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Current status of influenza: What do we know so far?

Panorama atual da influenza: O que sabemos até agora?

Perspectiva actual sobre la influenza: ¿Qué se sabe hasta ahora?

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Abstract
Over the last years much research has been carried out, especially after the influenza pandemic in 2009. It is known that many strains of influenza virus are widely spread in the global population causing seasonal outbreaks every year. Influenza leads to flu-like symptoms, which present favorable prognosis, since most patients completely recover from it within two to five days. Many new antiviral drugs have been developed in the last few years, but since the infection generally presents a mild course, symptom-based care is often enough. Influenza virus can undergo mutations through some mechanisms, like antigenic drift and antigenic shift. Alongside with its high infectivity such mechanisms probably have worked together to keep influenza infection viable through the years, despite all new drugs and preventive measures. This review aimed to bring the most relevant data about influenza obtained in the past years, including some historical aspects, pathophysiology, clinical findings, and diagnostic and therapeutic approach.
Keywords: Human flu; Viral diseases; Severe acute respiratory syndrome; Pandemics.

Resumo
Nos últimos anos, muitas pesquisas foram realizadas, especialmente após a pandemia de Influenza em 2009. Sabe-se que muitas cepas do vírus da Influenza estão amplamente disseminadas na população mundial, causando surtos sazonais a cada ano. A Influenza causa sintomas semelhantes aos da gripe, que têm um prognóstico favorável, já que a maioria

dos pacientes se recupera totalmente da gripe em dois a cinco dias. Muitos novos medicamentos antivirais foram desenvolvidos nos últimos anos, mas como a infecção geralmente segue um curso leve, o tratamento baseado em sintomas geralmente é suficiente. O vírus Influenza pode sofrer mutações por meio de alguns mecanismos, como deriva antigênica e deslocamento antigênico. Junto com sua alta infectividade, esses mecanismos provavelmente atuam juntos para manter a infecção por influenza viável ao longo dos anos, apesar de todos os novos medicamentos e medidas preventivas. Esta revisão objetivou reunir os dados mais relevantes sobre influenza obtidos nos últimos anos, incluindo alguns aspectos históricos, fisiopatologia, achados clínicos e abordagem diagnóstica e terapêutica.
Palavras-chave: Influenza humana; Viroses; Síndrome respiratória aguda grave; Pandemias.

Resumen
En los últimos años se han llevado a cabo muchas investigaciones, especialmente después de la pandemia de Influenza en 2009. Se sabe que muchas cepas del virus de la Influenza están ampliamente diseminadas en la población mundial provocando brotes estacionales cada año. La Influenza provoca síntomas similares a los de la gripe, que presentan un pronóstico favorable, ya que la mayoría de los pacientes se recuperan completamente de la misma en un plazo de dos a cinco días. En los últimos años se han desarrollado muchos medicamentos antivirales nuevos, pero dado que la infección generalmente presenta un curso leve, la atención basada en los síntomas suele ser suficiente. El virus de la Influenza puede sufrir mutaciones a través de algunos mecanismos, como la deriva antigénica y el cambio antigénico. Junto con su alta infectividad, estos mecanismos probablemente han trabajado juntos para mantener viable la infección por influenza a lo largo de los años, a pesar de todos los nuevos medicamentos y medidas preventivas. Esta revisión buscó reunir los datos más relevantes sobre la influenza obtenidos en los últimos años, incluidos algunos aspectos históricos, fisiopatología, hallazgos clínicos y abordaje diagnóstico y terapéutico.
Palabras-clave: Influenza humana; Virosis; Síndrome respiratorio agudo grave; Pandemias.

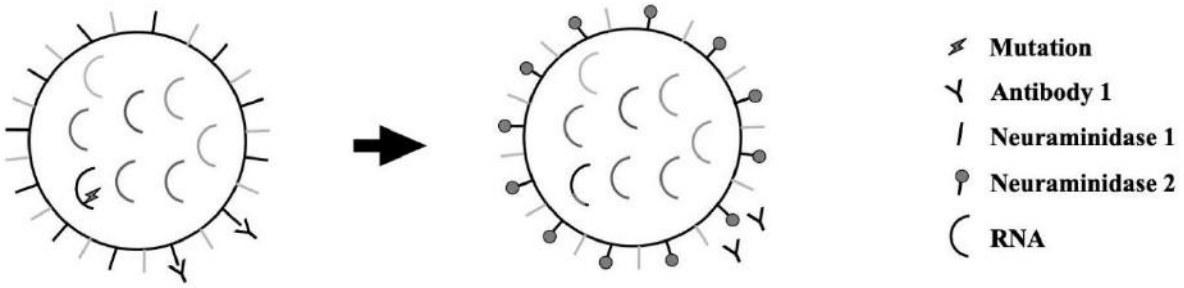
1. Introduction

In modern history, humanity has been damaged by many viral infections. Although many different viruses are responsible for a wide spectrum of diseases, influenza has a major importance and is frequently reported as a public health concern. Influenza represents a respiratory illness and is often associated with myalgia, malaise, fever, and other systemic symptoms. The main etiologic agents are influenza virus A (IAV), B (IBV), and C (ICV), which belong to the family *Orthomyxoviridae* (Murray et al., 2015; Jedrzejek et al., 2022; Kim et al., 2022).

Those three influenza viruses share similarities, but also a few differences. They have an irregular circular shape, measure 80 to 120 nm in diameter, are involved by a lipid envelope with two predominant glycoproteins on it (hemagglutinin (HA) and neuraminidase (NA)) and display a segmented negative-sense RNA. Segmented RNA facilitates the development of new strains through mutations and genetic reassortment. The development of different strains, named after the variations on its surface glycoproteins (e.g. H1N1), demonstrates the high viral plasticity and represents a major public health challenge (Bouvier & Palese, 2008; Murray et al., 2015; Jameson et al., 2018).

Influenza incidence usually rises during the cooler months and may be geographically limited. When a new strain arises, it reaches epidemic proportions. The most known episode of an influenza epidemic was called the Spanish flu, between 1918 and 1919, and caused over 50 million deaths. Despite those huge proportions, many other alarming rises of influenza-associated illness happened over the last century. The main etiologic agents of the annual epidemics are H1N1 and/or H3N2 strains (Jameson et al., 2018). Every one to three years, the virus undergoes antigenic drift (Figure 1).

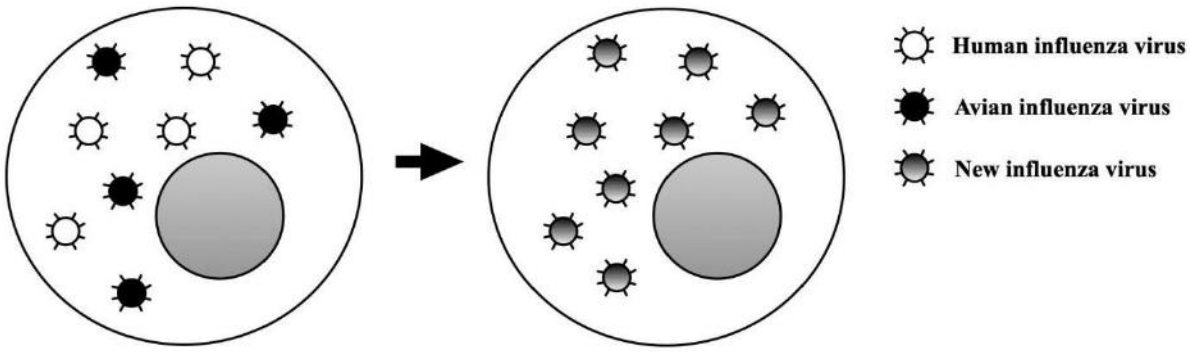
Figure 1. Antigenic drift. The influenza virus undergoes minimal alterations on its RNA, resulting on changes in its surface glycoproteins (HA and NA). After that, pre-existing antibodies lose their ability to bind to the virus and neutralize it.



Source: Authors.

Minimal genetic changes on its surface glycoproteins (HA and NA) allow it to escape the immune response. Sporadically, the virus undergoes antigenic shift (Figure 2).

Figure 2. Antigenic shift. Two different strains of the influenza virus infect the same host cell and their genomes go through reassortment, generating a completely new virus strain.



Source: Authors.

When different strains infect the same host cell, major genetic changes occur. A new virus is originated from the reassortment of the genome. Both antigenic drift and antigenic shift may result in pandemics (Table 1) (Labella & Mersel, 2013; Jameson et al., 2018).

Table 1. Influenza pandemics over the years.

Years	Subtype	Estimated number of deaths	Estimated case-fatality rate
1918-1919	H1N1	40-50 million	1.0-2.5%
1957-1958	H2N2	1.1 million	0.67%
1968-1969	H3N2	1.0 million	0.8%
2009-2010	H1N1	151,700-575,400	< 0.5%

Source: Taubenberger & Morens (2006); Bautista et al. (2010); Yoshikura (2014); Veronesi & Focaccia (2015); Saunders-Hastings & Krewski (2016); Jameson et al. (2018); CDC (2020).

Surface glycoproteins and endosomal properties allow the virus to fuse and infect a human cell by binding to sialic acid. Inside the cell, the virus replicates and causes cell death, which induces inflammation and immune activation. Systemic symptoms are associated with immune-mediated damage, while respiratory failure is more related with viral-mediated damage, due to viral tropism for respiratory cells (Bouvier & Palese, 2008; Murray et al., 2015).

Although the main clinical presentation of influenza virus infection is characterized by respiratory symptoms, fever, malaise and myalgia, some patients may also manifest ocular, neuropsychiatric, cardiac and renal impairment (Nakamura et al., 2010; Toovey et al., 2012; Dharmapalan, 2020).

Influenza's high plasticity, contagiousness, and variable clinical presentation represent a challenge to health professionals. In this context, many drugs have been developed, targeting different steps of viral infection. Currently, the most commonly used are neuraminidase inhibitors (NAIs), such as oseltamivir, while others have been investigated (Amerelle et al., 2017).

This review aimed to bring the most relevant data about influenza obtained in the past years, including some historical aspects, pathophysiology, clinical findings, and diagnostic and therapeutic approach.

2. Methodology

This study is a narrative literature review with methodological support by Estrela (2018). The electronic search was performed in the PubMed and Lilacs databases. In addition, the CAPES portal was accessed in addition to the websites of related Societies and Organizations. The search was performed using a combination of the search terms "Human Flu", "Viral Diseases", "Severe Acute Respiratory Syndrome", "Pandemic" and the Boolean operator "AND".

Articles on the topic were included, regardless of the period and considering the English and Portuguese languages. Dissertations and theses found in the search were excluded. Initially, titles and abstracts were read in order to identify relevant articles on the topic. After that, the full reading of the articles was carried out to made a content analysis, where those who entered the exclusion criteria have were used to extract the main informations. At the end, 57 references have been included on this study.

3. Literature Review

3.1 Epidemiology

The influenza A outbreaks are divided in pandemic and interpandemic periods (Zambon, 1999; Jameson et al., 2018) Both have high mortality and morbidity rates. The outbreaks cause significant school and work absence. In temperate regions,

influenza infection has a seasonal pattern, occurring mostly during winter. However, in tropical regions, it occurs throughout the year. The incidence is similar between different genders and races, but healthy young adults and children are most affected (Veronesi & Focaccia, 2015). Some underlying conditions can increase the risk of hospitalization and death, such as heart and lung diseases, chronic kidney disease, immunosuppression, age younger than five years, pregnancy, and morbid obesity (Jameson et al., 2018).

Epidemiological data on influenza is hard to be precisely quantified and certainly is underestimated, mainly because several infected individuals do not need to seek medical assistance (CDC, 2019). The incidence varies among regions, but influenza was responsible for the occurrence of 48.2% of the confirmed cases of flu syndrome and 21.5% of the cases of severe acute respiratory syndrome (SARS) in Brazil, up to epidemiological week 30/2019 (Brasil, 2019).

All three types of Influenza viruses (A, B and C) may infect humans. While ICV generally causes mild infections, IAV and IBV are responsible for seasonal epidemics, with IAV being the most aggressive one. Pandemics, such as 2009 H1N1 outbreak, occur when a new IAV strain infects humans in the absence of pre-existing antibody-mediated immunity on a population-based scale. Infection is promptly transmitted from human to human (Murray et al., 2015). Furthermore, other avian-derived viruses (e.g. H5N1, H5N6, H6N1 and H10N8) are highly virulent and probably able to develop epidemics and pandemics (Grant et al., 2016).

3.2 Pathophysiology

Influenza virus belongs to the *Orthomyxoviridae* family. IAV and IBV are characterized by eight-segment negative-strand RNA genomes, while ICV has a seven-segment negative-strand genome (Bouvier & Palese, 2008). Those genomes encode a series of proteins, such as nonstructural protein 1 (NS1), matrix M2 proteins, nucleoprotein (NP), HA, NA, polymerase subunits (PA, PB1 or PB2), N40 and PB1-F2. The virion is composed of eight viral ribonucleoproteins (vRNP) built from NP and polymerase subunits, which are surrounded by M1 and a lipid membrane, derived from infected cells. HA, NA and M2 are expressed in the surface of this membrane (Shim et al., 2017).

When the virus encounters a viable host, it infects upper and lower respiratory tract by attacking local epithelial cells, dendritic cells, type II pneumocytes and alveolar macrophages. This damage may lead to bronchial epithelium denudation, which compromises defensive strategies and facilitates bacterial adhesion. Consequently, pneumonia may be caused either by viruses or by secondary bacterial infections. Influenza causes intense inflammation, accompanied predominantly by monocytes and lymphocytes. Pulmonary tissue may present alveolar wall necrosis, hyaline membrane disease and alveolar emphysema.[1] Moreover, HA binds to sialic acid on the host cell surface, promoting phagocytosis. The acidic environment of the endosomes leads to hemagglutinin-mediated fusion between viral and endosomal membrane. This is followed by M1 degradation and vRNA release in the cytoplasm. vRNA enters the nucleus, where negative-strand vRNA is transcribed into positive-sense vRNA by viral polymerase. Also, viral polymerase builds viral pre-mRNA. Viral proteins are translated in the cytoplasm and then imported to the nucleus to participate in vRNA replication. Newly assembled vRNPs are transported to the apical membrane, where virions are constructed and released by NA (Shim et al., 2017; Jameson et al., 2018).

Immune response against influenza is mainly mediated by interferons, pro-inflammatory cytokines and CD8 T cells, while macrophages are depressed by the virus. Immune reaction peaks simultaneously to viral clearance by nasal cavity. Therefore, recovery usually precedes anti-HA and anti-NA antibodies detection in serum (Doherty et al., 1996; Murray et al., 2015; Grant et al., 2016). Many of the symptoms associated to the “flu-like” condition occur due to the systemic effects of interferons and cytokines. Recovery usually begins three to five days after the onset of symptoms, but can last as long as one month, especially in the elderly (Murray et al., 2015).

Influenza's replication process induces oxidative stress not only in infected cells (mainly dividing cells), but also in immune cells (Li et al., 2015). Host inflammatory response is partially responsible for DNA damage after the infection. Conversely, many studies have observed that IAV-specific CD8 T cells are extremely important to both recovery from influenza and immunological memory (McMichael et al., 1983; Murray et al., 2015; Sridhar et al., 2017). Those cells promote efficient recovery through the production of pro-inflammatory cytokines and direct killing of infected cells (Bender et al., 1992; Doherty et al., 1996). Earlier protective CD8 T cell immunity leads to less exuberant inflammatory responses. Different influenza strains might also induce enhanced defenses against those pathogens (Grant et al., 2016).

Besides respiratory manifestations, immune and ocular damage, acute kidney injury (AKI) and neuropsychiatric conditions were also observed. The most common cause of AKI is acute tubular necrosis (ATN) due to renal hypoperfusion. Furthermore, influenza virus has been shown to have the ability to replicate into renal cells. AKI is commonly accompanied by different amounts of myoglobinuria, due to progression of viral myositis to rhabdomyolysis (Dovč et al., 2017). Fulminant myocarditis and other sorts of cardiac damage have also been observed in children infected by H1N1 viruses (Bratincsák et al., 2010). Neuropsychiatric adverse events appear to be related to encephalitis, loss or depressed level of consciousness, delirium, convulsion and hallucination, which was associated to systemic inflammation caused by the virus (Nakamura et al., 2010; Toovey et al., 2012).

3.3 Clinical findings

After a typical incubation period of one to four days, the clinical manifestations tend to be variable and unspecific. Normally, influenza infection is characterized by the sudden onset of fever, which usually ranges from 37.8 to 40.0 ºC (100 to 104 ºF). Occasionally, patients can even precise the exact time that the symptoms started. Headache, myalgia, and malaise, as well as respiratory tract symptoms, such as dyspnea and unproductive cough, are usually associated with fever (Labella & Mersel, 2013). Other common symptoms are anorexia, runny nose, hoarseness, sore throat, conjunctivitis, respiratory pain, abdominal pain, diarrhea, nausea and vomiting. The four last symptoms are more common in infants (Labella & Mersel, 2013; Veronesi & Focaccia, 2015; Kumar, 2016).

Fever lasts about 72 to 96 hours. It is typically associated with chills, weakness, prostration, and dizziness. It is linked to an intense immune response against the virus. In children, fever tends to reach higher values than in adults (Labella & Mersel, 2013; Veronesi & Focaccia, 2015; Kumar, 2016).

During physical examination, only little pathological signs can be seen at early stages of the disease. The patient's skin usually seems hot and flushed. Moderate cervical lymphadenopathy may occur, especially in younger patients. Frequently, pulmonary auscultation reveals no alterations. However, rhonchi and crackles are most likely to be heard (Veronesi & Focaccia, 2015). In non-complicated patients, overall symptoms minimize in two to five days, although the disease lasts around seven days, in a self-limiting course. Patients may refer weakness and malaise for several weeks after cure (Hart, 2019).

Influenza complications can be very severe, despite being rare (Labella & Mersel, 2013; Sellers et al., 2017). The main complication is pneumonia, which should be suspected when symptoms do not alleviate after seven days, or even become worse over time. High fever, severe dyspnea and peripheral cyanosis can occur. Post-influenza pneumonia can be classified as primary, when caused by the actual virus, or secondary when there is a bacterial infection overlapping the viral infection. The most important bacterial agents are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and Group A beta-hemolytic *Streptococci* (Labella & Mersel, 2013).

Especially in those infected by the H1N1 virus, severe acute respiratory syndrome (SARS) comes up (Labella & Mersel, 2013). Influenza-related SARS is a remarkable complication, associated or not with alarm signs, such as blood oxygen saturation (SpO_2) < 95% in ambient air, visible signs of respiratory discomfort, tachypnea, hypotension and decompensation of the patient's

preexistent comorbidities (Veronesi & Focaccia, 2015). Besides the respiratory impairment, influenza infection can affect many organs and systems.

The main neurological complication is influenza-associated encephalopathy (IAE). Neurological symptoms, such as headache, tremors, delusions, and seizures may occur two to three weeks after the early onset of symptoms. The so-called triad of encephalitis lethargica can also be present: fever, lethargy, and abnormal eye movements (Jia et al., 2017). Guillain-Barré Syndrome (GBS), an immune-mediated symmetric and ascendant polyneuropathy, can appear around two to six weeks after the first influenza symptoms. Reye's syndrome may occur especially in children who use acetylsalicylic acid during this infection (Carlson et al., 2009).

Heart failure decompensation, acute coronary syndrome and acute myocarditis are some of the possible cardiac complications (Sellers et al., 2017). There is also an increased risk of strokes. Kidneys may be affected with the development of AKI, minimal change disease, acute glomerulonephritis and acute tubulointerstitial nephritis (Casas-Aparicio et al., 2018). Hepatic injury, thromboembolic events, hemolytic-uremic syndrome, hemophagocytic syndrome and thrombotic thrombocytopenic purpura, although uncommon, can also happen(Sellers et al., 2017). In pregnant women, complications of influenza include premature rupture of membranes, fetal neural tube defects, spontaneous abortion, non-reassuring fetal status, neonatal seizures, neonatal encephalopathy and cerebral palsy (Carlson et al., 2009).

3.4 Influenza diagnosis

Usually, diagnosis is based on clinical findings. Proper management may be established after clinical diagnosis, since influenza is mostly self-limited (Hayden et al., 1999; Hart, 2019). However, diagnostic and treatment approach may be changed upon laboratory findings in certain situations (e.g., people at high-risk for developing influenza-related complications) (CDC, 2018). In such scenario, patients may need a diagnosis test.

Laboratory methods for the diagnosis of Influenza have progressed in the last years. Nowadays, some of these tests can identify viruses within a few minutes, while it used to take some days in the past (Woźniak-Kosek et al., 2014). Since the benefits of antiviral therapy are proven to be greater when administered early in the course of the infection, such evolution had an important role on clinical outcomes.

According to the Infectious Disease Society of America (IDSA) 2018 Guidelines on the management of influenza, the need to perform a diagnostic test depends on some factors. One important consideration is whether the patient is hospitalized or not (Uyeki et al., 2019).

In general, clinicians should test every hospitalized patient with acute respiratory symptoms in periods when the activity of the disease is high. However, when the activity of the disease is low, specific tests should be considered for hospitalized patients who present with acute respiratory symptoms and have an epidemiological link to any influenza case. Regarding outpatients during periods of high influenza activity, specific diagnostic tests are recommended for those at high-risk of complications (e.g., immunocompromised patients) if the results determine changes in the clinical approach. In periods of low influenza activity, there is no strong recommendation to perform diagnostic tests, though they can be considered for immunocompromised and high-risk patients with acute febrile respiratory illness (Uyeki et al., 2019).

3.5 Treatment

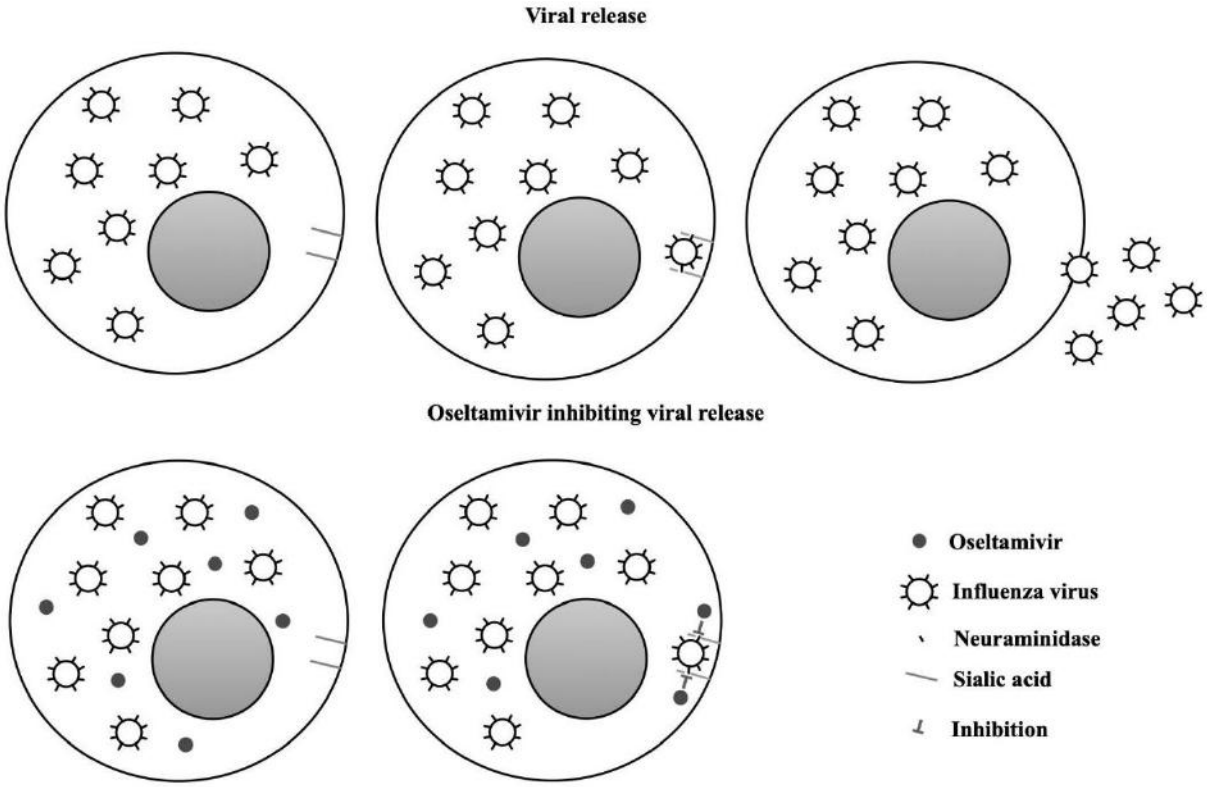
Influenza is usually a self-limited infection (Amarelle et al., 2017). Its symptoms are usually mild, and patients often use only over-the-counter (OTC) medications (Hart, 2019). Nevertheless, some patients meet criteria for antiviral treatment according to the IDSA 2018 Guidelines, requiring it to prevent progression of the disease (Uyeki et al., 2019).

In order to control the course of influenza, drugs with different targets have been developed. Nowadays, the most commonly used drugs are neuraminidase inhibitors (NAIs), such as oseltamivir, zanamivir and peramivir (Amarelle et al., 2017). Oseltamivir (Tamiflu®) is an oral administration drug, while zanamivir (Relenza®) is administrated through inhaling, and peramivir (Rapivab®) is an intravenous (IV) administration drug. M2 ion channel inhibitors (M2ICIs) were once the first choice for influenza treatment, although it has changed due to the development of amantadine-resistant viruses. Therefore, M2ICs are no longer recommended (Amarelle et al., 2017).

Neuraminidase is responsible for cleavage of sialic acid, with consequent release of virion. By inhibiting this event, virion release is stopped, preventing the spread of infection (Amarelle et al., 2017). Although the antiviral effect of oseltamivir was initially questioned, a meta-analysis published in 2015 found that oseltamivir accelerates symptom relief, reduces the risk of lower respiratory tract complications, and reduces the admittance to hospital in adults. On the other hand, adverse effects include nausea and vomiting (Jefferson et al., 2014; Dobson et al., 2015).

Oseltamivir is the first-line therapy (Amarelle et al., 2017). Since it is given orally, it can be difficult to use in some patients (e.g., patients at risk for aspiration and young children) (Hart, 2019; Uyeki et al., 2019). In these cases, other NAIs, such as zanamivir or peramivir, can be used. NAIs' mechanism of action is illustrated on Figure 3.

Figure 3. Neuraminidase inhibitors. The drugs act by blocking neuraminidase's cleavage of the sialic acid. Therefore, they inhibit viral release from the cell and its spread throughout the body.



Source: Authors.

Zanamivir is a dry powder which must be administrated either by nebulization or inhaling (Rewar et al., 2016; Amarelle et al., 2017; Uyeki et al., 2019). Bronchospasm is an important side effect. Therefore, it is not recommended for patients with underlying respiratory disease, such as asthma and COPD (Uyeki et al., 2019). A meta-analysis published in 2017 compared the efficacy of IV peramivir vs. oral oseltamivir. Peramivir was more effective than oseltamivir in regard to fever, although it was not possible to draw clear conclusions due to some limitations of the study (Lee et al., 2017).

In October 2018, the Food and Drug Administration (FDA) approved the use of Baloxavir marboxil (Xofluza™). It is recommended for acute uncomplicated influenza within the first 48 hours of symptoms onset, in patients older than 12 years of age (Uyeki et al., 2019). Baloxavir is an inhibitor of influenza virus' cap-dependent endonuclease and it was designed based on dolutegravir (O'Hanlon & Shaw, 2019). By inhibiting this enzyme, it is able to decrease influenza viral replication potential (Hayden et al., 2018; Fukao et al., 2019). Hayden et al. (2018) published an evaluation of baloxavir use in adolescents and adults with uncomplicated influenza. The time to relief the symptoms was 23.4 to 28.2 hours shorter in comparison with placebo. Adverse effects were found in 20.7% of those who used baloxavir, in 24.8% of those who used oseltamivir, and in 24.6% of those who used placebo. Fukao et al. (2019) has demonstrated that baloxavir acid, the active form of baloxavir marboxil, works in conjunction with NAIs, supporting the role of combined therapy.

3.6 Prevention strategies

Hand hygiene is a well-recognized non-pharmacological way to prevent health care-associated infections, such as influenza, due its high contagiousness (Pittet, 2001; Amorim et al., 2018). Therefore, this procedure should always be encouraged, especially after any contact with surfaces that are contaminated by respiratory secretions. Such attitude avoids self-contamination through respiratory or ocular mucosa. While sneezing and coughing, patients could also use tissues to protect the broad dissemination of viral particles (Veronesi & Focaccia, 2015).

However, it is worth mentioning that the most efficient way of preventing influenza is by vaccination with the same strains circulating in the community. It prevents up to 90% of the infections (Forleo-Neto et al., 2003; Houser & Subbarao, 2015). Some studies also showed reduction on the incidence of otitis media in children and remission of hospitalization, complications and death in elderly and institutionalized persons (Heikkinen et al., 1991; Clements et al., 1995; Forleo-Neto et al., 2003; Mameli et al., 2019).

The World Health Organization (WHO) usually guides the countries concerning the composition of the seasonal vaccines and to which groups these vaccines should be targeted. Generally, vaccination should be prioritized for (1) people with high risk of complication and (2) people who may transmit influenza to individuals with high risk of complication (Harper et al., 2005). These target groups are summarized on Table 2.

Table 2. Main priority groups for influenza vaccine.

Kids from 6 months to 59 months of age
Pregnant women
Elderly
Individuals with specific chronical medical diseases
Institutionalized individuals
Contactants of high-risk individuals (e.g. relatives, health-care professionals, and nursing home employees)

Source: Forleo-Neto et al. (2003); WHO (2012).

WHO also divides the recommended vaccines into trivalent and tetravalent. Trivalent vaccines contain one strain of H1N1, one of H3N2 and only one IBV strain, while tetravalent contains an additional IBV strain. In addition, influenza vaccines can be assorted in three classes: (1) inactivated virus, (2) live attenuated virus, and (3) recombinant haemagglutinin (Paules & Subbarao, 2017).

Since circulating virus strains typically vary throughout the seasons, the WHO annually updates its recommendations regarding the composition of the vaccines. These informs are useful for the laboratories to improve their vaccines, in order to make them adequate to face the next influenza season. Each country, then, licenses and provides the vaccines to the population (Peteranderl et al., 2016).

4. Final Considerations

Influenza is a common infection, which spreads all around the world. It presents in many ways, from a clinically mild condition to a severe infection. Throughout the years, many ways of establishing diagnosis and prevention have been developed – such as vaccines and encouraging of hygiene measures. Even so, influenza virus thrives, possibly due to its capacity of undergoing mutations easily and to its high contagiousness. Therefore, physicians should be aware of the influenza infection and its complications, offering the most adequate approach for each patient.

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