

## INFLUENZA VIRUS GENOTYPES AND CLINICAL COURSE OF THE DISEASE

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**Abstract:** *Influenza virus is a common cause of sporadic or epidemic respiratory infections. It is often associated with bacterial pneumonia. We examined the demographic, clinical and laboratory characteristics of patients with influenza, treated at the General Hospital in Uzice, from 2009 to 2014. The clinical diagnosis was confirmed by virus isolation from blood and nasopharyngeal secretion. The bacterial pneumonia was confirmed by isolation of pathogens from sputum. Half of the treated patients had bacterial pneumonia. Streptococcus pneumoniae was the most common isolated bacteria. Influenza virus H5N1 was isolated in 75% of patients with pneumonia. 62.2% patients had comorbidity. The disease is lethal ended at 5.9% of treated patients. Chronic patients older than 65 years with the H5N1 virus genotypes had severity course of the disease. Prevention of Influenza virus infection by vaccines is indicated for elderly patients with chronic diseases.*

**Keywords:** *Influenza virus, genotypes, bacterial pneumonia, clinical course*

### 1. INTRODUCTION

Influenza is a contagious respiratory illness caused by Influenza viruses. It is one of the most common causes of human respiratory infections [1], and among the most significant because they cause high morbidity and mortality. There are four types of influenza viruses: A, B, C and D. Human influenza A and B viruses cause seasonal epidemics of disease. The influenza A and B viruses that routinely spread in people are responsible for seasonal flu epidemics each year. Up to 50% of the population can be infected in a single pandemic year, and the number of deaths caused by influenza can dramatically exceed what is normally expected [2].

Influenza B viruses can periodically cause large epidemics [1], but do not cause pandemics. Influenza C viruses are endemic [1], and sporadically cause mild respiratory disease.

Influenza A viruses are divided into subtypes based on two proteins on the surface of the virus: the hemagglutinin (H) and the neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes [3]. H1N1 and H3N2 are currently pandemic in both human and pig populations. A variant of H1N1 was responsible for the Spanish flu pandemic that killed some 50 million to 100 million people worldwide over about a year in 1918 and 1919 [4]. H2N2 caused the Hong Kong flu pandemic of 1968 and 1969 that killed up to 750,000 [5].

Concern about the emergence of an influenza pandemic caused by a highly pathogenic avian influenza virus of H5N1 subtype [6, 7] makes reviewing the pathology of previous pandemics relevant.

The clinical course of influenza virus is often characterized by a rapid progression of lower respiratory tract disease, necessitating mechanical ventilation within days of admission to a hospital [8].

Influenza virus attaches to and replicates in epithelial cells of the respiratory tract. Viral replication combined with the immune response to infection lead to destruction and loss of cells lining. Secondary bacterial pneumonia often occurs during influenza. The reasons why infections with influenza virus may lead to pneumonia are not understood. Several

hypotheses have been proposed and disproved over the years, including one in which reduced numbers of lymphocytes allow increased susceptibility to superinfection [9].

Young children, adults aged 65 years and older, pregnant women, and people with certain chronic medical conditions are among those groups of people who are at high risk of serious flu complications, possibly requiring hospitalization and sometimes resulting in death [10].

## 2. PATIENTS AND METHODS

We retrospectively investigated the demographic, clinical and laboratory characteristics of a total of 405 patients with influenza who have been treated to Department for Infectious Diseases, General Hospital Uzice, between 01.01. 2009 to 31.12. 2014. Demographic data, information about the clinical course and evaluation of disease were obtained from hospital records. Influenza virus was identified from blood and nasopharyngeal secretions by polymerase chain reaction analysis (PCR) in Institute of Virology, Vaccines and Sera "Torlak" in Belgrade. Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Acinetobacter and other bacteria were identified from sputum. Patients were followed the leukocyte count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Radiographic pneumonia was diagnosed in all of patients. Patients with influenza and bacterial bronchopneumonia were treated with antiviral drugs during 5 days (oseltamivir or zanamivir) and antibiotics according to the antibiogram.

## 3. RESULTS

Of the total number of patients with influenza, 122 (30%) had an associated bacterial pneumonia (66.6% males, 33.4% females). Mean age at onset was 49.4+/-12.1 (range: 19-89).

The incubation period was average 3.2 days (from 2 to 5 days). Median hospitalization was 12 days.

Patients who needed mechanic ventilation (13.3%) were admitted to intensive care. The case fatality were 7 (9.3%) patients, 5 (72.7%) of them older then 65 years.

Subtypes of the Influenza virus are shown in Table 1.

**Table 1:** Subtypes of the Influenza virus

Influenza virus (subtypes)	Patients No. (%)
A H1N1	19 (15.6)
A H3N2	9 (7.4)
A H5N1	92 (75.0)
B	2 (1.6)

Most of the patients (75%) with pneumonia had Influenza virus H5N1.

The symptoms and signs are shown in Table 2.

**Table 2:** The symptoms and signs in patients with influenza and pneumonia

Symptoms and signs	Patients No. (%)
Fever	110 (90.2)
Throat pain	32 (26.2)
Cough	97 (79.5)
Myalgia	37 (30.3)
Gushing	95 (77.9)
Headache	82 (67.2)
Joint pain	28 (22.9)
Nausea and vomiting	17 (13.9)
Diarrhea	11 (9.0)

Most of the patients (90%) had fever, over 70% had cough and gushing.

The laboratory features are shown in Table 3.

**Table 3:** The laboratory features in patients with influenza and pneumonia

Laboratory test	Patients No. (%)
ESR >20 mm/h	120 (98.4)
Mean	68
Leukocyte (cells/mm <sup>3</sup> )	
NO. (%) of persons > 10,000	99 (81.1)
Mean	12.310
range cells/mm <sup>3</sup>	6.200-23.800
CRP >5 mg/L	120 (98.4)
Mean	102.6 (38-311)

All patients had elevated value of CRP.

The isolated bacteria are shown in Table 4.

**Table 4:** The sputum bacteria in patients with influenza

Sputum bacteria	Patients No. (%)
Streptococcus pneumoniae	49 (40.2)
Staphylococcus aureus	35 (28.7)
Haemophilus influenzae	18 (14.8)
Acinetobacter	7 (5.7)
Other bacteria	13 (10.7)

The most commonly bacteria was Streptococcus pneumoniae.

Out of a total of 122 patients, 76 (62.2% ) had comorbidities.

The comorbidities in patients with influenza and pneumonia are shown in Table 5.

**Table 5:** The comorbidities in patients with influenza and pneumonia

Comorbidities	Patients No. (%)
Diabetes mellitus	48 (64)
Chronic cardiovascular disease	50 (66.7)
Chronic pulmonary disease	39 (52)
Hematological disease	4 (5.3)
Chronic liver disease	12 (16)
Alcoholism	8 (10.7)

Most patients who received bacterial pneumonia had comorbidities, chronic cardiovascular diseases and diabetes mellitus, commonly.

#### 4. DISCUSSION

Influenza viruses type A and B causes recurrent epidemics almost every year, leading to significant human morbidity and mortality. These viruses are now panzootic across three continents, leading to huge economic losses, and have transmitted to humans with lethal consequences. However, only influenza A virus is associated with influenza virus pandemics.

We analyzed patients with influenza in the six-year period in region of western Serbia. The most common type of Influenza virus was A H5N1. The first human disease caused by H5N1 was reported in Hong Kong in 1997, with 18 cases and six deaths [11]. Now, H5N1 is the world's major influenza pandemic threat [2].

Pneumonia is a serious flu complication that can result from either influenza virus infection alone or from co-infection of flu virus. We have examined patients with influenza who had proven bacterial pneumonia. Streptococcus pneumoniae was the most common cause of bacterial co-infection in our patients. In recent years new evidence has emerged regarding the underlying mechanisms of influenza virus-induced susceptibility to secondary pneumococcal infections, in particular regarding the sustained suppression of innate recognition of Streptococcus pneumoniae [12]. Secondary

bacterial pneumonia, particularly sustained by *Streptococcus pneumoniae*, represents an important cause of excess mortality during both influenza epidemics and pandemics [13].

The average age of our patients was 49 years, while the literature [14] describes younger age as the most common. The explanation is that we analyzed only those older than 19 years. Incubation of 3.2 days is common for influenza, but longer incubation times of up to 8 days have been reported [8].

Most patients with influenza H5N1 virus present with symptoms of fever, cough, and shortness of breath [8,9] which also corresponds to our results. All of our respondents had additional bacterial coinfection which increased the symptoms. We did not notice symptoms of upper respiratory tract inflammation in our patients. This is in accordance with the literature data [9], unlike human infections with H7 viruses.

Nonrespiratory symptoms during influenza include diarrhea, vomiting and abdominal pain. In some reported cases, diarrhea was the presenting symptom, preceding other clinical manifestations [15] which in our study was in 11% of patients. Abnormalities on chest radiographs were bilateral in 15% and included diffuse, patchy, or interstitial infiltrates and segmental or lobular consolidation with air bronchograms. The laboratory parameters of our patients confirm bacterial coinfection: accelerated ESR, leukocytosis, elevated CRP. A quarter of our patients had liver and renal dysfunction. This may suggest a wider tissue tropism of the virus or may be the manifestations of multiple-organ dysfunction [16] that is related to the systemic effects.

Our patients did not have complications of the central nervous system, although in the literature there are described rare cases [17]. Progression to respiratory failure is frequently associated with manifestations of acute respiratory distress syndrome ARDS [14]. Bacterial superinfection increases this probability. The lethal outcome of our patients was the consequence of ARDS. All of patients with lethal clinical course had chronic pulmonary diseases.

Based on reported cases [14], the mortality of human influenza H5N1 virus was 60%, which is significantly more in relation to our finding. Case fatality rates of H5N1 disease were highest in the 10- to 19-year age group [14] and lowest in those over 50 years (40%). Our research did not cover the age of 19 years.

## 5. CONCLUSION

The most common Influenza virus was A H5N1. In patients with influenza, the most common cause of pneumonia was *Streptococcus pneumoniae*. The patients were mostly older men with other chronic diseases.

*Streptococcus pneumoniae* and influenza virus, which together are an important cause of global morbidity and mortality. Influenza vaccine is an important preventive measure, especially in the elderly.

The availability of a new generation of conjugate pneumococcal vaccine with an enlarged antigenic spectrum offers promising perspectives, to improve the control of influenza through the protection offered against its major complications.

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