

# A Narrative Review of Influenza: A Seasonal and Pandemic Disease

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## Abstract

Influenza is an acute respiratory disease caused by the influenza A or B virus. It often occurs in outbreaks and epidemics worldwide, mainly during the winter season. Significant numbers of influenza virus particles are present in the respiratory secretions of infected persons, so infection can be transmitted by sneezing and coughing via large particle droplets. The mean duration of influenza virus shedding in immunocompetent adult patients is around 5 days but may continue for up to 10 days or more—particularly in children, elderly adults, patients with chronic illnesses, and immunocompromised hosts. Influenza typically begins with the abrupt onset of high-grade fever, myalgia, headache, and malaise. These manifestations are accompanied by symptoms of respiratory tract illnesses such as nonproductive cough, sore throat, and nasal discharge. After a typical course, influenza can affect other organs such as the lungs, brain, and heart more than it can affect the respiratory tract and cause hospitalization. The best way to prevent influenza is to administer annual vaccinations. Among severely ill patients, an early commencement of antiviral treatment (<2 d from illness onset) is associated with reduced morbidity and mortality, with greater benefits allied to an earlier initiation of treatment. Given the significance of the disease burden, we reviewed the latest findings in the diagnosis and management of influenza.

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## What's Known

- Epidemiology, clinical manifestations, and high-risk group management are known as regards influenza.

## What's New

- We underscore the recent emphasis on the management of pregnant women without severe manifestations or the management beyond 48 hours of the clinical onset of flue. We also review data on drug resistance and various diagnostic tests and indications thereof.

## Introduction

Influenza (mostly referred to as “flu”) is a contagious viral infection caused primarily by the influenza virus A or B. It affects mainly the upper respiratory organs (i.e., the nose, throat, bronchi, and infrequently, lungs) but other organs such as the heart, brain, and muscles can be involved. It occurs worldwide and causes considerable morbidity and mortality with pandemic, epidemic, or seasonal patterns. Epidemics of flu happen annually during autumn and winter in temperate areas and produce significant mortality and morbidity each year.<sup>1</sup> The virus is transmitted from person to person with respiratory droplets produced when the patient coughs or sneezes. Close contact (<1 m) is frequently needed to get infected. Individuals usually recover after a few days, but influenza can give rise to complications and even lead to death—especially in high-risk groups like pregnant women and those with an underlying immunodeficiency state. The symptoms include high fever, body ache, headache, severe malaise, dry

cough, sore throat, and runny nose. It should be differentiated from the common cold by clinical presentations.

There are some unique features for influenza such as the epidemic nature of the disease due to its persistent antigenic changes and mortality, caused in part by pulmonary complications.<sup>2</sup>

We aimed to review different clinical aspects of the influenza infection vis-à-vis its annual incidence, significant mortality, and burden.

## History

The influenza virus has caused recurrent epidemics of acute febrile syndrome every 1 to 4 years for at least the recent centuries. The first epidemic report of an influenza-like illness was noted in 1173–74,<sup>3</sup> but the first definitive epidemic was reported in 1694.<sup>4</sup> The greatest pandemic in recorded history occurred between 1918 and 1919, when approximately 21 million deaths were recorded worldwide.<sup>5</sup> It was among the deadliest events in reported human history. Afterward, 3 other pandemics occurred in the 20th century: the 1957 H2N2 pandemic, the 1968 H3N2 pandemic, and the 2009 influenza A (H1N1) virus (pH1N1) pandemic. In the most recent event, an influenza strain with a combination of gene segments not previously reported in the swine or human influenza virus strains was identified firstly in Mexico and then in the United States of America.<sup>6</sup> After the involvement of many countries, the pandemic was declared to be over in August 2010.<sup>7</sup>

## Etiology

Influenza viruses belong to the family of viruses termed "*Orthomyxoviridae*", an RNA type virus with diverse antigenic characteristics. They are divided into 3 main types: A, B, and C. Most of the epidemics and outbreaks of flu are caused by types A and B, with type C being generally responsible for sporadic mild upper respiratory symptoms.<sup>8,9</sup>

Viruses have spherical or filamentous shapes with an envelope, containing glycoproteins and a single stranded RNA gene. The 2 most important glycoproteins over the outer layer of the flu virus are hemagglutinin (H, or HA) and neuraminidase (N, or NA). Both of them have important roles in the pathogenesis of the disease.

For influenza type A, at least 16 highly variable hemagglutinins (H1 to H16) and 9 distinct NAs (N1 to N9) have been recognized so far. With the aid of these different antigens, the influenza type A virus is further subdivided into subtypes on the basis of variable combination patterns of

their own specific H or N proteins (e.g., H1N1 or H3N2). Nonetheless, in the nomenclature of the viruses, other variables such as the place of initial isolation and the year of isolation are included.<sup>10</sup>

The influenza B virus has a similar viral structure to type A; however, due to the fixed antigenic characters of HA and NA, there are no subtypes in this virus. Still, some small antigenic variabilities have been reported since 1970 in this virus, with the virus having started to diverge into 2 antigenically distinguishable lineages.<sup>11</sup>

## Epidemiology

Flu occurs in distinct outbreaks of varying extension and intensity every year. This epidemiologic pattern of influenza is based on multiple factors such as the changing nature of the antigenic properties of the virus, transmissibility power of the virus, and the susceptibility of the population. The susceptibility of community is one of the most important factors in the strength of epidemics and its mortality or morbidity effects in specific. For example, in a recent pandemic due to the presence of baseline partial immunity in the Iranian community, the country did not have a high mortality rate.<sup>12</sup>

The influenza A virus, in particular, has a specific ability to undergo periodic changes in the antigenic characteristics of its surface glycoproteins, hemagglutinin, and neuraminidase. Major changes in these proteins are termed "antigenic shifts", and minor changes are termed "antigenic drifts". Antigenic shifts are associated with the epidemics and pandemics of influenza A, whereas antigenic drifts are responsible for more localized outbreaks of varying extent.

Due to the segmented pattern of the influenza virus gene and the high rates of reassortment on its genome, the emergence of pandemic strains usually has been caused by animal- and human-type reassortment and the resultant antigenic shifts.

Between the years of antigenic shifts, antigenic drifts have happened almost annually and have resulted in outbreaks of variable extent and severity. The outbreaks of antigenic drifts are usually less extensive and severe than the epidemics or pandemics associated with antigenic shifts. Antigenic drifts are resulted from point mutations in the RNA gene segments that are responsible for hemagglutinin or neuraminidase; accordingly, they occur sequentially as the virus spreads through susceptible populations.<sup>13</sup>

Influenza usually has the highest attack rates among young people, while high mortality rates

are reported among older adults. In addition to the elderly, mortality and morbidity are specifically high in those with definite high-risk medical conditions—including extreme of ages, cardiovascular diseases, and metabolic diseases such as diabetes mellitus. A summary of these conditions are shown in table 1. Specifically, the increased risk of influenza morbidity and mortality during pregnancy were observed during the 2009 pandemic.<sup>14</sup> Also, the data from previous pandemics and seasonal influenza outbreaks suggest that the risk of influenza complications may be higher in the 2nd and 3rd trimesters of pregnancy in comparison to the 1st trimester.<sup>15</sup>

## Transmission

In the respiratory secretion of the patients suffering from influenza, large amounts of virus load are often present and, as a result, each infected person can be transmitting infection to other individuals by sneezing and coughing. It has been posited that the disease is transmitted primarily via large particle droplets (>5  $\mu$ ).<sup>16</sup>

Owing to the large size of infectious droplets, close contact is needed for the acquisition of the disease. These large particles usually do not remain suspended in the air for a long time and they travel only short distances. Airborne transmission is, therefore, not often considered for disease spread.<sup>17</sup> However, limited data show that small particle respiratory droplets, which become aerosolized and can stay suspended in the air for a long time, also contain the influenza virus and can potentially cause disease

**Table 1:** Groups at risk of influenza complications

Unvaccinated infants aged 12–24 months
Persons with asthma or other chronic pulmonary diseases such as cystic fibrosis in children or chronic obstructive pulmonary disease in adults
Persons with hemodynamically significant cardiac disease
Persons who have immunosuppressive disorders or who are receiving immunosuppressive therapy
HIV-infected persons
Persons with sickle-cell anemia and other hemoglobinopathies
Persons with diseases requiring long-term aspirin therapy such as rheumatoid arthritis
Persons with chronic renal dysfunction
Persons with cancer
Persons with chronic metabolic diseases such as diabetes mellitus
Persons with neuromuscular disorders, seizure disorders, or cognitive dysfunction—which may compromise the handling of respiratory secretions
Adults aged >65 years
Residents of any age of nursing homes or other long-term care institutions

spread.<sup>18</sup> In a recent study, aerosol transmission accounted for around half of all the transmission events. This suggests that activities to reduce transmission by contact or large droplets may not be enough to control the transmission of the influenza A virus in households or communities.<sup>19</sup> Thus, the prevention strategies that are drawn upon routinely in hospitals require further re-evaluation.

Moreover, contact with contaminated surfaces containing respiratory droplets is another potential source of disease transmission. In adults without other underlying diseases, the shedding of virus starts from 24 to 48 hours before disease manifestation and the shedding stops after 6 or 7 days according to most studies and after 10 days according to some other investigations.<sup>20</sup> It should be considered that longer periods of shedding and infectiousness can occur in children, elderly adults, immunocompromised hosts, and patients with chronic illnesses.<sup>21,22</sup>

## Clinical Manifestations

### *Uncomplicated Influenza*

Influenza typically begins with the abrupt onset of symptoms following an incubation period of 1 to 2 days. Primarily, these symptoms are systemic and consist of fever sensation, true chills, headache, severe myalgia, malaise, and anorexia. Mostly headache, myalgia, and fever determine the severity of the disease insofar as they are more prominent.<sup>23</sup> Myalgia is prominent in the calf muscle (especially in children) and the paravertebral and back muscles, but all striated muscles may become involved such as the extraocular muscle, which causes painful eye movement. These symptoms are mostly accompanied by the manifestations of respiratory tract illnesses such as dry cough, nasal discharge, and sore throat. Often, so abrupt is the onset that the patient can remember the precise onset of the disease. However, the manifestations of influenza infections can range from afebrile respiratory illnesses similar to the common cold, to diseases in which systemic signs and symptoms predominate with relatively little respiratory tract infection symptoms.<sup>24,25</sup> In the early days, the patient has high-grade fever and on the 2nd and 3rd days, the fever decreases and diminishes gradually. It may, nonetheless, last for 4 to 8 days. Early in the course of the disease, the patient's face is plethoric with watery and red eyes. A convalescent period of some weeks may ensue, during which dry cough and malaise are the most salient complaints of the patient.

## Complications of Influenza

### *Pneumonia*

The most important and common complication of influenza is pneumonia, not least in high-risk individuals. Pneumonia may happen as a continuum of the acute influenza syndrome when caused by the influenza virus (primary pneumonia) or as a mixed viral and bacterial infection after a gap of a few days (secondary pneumonia).

### *Primary Influenza Viral Pneumonia*

The illness occurs after the typical course of flu with a rapid progression of fever, dyspnea, cough, cyanosis, and difficult breathing. It happens predominantly among individuals with cardiovascular or underlying pulmonary diseases such as asthma. Physical examination is in favor of bilateral lung involvement, and imaging findings in the lungs constitute reticular or reticulonodular opacities with or without superimposed consolidation. Sometimes the radiological appearance of primary influenza pneumonia can be difficult to distinguish from pulmonary edema because of the presence of perihilar congestion and hazy opacification, at least in the lower lobes. Less frequently, radiographs show focal areas of infiltration. Commonly used pneumonia severity assessment tools such as the CURB65 or the Pneumonia Severity Index are not useful in determining which patients to hospitalize due to primary influenza pneumonia since these tools have not been developed and validated during an influenza pandemic.<sup>26</sup> Thus, careful history taking and examination, determination of pregnancy or hypotension, and early identification of young patients with decreased oxygen saturation, respiratory rate >25 per minute, and concomitant diarrhea are crucial for admission decision-making. The typical radiographic findings of primary influenza pneumonia are bilateral reticular or reticulonodular opacities, sometimes accompanied by superimposed consolidation. Less frequently, radiographs show focal areas of consolidation without reticular opacities. High-resolution computed tomography often shows multifocal peribronchovascular or subpleural consolidation with or without ground-glass opacities.<sup>27</sup> The most severe cases progress rapidly to acute respiratory distress syndrome and multilobar alveolar infiltrations. These patients usually present with progressive dyspnea and severe hypoxemia 2 to 5 days after the onset of typical influenza symptoms. Hypoxemia increases rapidly and causes

respiratory failure, requiring intubation and mechanical ventilation, maybe after only 1 day of hospitalization.<sup>28</sup>

### *Secondary Bacterial Pneumonia*

The incidence of secondary bacterial pneumonia ranged from 2% to 18% during the influenza pandemic in 1957–58.<sup>29</sup> A threefold increase in the incidence of secondary *Staphylococcus aureus pneumonia* during the influenza pandemic of 1968–9 compared to a non-epidemic period of pneumonia etiologies was observed.<sup>30</sup> Recently, community-acquired methicillin-resistant *Staphylococcus aureus* was determined after seasonal influenza,<sup>31</sup> but another very common etiologic bacterium is *Streptococcus pneumoniae*. The patient has a classic influenza disease, followed by an improvement period lasting maximally 2 weeks. The recurrence of the symptoms such as fever, productive cough, and dyspnea and findings of new consolidations in chest imaging can be found in involved patients. Accordingly, a biphasic pattern of signs and symptoms in influenza-labeled patients should be considered as secondary superimposed bacterial pneumonia.

### *Non-Pulmonary Complications*

In addition to its respiratory effects, the virus can exert effects on other body systems such as the musculoskeletal, cardiac, and neurologic systems. Myocarditis and pericarditis constitute unusual but significant complications of seasonal or pandemic flu. In a prospective study, half of adult flu patients without cardiac complaints had abnormal ECG findings at presentation.<sup>32</sup> Myocarditis mostly resolves by 28 days, and the patients has a good heart-muscle function without a reduced ejection fraction. Significant myositis and rhabdomyolysis have rarely been reported with seasonal influenza,<sup>25</sup> but different amounts of creatine phosphokinase elevation have been reported in many studies after seasonal or pandemic flues.<sup>33–35</sup> Mild myositis and myoglobinuria with tender leg or back muscles can mainly be seen in children, although they can occur in adults and be accompanied by symptoms of painful walking or standing. Other rare complications such as the Guillain–Barré syndrome, encephalitis, acute liver failure, and the Reye syndrome may happen after influenza A infection.

## Diagnosis

The majority of influenza cases are diagnosed by their clinical manifestations and there is no need for laboratory tests. Be that as it may, in special

circumstances, the diagnosis of flu necessitates laboratory confirmation using available tests such as nucleic acid tests (e.g., polymerase chain reaction [PCR]) or rapid diagnosis kits or rarely virus isolation by culture methods.

#### *Rapid Diagnosis Influenza Tests*

Rapid influenza diagnostic tests detect influenza viral antigens and screen patients with suspected influenza in a timely manner in comparison to other diagnostic modalities. The most widely used technique is based on the detection of viral antigens in the respiratory secretions of patients by immunologic methods. All rapid tests are performed with ease and can provide results within 30 minutes. Each test varies with regard to whether it can distinguish between influenza A and B. Nevertheless, these tests have thus far been unable to specify types of influenza A such as H1N1 and H3N2. The overall specificities achieved by these tests are high and comparable between the manufacturers. However, their sensitivities have shown great heterogeneity across studies depending on the nature of the samples tested and the patients, ranging from 4.4% to 80% in comparison to cell culture as a gold standard test.<sup>36-38</sup> As a general concept, sensitivity in adults is less than that reported in younger patients. Also, the sensitivity may be higher at the onset of the disease, when a higher load of the virus exists. Economic studies comparing rapid testing to the clinical diagnosis of influenza remain inconclusive. Indeed, some studies have suggested that, in most cases, clinical judgment combined with antiviral treatment is the most cost-effective strategy,<sup>39</sup> while new studies have suggested that testing may be the most cost-effective strategy and shown that oseltamivir treatment based on the point-of-care (POC) test is a dominant option compared to conventional approaches without screening tests in the baseline scenario and that they could be cost-effective in 80% of cases according to the cost-effectiveness acceptability curve.<sup>39</sup> Furthermore, influenza antiviral treatment based on POC could be cost-effective in specific conditions of performance, price, and disease prevalence.<sup>40</sup>

#### *Molecular Tests*

Due to the limitation in other diagnostic modalities in influenza detection, molecular assays have increasingly been considered the gold standard diagnostic method for the detection of the influenza virus in hospital-based diagnostic laboratories. Although several amplification methods have been developed, the majority of the current assays—particularly those

used in clinical laboratories—are based on the PCR amplification method. These tests have the ability to check several targets concurrently and thereby provide type and subtype information for each virus. Additionally, they have the ability to be adapted rapidly for the detection of novel targets; these features<sup>41</sup> played a critical role during the influenza pandemic of 2009. PCR is potentially more sensitive than cell culture, and it can detect the nonviable virus in samples. The sensitivity of these tests is dependent on the sample site of the patient and is similar to that of the rapid tests. Higher sensitivity can be obtained by swab samples of a nasopharyngeal origin. PCR-based molecular assays have yielded excellent clinical utility for the detection and identification of influenza viruses at bedside as POC, and numerous Food and Drug Administration (FDA)-cleared commercial devices are now available.<sup>42-44</sup>

#### *Role of the Laboratory Diagnosis of Flu in Clinical Case Management*

Given the self-limiting nature of the disease in otherwise healthy individuals, there is no need for diagnostic tests in all presenting cases. Diagnostic tests should be conducted if the results of the test are thought to be able to influence subsequent clinical management and if the results of the test are deemed influential in decisions on the initiation of specific antiviral treatment, impact on other diagnostic tests, antibiotic treatment decision-making, and infection control practices.<sup>45</sup> In addition, during influenza seasons, hospitalized individuals of any age with fever and severe respiratory symptoms—including those with a diagnosis of community-acquired pneumonia—need laboratory testing irrespective of time from illness onset.

#### **Therapy**

Currently, at least 4 antiviral drugs are available for the treatment and prevention of influenza. It is deserving of note that in healthy immunocompetent individuals with intact immunity, there is a rapid limitation in the ability of the influenza virus; therefore, the anti-replication power of antiviral drugs is limited and has no theoretical effect. Also, no study to date has demonstrated a beneficial effect for antiviral agents starting beyond 48 hours of symptom onset. The greatest effect is classically seen when therapy is started in the first 24 hours. Treatment is recommended for both adults and children with the influenza virus infection with the following criteria:<sup>46</sup>

- 1) Persons with laboratory-confirmed or highly suspected influenza virus infection in high-risk groups (table 1), within 48 hours after symptom onset
- 2) Patients requiring hospitalization for laboratory-confirmed or highly suspected influenza disease, regardless of underlying illnesses, if treatment can be initiated within 48 hours after symptom onset
- 3) Outpatients at high risk of complications (table 1) with an illness that is not improving and outpatients with a positive influenza test result from a specimen obtained >48 hours after symptom onset.

Individuals whose onset of symptoms is >48 hours before presentation with persisting moderate-to-severe illness.

During the last pandemic wave, neuraminidase inhibitors (NAIs)—primarily oseltamivir and zanamivir—were widely prescribed for patients with confirmed or suspected A H1N1pdm09 infection.<sup>47,48</sup> However, before the 2009–10 pandemic, evidence of their effectiveness in seasonal influenza, while strong for modest symptom reduction, was less strong for decreases in pneumonia incidence or pneumonia outcome improvement.<sup>49–52</sup> Recent data demonstrated that patients with influenza-related pneumonia treated early ( $\leq 48$  h after illness onset) with an NAI experienced around one-third lower likelihood of dying or requiring ventilator assistance compared to those treated at later hours.<sup>53</sup> Influenza viruses and their susceptibilities to available antiviral medications are changing rapidly. Clinicians should be aware of the local patterns of influenza circulations and susceptibilities. For instance, a meta-analysis showed that NAIs were able to lessen mortality in patients admitted to the hospital with A H1N1pdm09 infection.<sup>30</sup> Sporadic oseltamivir-resistant infections have been identified, together with rare episodes of limited transmission.<sup>54</sup> Given the currently circulating influenza A (H3N2) and 2009 H1N1 virus resistance to adamantanes, these medications are not recommended for use against influenza A virus-induced infections. However, most influenza A and B virus strains are still susceptible to neuraminidases such as oseltamivir and zanamivir, with these drugs being selected for treatment in indicated persons (table 2). In addition, it should be considered that the development of resistance to oseltamivir during treatment was more common among seasonal influenza A (H1N1) virus infections (27%) than among seasonal influenza A (H3N2) (3%) or B (0%) virus infections in a recent study.<sup>55</sup>

Due to the limitations in the current therapeutic options for the treatment of influenza

**Table 2:** Recommended dosages and durations of influenza antiviral medications for treatment or chemoprophylaxis

Antiviral agent	Use	Adults
Oseltamivir	Treatment (5 d)	75 mg twice daily
	Chemoprophylaxis (7 d)	75 mg once daily
Zanamivir	Treatment (5 d)	10 mg (two 5-mg inhalations) twice daily
	Chemoprophylaxis (7 d)	10 mg (two 5-mg inhalations) once daily

virus infections, additional treatment options with a different mechanism of action have been investigated as treatment for individuals with severe influenza virus disease. For example, a handful of mAbs against influenza virus proteins are currently in the early phases of evaluation for human infection control.<sup>56</sup> These mAbs target the external portions (i.e. ectodomain) of the M2 protein (M2e). The M2e is an attractive target for influenza vaccines and therapeutic antibodies because of the extremely conserved nature of the amino acid sequences of its domains among isolates from different subtypes of influenza A viruses.<sup>57</sup>

The mechanisms of anti-M2e Ab-mediated protection are not completely determined. Anti-M2 Abs do not have hemagglutination inhibition ability or *in vitro* virus neutralization properties.<sup>58</sup> It is supposed that the main target for the anti-M2e antibody is virus-infected human cells, which heavily express M2e on their surface.<sup>59</sup>

Most studies have reported that corticosteroid therapy adversely influences influenza-related outcomes. During the 2009 influenza pandemic, 37% to 55% of the patients admitted to ICUs in Europe received corticosteroids as part of their treatment.<sup>60–62</sup> Nonetheless, in a recent meta-analysis report, evidence from observational studies—albeit with important limitations—suggested that corticosteroid therapy for presumed influenza-associated complications was associated with increased mortality.<sup>63</sup>

## Prevention

### Vaccination

The most important strategy for the prevention of influenza and its severe outcomes is annual vaccination against seasonal influenza. The influenza virus is characterized for its high rate of mutation, beating the immune system's function against new variants,<sup>64</sup> which is why

new vaccines are produced annually to match circulating viruses.<sup>65</sup> The selection of influenza antigens to include in the vaccines is based upon the global surveillance of influenza viruses in circulation and the spread of new strains of the influenza virus around the world.<sup>66</sup> For the following influenza season in the southern hemisphere, recommendations are made in September and for the influenza season in the northern hemisphere in February because around 6 to 8 months are needed to manufacture and approve new vaccines. Recently, the World Health Organization (WHO) recommended that trivalent influenza vaccines for use in the 2016 southern hemisphere influenza season contain the following virus antigens:<sup>67</sup>

- An A/California/7/2009 (H1N1) pdm09-like virus
- An A/Hong Kong/4801/2014 (H3N2)-like virus
- A B/Brisbane/60/2008-like virus.

The WHO stresses that vaccination is especially important for individuals at higher risk of serious influenza complications, with the highest priority afforded to pregnant ladies—followed by children aged between 6 and 59 months, elderly and individuals with specific chronic medical conditions (e.g., renal failure and diabetes mellitus), and finally individuals at high risk (e.g., health staff).<sup>68</sup> In contrast in 2010, the United States' Advisory Committee on Immunization Practices (ACIP) extended the recommendation for annual influenza vaccination to encompass all individuals 6 months of age and older individuals who did not have contraindications without any priority.<sup>69</sup>

#### *Schedule*

The outbreaks of influenza generally occur during the last autumn and whole winter months. A single dose (0.5 cc) of an influenza vaccine should be injected to adults annually, preferably by October in the northern hemisphere and May in the southern hemisphere. Children aged between 6 months and 8 years require 2 doses of influenza vaccine (with at least 4 weeks apart) during their 1st season of vaccination for optimal response.<sup>69</sup>

#### *Efficacy*

The vaccine effectiveness of influenza vaccines is a determinant of how much the seasonal influenza vaccine can prevent influenza virus infections in the given population during an influenza season.<sup>70</sup> Recently, the documentation of the antigenic drift from the vaccine strain in a majority of considered isolates raised concern that vaccine effectiveness might be suboptimal,

especially in older ages or specific high-risk groups. The Centers for Disease Control and Prevention (CDC) in the United States of America had an estimation of 23% of vaccine effectiveness for the northern hemisphere 2014–15 seasonal influenza vaccine due to a mismatch in the circulating viruses and vaccine contained viruses.<sup>71</sup> What should be taken into consideration is that even if a vaccine is not completely related to the predominant circulating virus, it can protect several different influenza viruses and can, as such, confer good protection and prevent influenza-related illnesses. It is also a fact that influenza vaccines are safe and are especially important for reducing severe disease in some high-risk populations. Accordingly, the WHO recommends seasonal influenza vaccines even if they are not closely related to the predominant circulating influenza viruses each year for the above-mentioned groups.<sup>72</sup>

#### *Chemoprophylaxis Strategy*

Available antiviral drugs play an important role for patients who have not been immunized or who are nonresponsive to vaccines. Oseltamivir and zanamivir are the recommended drugs for the prevention of influenza based on their established efficacy and low rates of resistance in comparison to adamantanes.<sup>73</sup> These agents are effective for the prevention of influenza in healthy individuals, persons at high risk of influenza complications, and those residing in long-term care facilities. The efficacy of oseltamivir and zanamivir has yet to be compared with each other.<sup>74</sup> It should be emphasized that when choosing a strategy of antiviral chemoprophylaxis, some parameters such as preventing complications in patients at high risk and reducing the risk of promoting antiviral drug resistance should be considered. There are, therefore, some indications for this approach, as follows:<sup>18</sup>

- 1) Influenza prophylaxis during influenza outbreaks in long-term care centers in the elderly regardless of prior influenza vaccinations
- 2) In unvaccinated individuals at high risk of influenza complications who have been exposed to an individual with influenza infections within the previous 48 hours
- 3) Antiviral prophylaxis for vaccinated persons at high risk of influenza complications who have had close contact with an individual with influenza within the previous 48 hours when there is a poor match between the vaccine and circulating viruses in a given year
- 4) The United States' ACIP recommends that antiviral chemoprophylaxis be considered

in pregnant women and in women up to 2 weeks postpartum who have close contact with suspected or confirmed influenza A-infected individuals. Zanamivir may be the drug of choice for prophylaxis due to its limited systemic absorption.<sup>75</sup>

## Conclusion

Influenza epidemics and pandemics impose a heavy socioeconomic burden on all societies. Hospital admission and treatment and ICU care are more often necessary in high-risk individuals such as the elderly and pregnant ladies. However, the impact of influenza cannot be neglected even in young adults, mainly because of the loss of productivity.

Given the nature of the virus and the increasing patterns of the available antiviral drugs against the influenza virus, the best strategy is the vaccination of high-risk groups (table 1) at appropriate times. Inactivated influenza vaccines are always well-tolerated, with the most common side effect being burning pain at the injection site. In clinical trials, serious adverse events have been reported in <1% of the individuals vaccinated. Consequently, the vaccination policy in high-risk groups should be the priority in the battle against flu.

With concerns over increasing resistance against both adamantanes and NAIs, the risk of the development of antiviral drug resistance should be considered if we opt to treat all patients who are labeled as suffering from flu. Individuals with suspected flu with severe disease such as those with signs and symptoms of lower respiratory tract infections (e.g., dyspnea, tachypnea, and low oxygen saturation) and those who have signs of rapid clinical deterioration or those at high risk of complications should receive antiviral therapy. In all cases, antivirals should be started <48 hours after symptom onset. In pregnant patients due to higher mortality, there is a suggestion that all patients with suspected or confirmed influenza—even those who present >48 hours after symptom onset—be treated provided that they are not improving. In addition, a new look at antiviral chemoprophylaxis and its appropriate use may effect a reduction in morbidity and mortality allied to flu in high-risk groups.

**Conflict of Interest:** None declared.

## References

1. Shrestha S, Foxman B, Berus J, van Panhuis WG, Steiner C, Viboud C, et al.

- The role of influenza in the epidemiology of pneumonia. *Sci Rep.* 2015;5:15314. doi: 10.1038/srep15314. PubMed PMID: 26486591; PubMed Central PMCID: PMC4614252.
2. Heesterbeek H, Anderson RM, Andreasen V, Bansal S, De Angelis D, Dye C, et al. Modeling infectious disease dynamics in the complex landscape of global health. *Science.* 2015;347:aaa4339. doi: 10.1126/science.aaa4339. PubMed PMID: 25766240; PubMed Central PMCID: PMC4445966.
  3. Hirsch A. *Handbook of geographical and historical pathology.* London: New Sydenham Society; 1883.
  4. Molineux D. *Dr. Molineux's Historical Account of the Late General Coughs and Colds; with Some Observations on Other Epidemick Distempers.* Philosophical Transactions (1683-1775). 1694:105-11.
  5. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. *Bull Hist Med.* 2002;76:105-15. PubMed PMID: 11875246.
  6. Novel Swine-Origin Influenza AVIT, Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med.* 2009;360:2605-15. doi: 10.1056/NEJMoa0903810. PubMed PMID: 19423869.
  7. Influenza WP. Report of the WHO pandemic influenza A (H1N1) vaccine deployment initiative. 2012.
  8. Mosnier A, Caini S, Daviaud I, Nauleau E, Bui TT, Debost E, et al. Clinical Characteristics Are Similar across Type A and B Influenza Virus Infections. *PLoS One.* 2015;10:e0136186. doi: 10.1371/journal.pone.0136186. PubMed PMID: 26325069; PubMed Central PMCID: PMC4556513.
  9. Poon LL, Song T, Rosenfeld R, Lin X, Rogers MB, Zhou B, et al. Quantifying influenza virus diversity and transmission in humans. *Nat Genet.* 2016;48:195-200. doi: 10.1038/ng.3479. PubMed PMID: 26727660; PubMed Central PMCID: PMC4731279.
  10. Fuller TL, Gilbert M, Martin V, Cappelle J, Hosseini P, Njabo KY, et al. Predicting hotspots for influenza virus reassortment. *Emerg Infect Dis.* 2013;19:581-8. doi: 10.3201/eid1904.120903. PubMed PMID: 23628436; PubMed Central PMCID: PMC3647410.
  11. Kanegae Y, Sugita S, Endo A, Ishida M, Senya S, Osako K, et al. Evolutionary pattern of the hemagglutinin gene of influenza B viruses isolated in Japan:



- cocirculating lineages in the same epidemic season. *J Virol.* 1990;64:2860-5. PubMed PMID: 2335820; PubMed Central PMCID: PMC249468.
12. Moghadami M, Moattari A, Tabatabaee HR, Mirahmadizadeh A, Rezaianzadeh A, Hasanzadeh J, et al. High titers of hemagglutination inhibition antibodies against 2009 H1N1 influenza virus in Southern Iran. *Iran J Immunol.* 2010;7:39-48. doi: IJlv7i1A5. PubMed PMID: 20371918.
  13. Webster RG, Kendal AP, Gerhard W. Analysis of antigenic drift in recently isolated influenza A (H1N1) viruses using monoclonal antibody preparations. *Virology.* 1979;96:258-64. PubMed PMID: 88798.
  14. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA.* 2010;303:1517-25. doi: 10.1001/jama.2010.479. PubMed PMID: 20407061.
  15. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. *Am J Obstet Gynecol.* 1959;78:1172-5. PubMed PMID: 13824729.
  16. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, et al. Influenza-associated deaths among children in the United States, 2003-2004. *N Engl J Med.* 2005;353:2559-67. doi: 10.1056/NEJMoa051721. PubMed PMID: 16354892.
  17. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis.* 2007;7:257-65. doi: 10.1016/S1473-3099(07)70029-4. PubMed PMID: 17376383.
  18. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60:1-24. PubMed PMID: 21248682.
  19. Cowling BJ, Ip DK, Fang VJ, Suntarattiwong P, Olsen SJ, Levy J, et al. Aerosol transmission is an important mode of influenza A virus spread. *Nat Commun.* 2013;4:1935. doi: 10.1038/ncomms2922. PubMed PMID: 23736803; PubMed Central PMCID: PMC3682679.
  20. Wong BC, Lee N, Li Y, Chan PK, Qiu H, Luo Z, et al. Possible role of aerosol transmission in a hospital outbreak of influenza. *Clin Infect Dis.* 2010;51:1176-83. doi: 10.1086/656743. PubMed PMID: 20942655.
  21. Carrat F, Vergu E, Ferguson NM, Lemaître M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol.* 2008;167:775-85. doi: 10.1093/aje/kwm375. PubMed PMID: 18230677.
  22. Boivin G, Goyette N, Bernatchez H. Prolonged excretion of amantadine-resistant influenza A virus quasi species after cessation of antiviral therapy in an immunocompromised patient. *Clin Infect Dis.* 2002;34:E23-5. doi: 10.1086/338870. PubMed PMID: 11807683.
  23. Weinstock DM, Gubareva LV, Zuccotti G. Prolonged shedding of multidrug-resistant influenza A virus in an immunocompromised patient. *N Engl J Med.* 2003;348:867-8. doi: 10.1056/NEJM200302273480923. PubMed PMID: 12606750.
  24. Liu W, Peng L, Liu H, Hua S. Pulmonary Function and Clinical Manifestations of Patients Infected with Mild Influenza A Virus Subtype H1N1: A One-Year Follow-Up. *PLoS One.* 2015;10:e0133698. doi: 10.1371/journal.pone.0133698. PubMed PMID: 26218647; PubMed Central PMCID: PMC4517883.
  25. Rello J, Pop-Vicas A. Clinical review: primary influenza viral pneumonia. *Crit Care.* 2009;13:235. doi: 10.1186/cc8183. PubMed PMID: 20085663; PubMed Central PMCID: PMC2811908.
  26. Minodier L, Charrel RN, Ceccaldi PE, van der Werf S, Blanchon T, Hanslik T, et al. Prevalence of gastrointestinal symptoms in patients with influenza, clinical significance, and pathophysiology of human influenza viruses in faecal samples: what do we know? *Virology.* 2015;12:215. doi: 10.1186/s12985-015-0448-4. PubMed PMID: 26651485; PubMed Central PMCID: PMC4676820.
  27. Kloth C, Forler S, Gatidis S, Beck R, Spira D, Nikolaou K, et al. Comparison of chest-CT findings of Influenza virus-associated pneumonia in immunocompetent vs. immunocompromised patients. *Eur J Radiol.* 2015;84:1177-83. doi: 10.1016/j.ejrad.2015.02.014. PubMed PMID: 25796425.
  28. Mancinelli L, Onori M, Concato C, Sorge R, Chiavelli S, Coltella L, et al. Clinical features of children hospitalized with influenza A and B infections during the 2012-2013 influenza season in Italy. *BMC Infect Dis.* 2016;16:6. doi: 10.1186/s12879-015-1333-x. PubMed PMID: 26743673; PubMed Central PMCID: PMC4705698.

29. Rello J, Rodriguez A, Ibanez P, Socias L, Cebrian J, Marques A, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care*. 2009;13:R148. doi: 10.1186/cc8044. PubMed PMID: 19747383; PubMed Central PMCID: PMC2784367.
30. To KK, Hung IF, Li IW, Lee KL, Koo CK, Yan WW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis*. 2010;50:850-9. doi: 10.1086/650581. PubMed PMID: 20136415.
31. Schwarzmann SW, Adler JL, Sullivan RJ, Jr., Marine WM. Bacterial pneumonia during the Hong Kong influenza epidemic of 1968-1969. *Arch Intern Med*. 1971;127:1037-41. PubMed PMID: 5578560.
32. Kallen AJ, Brunkard J, Moore Z, Budge P, Arnold KE, Fosheim G, et al. Staphylococcus aureus community-acquired pneumonia during the 2006 to 2007 influenza season. *Ann Emerg Med*. 2009;53:358-65. doi: 10.1016/j.annemergmed.2008.04.027. PubMed PMID: 18534715.
33. Ison MG, Campbell V, Rembold C, Dent J, Hayden FG. Cardiac findings during uncomplicated acute influenza in ambulatory adults. *Clin Infect Dis*. 2005;40:415-22. doi: 10.1086/427282. PubMed PMID: 15668866.
34. Foulkes W, Rees J, Sewry C. Influenza A and rhabdomyolysis. *J Infect*. 1990;21:303-4. PubMed PMID: 2177078.
35. Chen KF, Gaydos C, Rothman RE. Update on emerging infections: news from the Centers for Disease Control and Prevention. Hospitalized patients with novel influenza A (H1N1) virus infection--California, April-May, 2009. *Ann Emerg Med*. 2009;54:732-6. PubMed PMID: 19866495.
36. Kaufman MA, Duke GJ, McGain F, French C, Aboltins C, Lane G, et al. Life-threatening respiratory failure from H1N1 influenza 09 (human swine influenza). *Med J Aust*. 2009;191:154-6. PubMed PMID: 19645645.
37. Chu H, Lofgren ET, Halloran ME, Kuan PF, Hudgens M, Cole SR. Performance of rapid influenza H1N1 diagnostic tests: a meta-analysis. *Influenza Other Respir Viruses*. 2012;6:80-6. doi: 10.1111/j.1750-2659.2011.00284.x. PubMed PMID: 21883964; PubMed Central PMCID: PMC3288365.
38. Chartrand C, Leeflang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med*. 2012;156:500-11. doi: 10.7326/0003-4819-156-7-201204030-00403. PubMed PMID: 22371850.
39. Lee BY, McGlone SM, Bailey RR, Wiringa AE, Zimmer SM, Smith KJ, et al. To test or to treat? An analysis of influenza testing and antiviral treatment strategies using economic computer modeling. *PLoS One*. 2010;5:e11284. doi: 10.1371/journal.pone.0011284. PubMed PMID: 20585642; PubMed Central PMCID: PMC2890406.
40. Nagase H, Moriwaki K, Kamae M, Yanagisawa S, Kamae I. Cost-effectiveness analysis of oseltamivir for influenza treatment considering the virus emerging resistant to the drug in Japan. *Value Health*. 2009;12 Suppl 3:S62-5. doi: 10.1111/j.1524-4733.2009.00629.x. PubMed PMID: 20586984.
41. Nshimyumukiza L, Douville X, Fournier D, Duplantie J, Daher RK, Charlebois I, et al. Cost-effectiveness analysis of antiviral treatment in the management of seasonal influenza A: point-of-care rapid test versus clinical judgment. *Influenza Other Respir Viruses*. 2016;10:113-21. doi: 10.1111/irv.12359. PubMed PMID: 26574910; PubMed Central PMCID: PMC4746566.
42. Kumar S, Henrickson KJ. Update on influenza diagnostics: lessons from the novel H1N1 influenza A pandemic. *Clin Microbiol Rev*. 2012;25:344-61. doi: 10.1128/CMR.05016-11. PubMed PMID: 22491775; PubMed Central PMCID: PMC3346302.
43. Teo J, Di Pietro P, San Biagio F, Capozzoli M, Deng YM, Barr I, et al. VereFlu: an integrated multiplex RT-PCR and microarray assay for rapid detection and identification of human influenza A and B viruses using lab-on-chip technology. *Arch Virol*. 2011;156:1371-8. doi: 10.1007/s00705-011-0999-7. PubMed PMID: 21503642.
44. Tang YW, Lowery KS, Valsamakis A, Schaefer VC, Chappell JD, White-Abell J, et al. Clinical accuracy of a PLEX-ID flu device for simultaneous detection and identification of influenza viruses A and B. *J Clin Microbiol*. 2013;51:40-5. doi: 10.1128/JCM.01978-12. PubMed PMID: 23077123; PubMed Central PMCID: PMC3536229.
45. Loeffelholz MJ, Pong DL, Pyles RB, Xiong Y, Miller AL, Bufton KK, et al. Comparison of the FilmArray Respiratory Panel and Prodesse real-time PCR assays for detection of respiratory pathogens. *J Clin Microbiol*. 2011;49:4083-8. doi: 10.1128/JCM.05010-11. PubMed PMID: 21998418; PubMed Central PMCID: PMC3232999.
46. Harper SA, Bradley JS, Englund JA, File TM,

- Gravenstein S, Hayden FG, et al. Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:1003-32. doi: 10.1086/598513. PubMed PMID: 19281331.
47. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med.* 2014;2:395-404. doi: 10.1016/S2213-2600(14)70041-4. PubMed PMID: 24815805.
  48. Gasparini R, Amicizia D, Lai PL, Bragazzi NL, Panatto D. Compounds with anti-influenza activity: present and future of strategies for the optimal treatment and management of influenza. Part I: Influenza life-cycle and currently available drugs. *J Prev Med Hyg.* 2014;55:69-85. PubMed PMID: 25902573; PubMed Central PMCID: PMC4718311.
  49. World Health Organization (WHO) [Internet]. Clinical management of human infection with pandemic (H1N1) 2009: Revised guidance. [cited 2014 November 18]. Available from: [http://www.who.int/csr/resources/publications/swineflu/clinical\\_management\\_h1n1.pdf](http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf)
  50. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med.* 2003;163:1667-72. doi: 10.1001/archinte.163.14.1667. PubMed PMID: 12885681.
  51. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med.* 2012;156:512-24. doi: 10.7326/0003-4819-156-7-201204030-00411. PubMed PMID: 22371849.
  52. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLoS Med.* 2012;9:e1001201. doi: 10.1371/journal.pmed.1001201. PubMed PMID: 22505850; PubMed Central PMCID: PMC3323511.
  53. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Lim WS, Al Mamun A, et al. Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant data meta-analysis. *Influenza Other Respir Viruses.* 2016;10:192-204. doi: 10.1111/irv.12363. PubMed PMID: 26602067; PubMed Central PMCID: PMC4814862.
  54. Chen LF, Dailey NJ, Rao AK, Fleischauer AT, Greenwald I, Deyde VM, et al. Cluster of oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infections on a hospital ward among immunocompromised patients--North Carolina, 2009. *J Infect Dis.* 2011;203:838-46. doi: 10.1093/infdis/jiq124. PubMed PMID: 21343149; PubMed Central PMCID: PMC3307091.
  55. Stephenson I, Democratis J, Lackenby A, McNally T, Smith J, Pareek M, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis.* 2009;48:389-96. doi: 10.1086/596311. PubMed PMID: 19133796.
  56. Ramos EL, Mitcham JL, Koller TD, Bonavia A, Usner DW, Balaratnam G, et al. Efficacy and safety of treatment with an anti-m2e monoclonal antibody in experimental human influenza. *J Infect Dis.* 2015;211:1038-44. doi: 10.1093/infdis/jiu539. PubMed PMID: 25281755.
  57. Schotsaert M, De Filette M, Fiers W, Saelens X. Universal M2 ectodomain-based influenza A vaccines: preclinical and clinical developments. *Expert Rev Vaccines.* 2009;8:499-508. doi: 10.1586/erv.09.6. PubMed PMID: 19348565; PubMed Central PMCID: PMC2706389.
  58. Jegerlehner A, Schmitz N, Storni T, Bachmann MF. Influenza A vaccine based on the extracellular domain of M2: weak protection mediated via antibody-dependent NK cell activity. *J Immunol.* 2004;172:5598-605. PubMed PMID: 15100303.
  59. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015;211:80-90. doi: 10.1093/infdis/jiu396. PubMed PMID: 25030060; PubMed Central PMCID: PMC4264590.
  60. Diaz E, Martin-Loeches I, Canadell L, Vidaur L, Suarez D, Socias L, et al. Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. *J Infect.* 2012;64:311-8. doi: 10.1016/j.jinf.2011.12.010. PubMed PMID: 22240033.

61. Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L, Group R-SAHNvR. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2011;183:1200-6. doi: 10.1164/rccm.201101-0135OC. PubMed PMID: 21471082.
62. Linko R, Pettila V, Ruokonen E, Varpula T, Karlsson S, Tenhunen J, et al. Corticosteroid therapy in intensive care unit patients with PCR-confirmed influenza A(H1N1) infection in Finland. *Acta Anaesthesiol Scand.* 2011;55:971-9. doi: 10.1111/j.1399-6576.2011.02491.x. PubMed PMID: 22092165.
63. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam JS, Lim WS. Effect of corticosteroid therapy on influenza-related mortality: a systematic review and meta-analysis. *J Infect Dis.* 2015;212:183-94. doi: 10.1093/infdis/jiu645. PubMed PMID: 25406333.
64. Kilbourne ED. Influenza immunity: new insights from old studies. *J Infect Dis.* 2006;193:7-8. doi: 10.1086/498984. PubMed PMID: 16323125.
65. Glezen WP. Clinical practice. Prevention and treatment of seasonal influenza. *N Engl J Med.* 2008;359:2579-85. doi: 10.1056/NEJMcp0807498. PubMed PMID: 19073977.
66. Ang LW, Tien WS, Lin RT, Cui L, Cutter J, James L, et al. Characterization of influenza activity based on virological surveillance of influenza-like illness in tropical Singapore, 2010-2014. *J Med Virol.* 2016;88:2069-77. doi: 10.1002/jmv.24566. PubMed PMID: 27152935.
67. Zhao B, Qin S, Teng Z, Chen J, Yu X, Gao Y, et al. Epidemiological study of influenza B in Shanghai during the 2009-2014 seasons: implications for influenza vaccination strategy. *Clin Microbiol Infect.* 2015;21:694-700. doi: 10.1016/j.cmi.2015.03.009. PubMed PMID: 25882368.
68. Meerhoff TJ, Simaku A, Ulqinaku D, Torosyan L, Gribkova N, Shimanovich V, et al. Surveillance for severe acute respiratory infections (SARI) in hospitals in the WHO European region - an exploratory analysis of risk factors for a severe outcome in influenza-positive SARI cases. *BMC Infect Dis.* 2015;15:1. doi: 10.1186/s12879-014-0722-x. PubMed PMID: 25567701; PubMed Central PMCID: PMC4314771.
69. Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 Influenza Season. *MMWR Morb Mortal Wkly Rep.* 2015;64:818-25. PubMed PMID: 26247435.
70. Ohmit SE, Petrie JG, Malosh RE, Fry AM, Thompson MG, Monto AS. Influenza vaccine effectiveness in households with children during the 2012-2013 season: assessments of prior vaccination and serologic susceptibility. *J Infect Dis.* 2015;211:1519-28. doi: 10.1093/infdis/jiu650. PubMed PMID: 25416812; PubMed Central PMCID: PMC4462665.
71. Flannery B, Clippard J, Zimmerman RK, Nowalk MP, Jackson ML, Jackson LA, et al. Early estimates of seasonal influenza vaccine effectiveness - United States, January 2015. *MMWR Morb Mortal Wkly Rep.* 2015;64:10-5. PubMed PMID: 25590680.
72. Ampofo WK, Azziz-Baumgartner E, Bashir U, Cox NJ, Fasce R, Giovanni M, et al. Strengthening the influenza vaccine virus selection and development process: Report of the 3rd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at WHO headquarters, Geneva, Switzerland, 1-3 April 2014. *Vaccine.* 2015;33:4368-82. doi: 10.1016/j.vaccine.2015.06.090. PubMed PMID: 26148877.
73. Li TC, Chan MC, Lee N. Clinical Implications of Antiviral Resistance in Influenza. *Viruses.* 2015;7:4929-44. doi: 10.3390/v7092850. PubMed PMID: 26389935; PubMed Central PMCID: PMC4584294.
74. Merritt T, Hope K, Butler M, Durrheim D, Gupta L, Najjar Z, et al. Effect of antiviral prophylaxis on influenza outbreaks in aged care facilities in three local health districts in New South Wales, Australia, 2014. *Western Pac Surveill Response J.* 2016;7:14-20. doi: 10.5365/WPSAR.2015.6.3.005. PubMed PMID: 27757249.
75. Louie JK, Salibay CJ, Kang M, Glenn-Finer RE, Murray EL, Jamieson DJ. Pregnancy and severe influenza infection in the 2013-2014 influenza season. *Obstet Gynecol.* 2015;125:184-92. doi: 10.1097/AOG.0000000000000593. PubMed PMID: 25560123.