, sneezing and coughing come in direct contact with the mucous membranes of a healthy individual. Indirectly, this contact is mediated by the hands of the healthy individual who, after touching a surface contaminated by secretions of an infected person, touches his own mouth,
nose or eyes. The communicability period, i.e., in which the infected person can transmit the disease to healthy individuals, varies from two days before the symptoms appear to five days after (MS, 2009).

Because of the relative easiness of influenza transmission, the annual vaccination campaign is an important tool in combating the disease. According to the World Health Organization (WHO), “a vaccine is any preparation intended to produce immunity to a disease by stimulating the production of antibodies”, and can include, for example, a suspension of pathogenic microorganisms, killed or attenuated (WHO, 2012). The influenza vaccine is manufactured using several virus subtypes, in accordance with those that are predominantly circulating, in order to give greater protection. However, in addition to the protection against the influenza virus and the complications that can arise from an infection, vaccination can cause the appearance of adverse reactions to the vaccine, such as pain, redness and hardening of the application site, which occur in the first 72 hours after vaccine administration. Additionally, less common reactions include fever (less than 1%), anaphylaxis, neuralgia, paresthesia and muscle weakness (MS, 2009).

In order to avoid the contamination and the spread of the disease, some care must be taken, especially during an epidemic outbreak of influenza: hand washing with soap and water, especially after coughing or sneezing, after using the bathroom and before eating; avoid touching your eyes, nose and mouth; use disposable tissues; protect your mouth and nose with a tissue when coughing or sneezing; have healthy habits, such as a balanced diet, fluid intake and physical activity; avoid crowds and indoors spaces (MS, 2009).

Once the disease has been diagnosed, the treatment includes rest, hydration and light feeding, as well as symptomatic medications. When necessary, there are two classes of drugs that doctors can prescribe to fight the virus action: the M2 channel blockers and the neuraminidase inhibitors. There are advantages and disadvantages to using both, and the physician must review the case and make the prescription when consider it to be necessary (MS, 2009).

Influenza pandemics have been occurring for more than a century. In 1781-1782, the influenza virus reached nearly two-thirds of the population of Rome and three quarters of the population of Great-Britain. In 1889-1890, the Russian Flu hit Russia, Asia, China and Western Europe, with an estimative of at least 250,000 deaths in Europe and about 750,000 deaths worldwide. In 1917-1919, the Spanish Flu, considered the most severe of all, led to the deaths of over 20 million people, which exceeded the number of combat deaths on the First World War. In 1957-1958, the Asian Flu hit 10-35% of the world, killing 0.25% of the population. In 1968-1969, the Hong Kong Flu killed 700,000 people around the world (MS, 2003). More recently, the Avian Flu (Influenza A/H5N1) left more than 280 dead between 2003 and 2009 (WHO, 2009). The latest outbreak of influenza began in March 2009, in Veracruz, Mexico, and spread around the world throughout that year. On April 12th, the Mexican General Director of Epidemiology reported the outbreak to the Pan American Health Organization, in accordance with the International Health Regulations, and on April 23rd, several cases of laboratory confirmed swine-origin Influenza A (H1N1) were reported (CDC, 2009). With the increasing number of cases, the emergence of the new strain of influenza virus was elevated to a pandemic on June 11th, 2009 through a press statement made by the World Health Organization General Director, Dr. Margaret Chan, moment in which there were approximately 30,000 confirmed cases in 74 countries (WHO, 2009). On August 10th 2010, a little over a year after the outbreak of Influenza A (H1N1) was elevated to a pandemic level, the World Health Organization General Director, Dr. Margaret Chan, announced that the influenza event had been moved into the post-pandemic period, after numerous laboratory confirmed cases were recorded in more than 214 countries and overseas territories or communities between 2009 and 2010, leaving over 18.449 deaths worldwide (WHO, 2010).

The transmission and symptoms of Influenza A (H1N1) are similar to the common flu, and the lethality and worsening of both also occur in a similar way: of the 1,566 confirmed cases of the new virus until July 24th 2009, 14.2% of patients showed acute or severe respiratory distress, fever and coughing; in the same period, from 528 people diagnosed with the common flu, 17% showed the same trend. In both groups, more than 60% of infections occurred in people between 20 and 49 years-old (MS, 2009).

However, incubation periods and transmissivity are different, respectively 3-5 days and 7-14 days (children/adults) for the Influenza A (H1N1). Also, more than 90% of deaths due to seasonal outbreaks of influenza usually occur in the elderly; however, the attack rates of the Influenza A (H1N1) were highest among children and young adults. Less than 10% of the cases were in adults over 60 years old, likely due to preexisting antibodies against other H1N1 viruses. Furthermore, the treatment of people infected with the new strain of the virus is done only with neuraminidase inhibitors, limited to just two drugs. This, combined with the indiscriminate use due to the panic of the population, contributes to the appearance of resistance to these antimicrobials (MS, 2009; Clark et al, 2011).

The objective of this study was to collect information on the structure of the influenza virus, its cycle and the pharmacological treatment of the disease, with emphasis on the Influenza A (H1N1) pandemic, the new strain of the virus and the appearance of resistance to oseltamivir, the neuraminidase inhibitor recommended
by the World Health Organization and the Brazilian Ministry of Health for the treatment of this new strain.

For this, an essentially bibliographic study was performed, through a systematic review of studies published in scientific journals between 2009 and 2012. In addition, the data available on the websites of health entities such as the World Health Organization, the Pan American Health Organization, the Brazilian Ministry of Health, among others, was obtained and compiled.

The influenza virus

The Orthomyxoviridae virus family is subdivided into three genus, influenza A/B, influenza C and Thogoto. While the first two are transmitted between birds and mammals, the last is consistent with a group of tick viruses. The influenza virus, the main one of the family, contains a single strand of ribonucleic acid (RNA) wrapped in a helical nucleocapsid, in which are present the hemagglutinin and neuraminidase, viral proteins essential for the virus replication (Stanford, 2009; van der Vries et al, 2011).

Human influenza viruses are divided into three types, A, B and C, different from each other based on antigenic differences on their nucleoprotein and matrix proteins which are specific for each type (Chairat et al, 2012). Type A viruses are able to infect a large number of species, including humans, swine, birds, seals and horses. Type B viruses only infect humans, while type C viruses are capable of infecting humans and swine (IFPMA, 2009). The three types are highly communicable and mutagenic virus, type A being the most mutagenic of the three. Viruses A and B cause more morbidity and mortality than type C, and type A is normally associated with seasonal epidemics, usually in the winter, and influenza pandemics (CDC, 2009; Clark et al, 2011).

The type C virus is normally associated with infections in children, but it is not a major cause of illness. Types A and B viruses are more closely associated with the occurrence of influenza, both of which are able to undergo antigenic variation, meaning that the mutation they both suffer is punctual. Furthermore, the type A virus is also capable of drastically altering its genome, since it can undergo antigenic drift, a mutation by which recombination occurs between different strains (Stanford, 2009).

The virions of the type A virus have a pleomorphic structure, with spherical and filamentous shapes of 80-120 nm in diameter and up to 300 nm in length. In the lipid bilayer, there are approximately 500 surface glycoproteins, generally in the ratio of four hemagglutinins to one neuraminidase. The M2 ion channel passes through the membrane, while the M1 structural protein is adjacent to the bilayer. Within the nucleus, the single strand of RNA is associated with six other viral proteins expressed in its genome: a nucleoprotein (NP), three transcriptases (PB2, PB1 and PA) and two non-structural proteins (NS1 and NS2). The influenza virus genome consists of eight segments, which allows the genes rearrangement (IFPMA, 2009).

The figure below illustrates the structure of an influenza A virus, identifying the hemagglutinin, the neuraminidase, the M2 ion channel, the lipid bilayer, the M2 matrix protein, the RNA, and the viral proteins (PB2, PB1, PA, HA, NP, NA, M1, M2, NS1, NS2).

Fig. 1 - Structural diagram of Influenza A Virus Source: IFPMA, 2009
Influenza B and C both have only 1 serotype, whereas influenza A viruses are further subdivided according to the antigenic characterization of their two surface glycoproteins: 16 subtypes of hemagglutinin (H) and 9 subtypes of neuraminidase (N). Historically, human influenza A has been caused by three subtypes of hemagglutinin (H1, H2 and H3) combined with two subtypes of neuraminidase (N1 and N2). However, recently it were identified three other types of hemagglutinin associated with human influenza (H5, H7 and H9), which were previously restricted to influenza subtypes detected in birds (IFPMA, 2009; Pizzorno et al, 2011; Chairat et al, 2012; Karthick et al, 2012; Li et al, 2012).

The subtypes of type A viruses are further classified into cell strains. Although the subtype of the influenza A (H1N1) involved in the Spanish flu at the beginning of the last century is the same subtype as the virus responsible for the 2009 pandemic, they are of different strains. In fact, all influenza pandemics that occurred in the last century were caused by descendants of the 1918 virus, in other words, new strains of the same subtype of type A virus. This new strain identified in 2009 contains a combination of genes from the genetic material found in viruses from swine, avian and human influenza, and is continually changing, showing a high transmissible ability among humans (CDC, 2006, CDC, 2009; IFPMA, 2009; Rungrotmongkol et al, 2009; Wang et al, 2009; Li et al, 2012).

The influenza virus cycle

The influenza virus binds to the host cell through an interaction between a hemagglutinin glycoprotein and the sialic acid present on the surface of epithelial cells of the respiratory system (Step 1 in Fig. 2). The endocytosis occurs, after which the acidity of the endosome and the hemagglutinin causes the fusion of the viral envelope with the membrane of the vacuole. Then, the M2 ion channels are opened, allowing the entry of protons in the viral envelope, which acidify the nucleus of the virus, leading to the disintegration of the nucleus and consequent release of viral RNA and viral proteins. Next, the viral RNA molecules, the accessory proteins and the RNA-dependent RNA-polymerase are released into the cytoplasm (Step 2 in Fig. 2).

Viral proteins and RNA form a complex that is transported to the cell nucleus, where the RNA-dependent RNA-polymerase starts the transcription of the viral RNA positive tapes (Steps 3a and 3b in Fig. 2), which may remain within the cell or be exported to the cytoplasm for translation (Step 4 in Fig. 2). In the last case, translated viral proteins are secreted by the Golgi apparatus (Fig. 5b Step II) or transported back to the nucleus in order to form new viral RNA strips (Step 5a in Fig. 2).

The viral RNA negative strips which will form the new viruses, the RNA-dependent RNA-polymerase and other viral proteins are assembled to form the virion. The hemagglutinin and neuraminidase molecules are accumulated in the membrane along with the viral RNA and viral proteins that promote protrusion of the membrane (Step 6 in Fig. 2). The mature viruses adhere to the host cell membrane through the action of hemagglutinin, and are released once the neuraminidase has cleaved the sialic acid residues (Step 7 in Fig. 2).

![Fig. 2 - Influenza Virus Replication Source: Flu Virus Today, 2009](image-url)
Due to the absence of RNA revision enzymes, the RNA-dependent RNA-polymerase that replicates the viral genome makes an error every 10,000 nucleotides, which is the approximate length of influenza virus RNA. Thus, most of the viruses formed are mutant, resulting in the antigenic variation, a slow change over time of the viral surface antigens (Moscona, 2005).

Furthermore, the separation of the genome into eight RNA segments enables the rearrangement of genes, thus resulting in the antigenic drift, which enables the combination of antigens from different strains, causing the virus to be capable of infecting new species and quickly overcome the mechanisms of immune protection (Flu Virus Today, 2009; Moscona, 2005).

The pharmacological treatment of influenza

M2 channel blockers (amantadine and rimantadine) are cyclic amines, which prevent the viral replication by avoiding the opening of the channels. Since there is no proton input in the viral envelope, there is no release of viral RNA and viral proteins, and the viral replication cycle is interrupted (Flu Virus Today, 2009). The M2 channel in the viral membrane is the primary target of this class of anti-influenza agents, which confer specificity to the type A influenza virus, since the type B has a different membrane protein (Katzung, 2003; van der Vries et al, 2011).

Unlike M2 channel blockers, which act by preventing the formation of new virus, the neuraminidase inhibitors act by preventing the release of viruses already formed and adhered to the host cell membrane. Since the neuraminidase does not cleave the sialic acid residues, the newly formed virus cannot be released by the host cell (Fig. 3), thus interrupting the viral infection. Due to this mechanism, this class is active against all human influenza viruses (Flu Virus Today, 2009; Moscona, 2005; van der Vries et al, 2011). Currently, two drugs are available in Brazil: oseltamivir and zanamivir (ANVISA, 2012). However, there have been studies using peramivir and laninamivir, both of which are more effective and rapid in treating influenza patients (Miyoshi-Akiyama et al, 2012).

The pharmacological treatment of influenza A (H1N1)

The most recent influenza pandemic was caused by a new strain of the influenza A (H1N1) virus, in its vast majority resistant to M2 channel blockers due to a single change in the M2-proton channel of serine to asparagine at position 31; fortunately the virus is sensitive to neuraminidase inhibitors (CDC, 2009; van der Vries et al, 2011). Considering this new strain’s resistance to amantadine and rimantadine, the protocol of the World Health Organization recommends the use of oseltamivir for the treatment of the disease, instead of zanamivir, considering it is the most effective antiviral agent and due to the greater ease of use, since oseltamivir is available in capsules (Rungrotmongkol et al, 2009; Li et al, 2012). Considering that the replication of influenza viruses reaches its peak in 24-72 hours after the illness onset, oseltamivir, which acts at the viral replication step, should be administered as soon as possible (Flu Virus Today, 2009).

The Brazilian Ministry of Health protocol, in accordance with the World Health Organization protocol, consists on the administration of oseltamivir, in no more than 48 hours from the onset of symptoms, to patients
considered at risk, as assessed by the treating physician. The prophylaxis with oseltamivir is contraindicated for the general population and should only be taken by laboratory professionals that have manipulated clinical samples, as well as by health professionals involved in the performing of invasive procedures or handling of secretions of patients with flu-like illness, without the use of personal protective equipment (PPE) or that used it improperly (MS, 2009).

Nevertheless, it is important to bear in mind that the neuraminidase inhibitors class is the only one available today to treat influenza A (H1N1) and that the use of oseltamivir as a single drug therapy predisposes the appearance of resistance to this drug. Despite today's viruses resistant to oseltamivir proven sensitive to zanamivir, it is quite possible that in the future resistance will be observed to both drugs in a single virus (Poland et al, 2009).

The vaccination campaigns would be a better approach than the recommendation of the widespread use of neuraminidase inhibitors, since its prophylactic use in a large number of healthy people raises two concerns: first, excessive preventing may not be the best way of using the limited supply of medicines, particularly because they may be most needed in case of a virulence increase of influenza; secondly, the indiscriminate use of drugs can bring on resistance from these viruses (Burch et al, 2009; Couzin-Frankel, 2009).

The resistance to oseltamivir

Developed by W. Lew, X. Chen and C. U. Kim, oseltamivir was first oral neuraminidase inhibitor currently commercially available and is sold today by Hoffmann-La Roche under the trade name Tamiflu®. Oseltamivir phosphate, the active ingredient of Tamiflu®, is a prodrug that only presents its antiviral activity after being absorbed by the gastrointestinal tract and metabolized by the liver into oseltamivir carboxylate. It has a half-life of 6-10 hours and is excreted primarily through the kidneys. With good oral availability, commercial presentations include gelatin capsule and powder for oral suspension (ANVISA, 2009; Lew et al, 2000).

Oseltamivir is the drug of choice for treatment of pandemic influenza A (H1N1), even though resistance is more common than for zanamivir, because it is the most effective antiviral agent and due to the greater ease of use. However, it is well-known that when drugs are widely used, the viruses evolve quickly, creating a selection pressure and causing the appearance of resistance mutations. Since the use of oseltamivir as a single drug predisposes the appearance of resistance, studies were conducted to evaluate the antiviral efficacy and tolerability of oseltamivir–zanamivir bitherapy compared to oseltamivir monotherapy. It was not possible to detect benefits from the bitherapy. However, due to the limited sample size, more studies are necessary to correctly assess if the combination of oseltamivir with zanamivir improves or reduces the effectiveness of the treatment (Escuret et al, 2012; Hurt et al, 2012; Karthick et al, 2012; Li et al, 2012). The most common oseltamivir-resistance mutation is the H274Y (or H275Y, depending on the type of neuraminidase used as reference), namely a substitution of a histidine by a tyrosine on the position 275, which changes the interaction of neuraminidase with oseltamivir, decreasing the affinity between the drug and the protein (BVS, 2009).

Advances have been made to detect this virus resistance to oseltamivir. A study of 40 samples of influenza A (H1N1) submitted to the CDC during the season of the disease in 2007-2008 aimed to develop a new method to detect the H274Y mutation. A new RT-PCR/RFLP technique was actually developed, allowing the identification of the resistant viruses that had the H274Y substitution among several samples of sensitive and resistant influenza A (H1N1), in a simple, fast and accurate way (Guo et al, 2009).

In the winter of 2007/2008, there was a widespread influenza A (H1N1) virus resistant to oseltamivir in Europe, which led to an investigation of possible causes. After the analysis of 1,040 samples collected from patients in Luxembourg, it was determined that 195 had the oseltamivir sensitive virus and 59 had the resistant virus. After collecting data from all patients, it was found that there were no significant differences in the distribution of the cases and symptoms presented by both groups. In addition, a retrospective study of 212 patients found no connection between drug resistance and prophylactic use, its storage, vaccination and attack rates. Nevertheless, this study was able to identify two mechanisms of resistance to oseltamivir: a H274Y substitution and a not silent D354G mutation (Mossong et al, 2009).

Around the same time, it was also verified a significant increase in the presence of influenza A virus (H1N1) resistant to oseltamivir in Oceania, Southeast Asia and South Africa. In Europe, there was a 25% average occurrence of resistant virus, a rate quite variable depending on the country, reaching 67% in Norway, and all strains tested had the H274Y substitution. Because of that, a study was made with 264 samples of influenza A (H1N1) received by the World Health Organization from 10 countries and territories in Oceania and Southeast Asia, among which 168 (64%) had the mutation H274Y (Hurt et al, 2009).

A study in New York and Wisconsin, in the United States, between 2006 and 2007 found no viruses resistant to oseltamivir among the 18 samples of influenza A (H1N1) analyzed. However, in the 91 samples collected between 2007 and 2008, 13 were found resistant to oseltamivir, due to the H274Y substitution (Laplante et al, 2009).
In the Americas, a study conducted between 2006 and 2008 found 7 viruses resistant to oseltamivir in 167 samples of influenza A (H1N1) collected, all featuring the H274Y substitution. The resistant cases found in greater numbers in Europe and the fact that the 7 resistant viruses found in this study were collected in 2008 in Central and South America (Honduras, Nicaragua and Venezuela) suggest that the resistant virus is coming from the northern hemisphere to the south (Garcia et al, 2009).

A German study accompanied two families to check the transmission from an infected person to a healthy one, of the oseltamivir-resistant with H274Y substitution influenza A (H1N1) virus. In the end, it was confirmed that such contamination is possible, since in one of the families, a 6 year old boy was able to infect the 3 year old brother, and on the other, a 12 year old boy was able to infect his 33 year old mother and 1 year old brother (Duwe et al, 2009).

In addition to the more commonly known substitution on the position 275, some other amino acid substitutions, including the ones on the positions 117, 119, 136, 152, 199, 223, 247, 292, 294 and 295, have been associated with resistance or reduced susceptibility to one or more neuraminidase inhibitors (Miyoshi-Akiyama et al, 2012; Viaus et al, 2012).

Particularly, the substitution of a isoleucine by an arginine on the position 223, known as I223R, was identified, and unlike H275Y, which causes selective resistance to oseltamivir, the I223R is associated with resistance to both oseltamivir and zanamivir. Soon after this mutation was identified, several cases were found of the I223R substitution as a single mutation or in combination with the H275Y, a double mutant that proved to have high levels of resistance to oseltamivir (van der Vries et al, 2012).

Once the resistance appears, it is likely that the drug-resistant strains will lead to a large scale outbreak, perhaps even a new influenza pandemic. The experiences during the 2009 pandemic, of detecting and responding to resistant viruses, provided important knowledge concerning public health, laboratory testing, clinical management and usage recommendations. It is important to have vaccination campaigns, use multi-drug therapies and develop newer neuraminidase inhibitors and other drugs with different mechanisms. In addition, the continuous monitoring of resistance markers is a necessary tool in the prevention and response to an influenza outbreak, since the proper treatment relies on the correct identification of the viral type as well as on the detection of the mutation(s) conferring drug resistance, and the identification of potential resistance sites allows the design of new drugs with better potency (Pizzorno et al, 2011; Hurt et al, 2012; Li et al, 2012; Miyoshi-Akiyama et al, 2012; Shankaran e Bearman, 2012).

CONCLUSIONS

Nearly a century after the worst pandemic in history, the descending viral strains of the Spanish Flu continue to affect humanity. Perhaps due to the ease air traffic inherent to the modern life, pandemics of influenza are becoming more frequent. The newest strain of influenza A (H1N1) virus, popularly known as swine flu, which swept the world in 2009 ended that year with more than 12,220 deaths.

Endowed with a natural resistance to the M2 channel blockers, the strain of the A (H1N1) virus has shown sensitivity to neuraminidase inhibitor, causing oseltamivir (Tamifu®) to be the drug of choice to combat the pandemic, as recommended by the World Health Organization and the Brazilian Ministry of Health. However, cases of oseltamivir-resistant viruses have been detected for more than two years, mainly due to a H274Y substitution.

Despite the fact that this resistance has not been associated with the use of oseltamivir, it is important to point out that the use as a single drug is a risk, because there is no guarantee that the indiscriminate use of the drug due to the fear of the pandemic will not lead to the appearance of new mutations that confer to the virus greater resistance oseltamivir. Moreover, today it is evident that the viruses resistant to oseltamivir due to the substitution H274Y remain sensitive to zanamivir, since this mutation does not interfere with its interaction with the neuraminidase. However, it is possible that future mutations arise and make a single virus resistance to both drugs.

Thus, it is recommended not only to review the treatment protocols as new discoveries are made, but also invest in the development of new drugs, particularly those that use other mechanisms to interfere with the virus replication, preventing that a possible resistance to the neuraminidase inhibitors class render them ineffective in treating the new strain of influenza A.

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