

The Evolution and Complications of the Influenza During Covid-19 Pandemic

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Abstract. *Seasonal influenza coupled with COVID-19, infection with the virus SARS-CoV2, represents a dual challenge to the primary care. As well as this, the staff in primary health care, ambulatory centers and hospitals are intensively involved in the diagnosis, treatment and monitoring of people with the flu during the peak periods of the disease. In Romania, in primary healthcare, the diagnosis is based more on clinical criteria and not always by determining the etiology of the respiratory infection. The use of rapid tests in the diagnosis of respiratory infections has increased in the last year. Given the current increase in cases of both COVID-19 and seasonal influenza, early diagnosis is also of great importance to enable efficient use of healthcare resources in primary care. Patients with influenza and risk factors should be monitored for complications, upper respiratory infections, secondary pneumonia and acute cardio and cerebrovascular events. Additionally, vaccination should be very strong recommended in patients with chronic diseases.*

Keywords: influenza, primary care, complications, immunization

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Influenza which occurs in seasonal epidemics is a public health problem due to its severity and consequences. Seasonal influenza coupled with COVID-19, infection with the virus SARS-CoV2, represents a dual challenge to the primary care [1]. Influenza complications occasionally require absenteeism from school or work, hospitalization, while other times they can cause death. Worldwide, seasonal influenza infection is estimated to result in approximately 3 to 5 million cases of severe illness and approximately 290,000 to 650,000 deaths [2]. In developed countries, most flu-related deaths occur among people over 65 years old regardless of comorbidities [2, 3]. It should be noted that seasonal infections cause an increase in the level of absenteeism of employees/pupils/students having socio-economic implications. As well as this, the staff in primary health care, ambulatory centers and hospitals are intensively involved in the diagnosis, treatment and monitoring of people with the flu during the peak periods of the disease [2].

Although influenza is considered an infectious disease under surveillance at national, European and global level, the number of cases with severe evolution, complications or deaths from influenza is underestimated. In Romania, in primary healthcare, the diagnosis is based more on clinical criteria and not always by determining the etiology of the respiratory infection. The use of rapid tests in the diagnosis of respiratory infections has increased in the last year. However due to the fact that the National Insurance Company only pays for the rapid diagnostic test for SARS-CoV2 virus infection, rapid flu tests are less often used in primary care.

The European Center for Disease Prevention and Control - ECDC reports for the current influenza season the presence of a high percentage of subtype A(H3) - 63.5%, A(H1)- 15.3% (see figure 1) collected through sentinel surveillance systems [4].

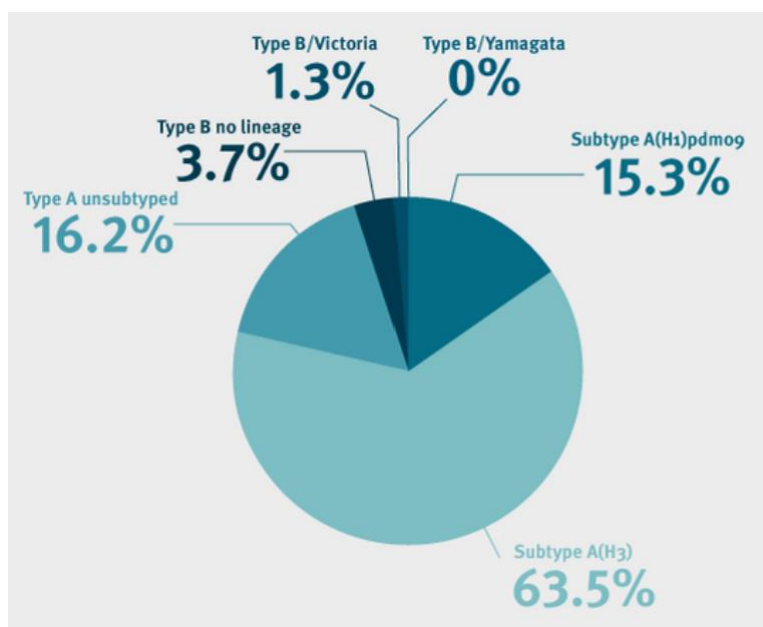


Fig. 1. Influenza virus types circulating in the 2022-2023 season according to ECDC sentinel surveillance systems [4]

In Romania, in the 2021-2022 season, the hospitalizations for clinical conditions compatible with influenza were as follows:

- out of the total of 13,228 cases of clinical conditions compatible with the influenza that were reported, 1,684 cases were hospitalized (12.7% of cases),
- most cases that required hospitalization were people between 50-64 years old (36-27%)[5].

Risk factors for severe influenza development

According to the WHO, people with risk factors for the severe evolution of influenza are represented by

- children aged < 5 years
- adults aged \geq 65 years
- pregnant women
- people with chronic conditions (cardiovascular, respiratory, digestive, renal, hematological diseases, dementia, stroke, and different cancers)
- people with immunosuppression (congenital, induced - infections: HIV; through different treatments: corticotherapy, cytostatics, radio-cobalt therapy)
- obesity degree III (BMI=40Kg/m²) [2].

In Romania, these categories of people also represent an indication of annual influenza vaccination supported by the Ministry of Health through primary medical care. The family physician recommends seasonal influenza vaccination to all women who have been trying to get pregnant or are pregnant. Influenza virus infection of pregnant women has been associated with an increased risk of perinatal morbidity, while pregnant women have shown changes in the immune response, cardiac and respiratory function that increase the severe evolution of influenza infection [6].

Current studies show that pregnant women and young children are protected against influenza infection and hospitalization by vaccination with influenza inactivated virus vaccine [7,8]. Current evidence suggests that the benefits of influenza inactivated vaccines are significant enough to necessitate the recommendation of vaccination for pregnant women and young children [7]. Pregnancy (especially in the third trimester), cardiovascular diseases, diabetes and obesity alter the T cell response inducing chronic inflammation with persistently elevated concentrations of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor- α [8].

Complications of Viral Influenza

Otitis media

Both children and adults, with risk factors can experience ear infections associated with influenza virus infection [8,9], although early antiviral therapy reduces the risk of otitis media following influenza virus infections [9]. The virus can directly affect the middle ear or promote fluid accumulation in the middle ear with secondary bacterial infection [8]. Ear infections, pneumonia and febrile convulsions are the most common complications of influenza in children [8,10]. The study conducted by Short KR et al have shown that normal nasopharyngeal flora, in the presence of an influenza virus infection has the ability to ascend the

Eustachian tube and determine middle ear inflammation [11]. Otitis media (OM) is more frequent in children under 3 years old and can complicate with meningitis, or on long-term with hearing loss, or learning difficulties [11-13].

Sinusitis

Less than 5% of children develop bacterial sinusitis secondary to influenza virus infection [14]. Sinusitis is a frequent complication for those in high-risk groups, especially adults [1]. A research conducted by Peltola VT et al., using animal models has showed that H3N2 subtype gripal viruses are better partners of *Streptococcus pneumoniae* in the induction of secondary bacterial infection such sinusitis [15]. The association between influenza, Covid-19 and invasive fungal sinusitis should not be neglected [16]. Cases of fulminant invasive fungal sinusitis after infection with SARS-CoV2 virus in the immunocompromised host have been reported [16,17].

Pneumonia

A common complication of influenza is pneumonia. Various studies have shown that approximately one-third of hospitalized patients with laboratory-confirmed influenza have pneumonia [18]. During an influenza season, mortality attributable to pneumonia and influenza in the United States ranges from 5.6% to 11.1% [19,20].

In patients with a depressed immune system, pneumonia associated with influenza infection is extremely common. Studies show that a respiratory viral pathogen is identified in nearly one-third of patients hospitalized with leukemia or hematopoietic stem cell transplantation and respiratory symptoms during an influenza season [20,21]. Immunocompromised patients are usually infected with the same type of influenza virus that causes infection in immunocompetent patients, but associations with RSV, SARS-CoV2 or other respiratory viruses (cytomegalovirus, varicella-zoster virus) frequently occur [21] or 194, .

Influenza pneumonia can be fatal both in immunocompetent patients and in those with a compromised immune system or with other such comorbidities (chronic heart disease, atherosclerosis, diabetes)[20,21].

In contrast to COVID-19 pneumonia, influenza-associated pneumonic CT features were not specific enough for true identification based on chest CT imaging, as assessed separately by a radiological suspicion score for influenza. Discrepancy in radiological performance between COVID-19 and influenza pneumonia indicates more specific CT patterns in patients with COVID-19 [21].

Cases of influenza infection complicated by pneumonia are often either primary viral infections (influenza virus + RSV, influenza virus + coronavirus) or viro-bacterial (influenza virus + pneumococcus - most common, influenza virus +

Haemophilus influenzae, influenza virus + staphylococcus MRSA - more frequent in children,) [20]. Studies report an increased hospitalization rate in cases of confirmed Covid-19 pneumonia, lower in cases of pneumonia associated only with influenza infection, but much higher compared to cases of pneumonia caused by non-covid 19, non-influenza viruses [21,22].

It is difficult to diagnose influenza or other respiratory viral infection only on clinical grounds such as in primary care. Rapid viral identification tests are recommended (SARS-CoV2, A or B influenza virus). The radiological characteristics, however, can help when the associated symptomatology and clinical examination are suggestive of the diagnosis of pneumonia [23].

Post-influenza secondary bacterial pneumonia had developed more often alongside factors associated with an increased risk of secondary infection such as immunocompromised host, pregnancy and postpartum periods, and patients with chronic diseases (asthma, cardiac disease, diabetes mellitus and obesity) [24].

Both pathogens influenza virus and SARS-CoV-2 virus have exhibited high transmissibility, associated complications, and are main causes of viral community-acquired and secondary pneumonia or secondary other bacterial infection [24-26]. The study conducted by Spindel J et al. have shown that patients hospitalized with influenza and pneumonia had more comorbidities and more severe symptoms than patients with SARS-CoV-2 and pneumonia [27]. Other studies have also reported the effects of SARS-CoV2 infection on other organs (thyroid, pancreas) [28, 29].

In addition, the proportion of viral pneumonia cases was less in adults than in children, but the proportion of bacterial secondary pneumonia was higher in adults than in children [27,30]. These conclusions evoked a need for vaccination (SARS-CoV2, influenza, pneumococcal), especially among the patients with risk factors, so as to prevent the severe complications of influenza or COVID-19 and to decrease the hospitalization and mortality rate[30].

Acute cardio and cerebrovascular events

Aside from the already presented pulmonary and extrapulmonary complications, several studies have presented the relationship between influenza and acute cardio or cerebrovascular complications.

A review conducted by Rubino et al. have investigated the relationship between thromboembolic events and influenza [31]. Thromboembolic events are complications seen during influenza virus infection, both in adults and children. Thrombotic events can occur in spite of thromboprophylaxis in hospitalized patients, caused by the stimulation of the extrinsic coagulation pathway [31].

Experimentally models have shown that influenza viral infection, additionally to inducing a systemic inflammatory reaction, could have a direct inflammatory response on atherosclerotic plaque with a possible rupture, as well as endothelial

dysfunction, changes in vasomotor tone, and the release of inflammation cytokines and triggering of prothrombotic events that precipitate the coronary artery occlusion [32]. In this study conducted by Muscente et al. the research showed a beneficial role of the influenza vaccine in cardiovascular prevention [32].

Influenza virus infection has been identified as both a potential chronic risk factor for cerebrovascular events and especially in people under 45 years old, an acute trigger for a stroke [33].

The estimated effectiveness of the influenza vaccine against acute cardio and cerebrovascular events was comparable with the efficacy of currently acquired therapies for secondary prevention of acute cardio and cerebrovascular events from clinical trial data [34].

Conclusions

In respiratory viral infection, the early identification of the patient's pathogenic supplier and risk factors for complications is crucial for the management of the patient and in order to determine the appropriate therapy. Given the current increase in cases of both COVID-19 and seasonal influenza, early diagnosis is also of great importance to enable efficient use of healthcare resources in primary care.

Patients with influenza and risk factors should be monitored for complications, upper respiratory infections, secondary pneumonia and acute cardio and cerebrovascular events. Additionally, vaccination should be very strong recommended in patients with chronic diseases.

Author Contributions:

M.A.I. conceived the original draft preparation. D.M.B., I.A.E., C.P. and A.K. were responsible for conception and design of the review. M.A.I., D.M.B., I.A.E., C.P. and A.K. were responsible for the data acquisition. M.A.I. was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. M.A.I., D.M.B., I.A.E., C.P. and A.K. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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"The authors declare no conflict of interest regarding this article".

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