

# Clinical Presentation, Laboratory Findings, Complications, and Mortality of Influenza During the Epidemic of October 2019-February 2020 in Iran

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## Research Article

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# Abstract

**Background:** Influenza is one of the most important viruses and causes millions of infections and 290-600 thousands deaths annually. We aimed to evaluate the hospitalization rates due to complications caused by the influenza virus (pneumonia, seizures, sinusitis, otitis, myositis and encephalitis), the frequency of clinical signs, and laboratory findings in children under 15 years of age infected with Influenza.

**Methods:** We conducted a cross-sectional study during the Influenza epidemic in Qom, Iran, from October 2019 to February 2020. Children under 15 years of age with the definitive diagnosis of influenza obtained by polymerase chain reaction (PCR) test were included.

**Results:** Out of 1225 patients who referred to us with flu-like symptoms; 1172 patients were referred by the emergency department and our hospital clinic but 53 patients were referred to us by other paediatricians. 375 patients (30.61%) who had a positive PCR test result for influenza and suffered from complications caused by the virus were hospitalized.

The number of male hospitalized patients was 231 (61.6% of hospitalized patients) and the number of female hospitalized patients was 144 (38.4% of hospitalized patients) respectively.

The highest age range of patients with pneumonia was of 13 months to 3 years with a hospitalization rate of 36.41% and the lowest hospitalization rate was of 12 years to 15 years with a hospitalization rate of 0.84%.

The most serious complication observed in patients caused by the influenza virus was pneumonia; with 17 cases (4.53%) reported.

89.6% of patients had fever at the time of referral causing it to be the most common clinical symptom among patients. Cough ranked second with 76.8%.

Lymphopenia and leukopenia was recognized as the most common laboratory findings with a frequency of 26.33% and 21.85%.

**Conclusions:** Complications of influenza was not uncommon in children and affected a fifth of the patients. The influenza epidemic of October 2019- February 2020 imposed a heavy burden on our hospital and the learned lessons should be implemented to further assist the physicians in future influenza epidemic.

## Background

Epidemics have not only been the biggest crises in health systems, but also one of the biggest problems in the world. The occurrence of the covid19 pandemic reminded everyone once again that the first, largest, and most serious epidemics known is the influenza virus.

Influenza virus as an RNA virus belongs to the family of orthomyxoviridae, which is divided into 3 types A-B-C

Type B and C strains has slight antigenic changes that only causes upper airway respiratory involvement but type A strain has an unstable antigenic structure that enables the means for multiple mutations and antigen shifting. Antigen shifting, which is caused by a lack of previous immunity to the mutation, causes very rapid transmission between populations and seasonal outbreaks and epidemics and pandemics. (1,2)

The flu pandemic causes seasonal outbreaks, epidemics, and pandemics each year. The first pandemic caused by the H1N1 flu virus in 1918 infected about 500 million people worldwide and almost 50 to 100 million people died. This accounted for 3-5% of the world's population at that time. (3)

However, these outbreaks and epidemics did not stop at 1918 and continued to this very day but increasing human awareness through numerous studies has reduced the burden caused by the virus. The virus is still a major health challenge; it is estimated that around 1 billion people become infected each year (4), of whom about 90 million are children under the age of five. However, the virus causes acute respiratory infections in only 1 million people by infecting their lower respiratory tract (5). This number leads to an annual death toll of 290,000 to 600,000 worldwide. (6)

The virus transmitted via droplets from one infected person to another, touching infected surfaces, having contact with infected mucus and, can thus easily lead to pandemics and outbreaks. (7, 8)

Among the incredible features of this virus is its short incubation period (1 to 2 days) and maximum shedding of virus on the first day of infection. Despite a short incubation period, it can be transmitted 7 to 10 days after the infection. (7)

Children are the most endangered group due to extensive gatherings and togetherness. This even results in the widespread transmission of the virus. Respiratory Diseases (ARDS, Pneumonia, and Other Respiratory Diseases) are the most common complaints. Also, neurological involvement such as encephalitis, encephalopathy, seizures, and febrile seizures can be very serious and life-threatening illnesses which can cause hospitalization and even death. (9, 10) Therefore, it is necessary to be aware of the common clinical signs of this disease in children. It is also noteworthy that various studies have shown that the frequency of each of these symptoms is higher and more pronounced in certain areas of the world.

Certain organs infected in some societies is associated with more mortality and therefore requires a more serious and aggressive approach to prevent unintended and irreparable consequences and also reduce the mortality rate, (11, 12) Therefore, in this retrospective cross-sectional study; from October 2019 to February 2020 during an outbreak, we reviewed the files of people who complained of being infected with the flu virus and described the frequency of symptoms and complications in the children between 6 months and 15 years.

## Methods

We designed a cross-sectional retrospective study from October 2019 to February 2020 during the influenza epidemic caused by this virus in Iran to evaluate and evaluate clinical information, laboratory signs, complications, mortality and course of the disease along with the underlying diseases mentioned in the records of hospitalized patients (under 15 years of age) in Hazrat Masoumeh Children's Center in Qom.

During this period, 1225 patients below 15 years of age with flu-like symptoms (fever, cough, myalgia, sore throat) were referred to the hospital from the emergency department, our hospital clinic and other paediatricians. Among them, 375 patients were identified according to the physical examinations, diagnostic tests and, positive PCR test result.

In this study, we included only individuals with a definite diagnosis of influenza having positive PCR test. We examined symptoms, complications and laboratory changes of patients along with estimating the prevalence and frequency of data to accurately report the frequency and prevalence of signs and symptoms and clinical complications of this disease in this geographical area (Asia-Middle East) to raise awareness for accurate diagnosis and selection of more invasive treatments when needed in epidemics, especially in children.

By examining and extracting the information contained in the written records, we found that the admission rate of 375 definitively diagnosed patients out of 1225 patients with flu-like symptoms were due to the presence of complications such as; Pneumonia-otitis-myositis-sinusitis-febrile and non-febrile seizures. Therefore, the presence of such complications requires more attention and care.

## Sample size

Initially, for the study to be scalable to a larger community, we estimated the sample size in terms of the first type error probability of 5% and sampling accuracy of 6% and 50% probability. In order to achieve the maximum sample volume, more than 270 patients were required.

## Statistical analysis

We analyzed and described the collected information to express the frequency and percentage of flu patients admitted to this medical center in the age range of below 15 years

They were classified based on age, sex, incidence and frequency of complications such as pneumonia, otitis, myositis, sinusitis and, seizures, the frequency of symptoms such as fever, cough, myalgia, vomiting, diarrhea, sore throat, lethargy, headache and myalgia, the frequency of laboratory findings as well as the frequency of underlying diseases.

All statistical analyzes were performed by SAS V.9.4 and we also considered p value to be <0.05 to indicate the importance of the presented statistics and to represent a larger statistical community.

# Patient and public involvement

None of the patients were actively involved in the intervention, the final results were extracted from the archives.

## Results

A summary of the number of patients diagnosed with the flu virus in this study is as follows;

Out of 1225 patients who referred to us with flu-like symptoms; 1172 patients were referred by the emergency department and our hospital clinic but 53 patients were referred to us by other paediatricians.

375 patients (30.61%) who had a positive PCR test result for influenza and suffered from complications caused by the virus were admitted to the emergency department and other wards of the hospital.

The number of male hospitalized patients was 231 (61.6% of hospitalized patients) and the number of female hospitalized patients was 144 (38.4% of hospitalized patients) respectively.

Age groups of hospitalized patients are listed in the table below:

A total of 357 people were identified because 18 of them were not classified as the mentioned age range or were hospitalized in the emergency department without consent and thus were excluded from our study.

Patients between 13 months and 3 years were the most prevalent group in our study with 36.41% and the lowest prevalence was in the age range of 12 years to 15 years with 0.84% of the admitted patients (Table 1).

Table 1  
Age groups of 357 hospitalized patients with influenza.

<b>Age group</b>	<b>Number of patients</b>	<b>Percentage</b>
<3 months	8 patients	2.40%
4 months to 6 months	8 patients	2.40%
7 months to 12 months	19 patients	5.32%
13 months to 3 years	130 patient	36.41%
4 years to 5 years	74 patients	20.71%
6 years to 7 years	82 patients	22.96%
8 years to 12 years	33 patients	9.23%
12 to 15 years	3 patients	0.84%

Complications of the disease were seen in 70/357 (19.6%) of the admitted patients. The most serious complication observed in patients with influenza was pneumonia with 17 (4.53%), followed by otitis and myositis (16, 4.48%), sinusitis and seizure (10, 2.8%), and encephalitis (1, 0.26%) (Table 2).

Table 2  
Frequency of complications observed in hospitalized patients diagnosed with influenza.

<b>Influenza complications</b>	<b>Number of patients</b>	<b>Percentage</b>
Pneumonia	17 patients	4.76%
Otitis	16 patients	4.48%
Myositis	16 patients	4.48%
Sinusitis	10 patients	2.8%
Seizure	10 patients	2.8%
Encephalitis	1 patient	0.26%

It is very important to highlight the clinical symptoms during the initial visit. 89.6% of patients had fever at the time of referral causing it to be the most common clinical symptom among patients. Cough ranked second with 76.8%. Other symptoms were much less prevalent than fever and cough (Table 3).

Table 3  
chief complaints during the initial visit of patients.

<b>Symptom</b>	<b>Prevalence</b>
Fever	89.6%
Cough	76.8%
Vomiting	25.6%
Myalgia	23.7%
Lethargy	17%
Headache	8.5%
Diarrhea	8%
Restlessness	2.4%
Throat ache	2.1%

Lymphopenia and leukopenia were recognized as the most common laboratory findings with a frequency of 26.33% and 21.85% (Table 4).

Table 4  
Laboratory findings in admitted patients.

<b>Laboratory findings</b>	<b>Number of patients</b>	<b>Percentage</b>
Leukocytosis	26	7.28%
Leukopenia	78	21.85%
Neutropenia	47	13.16%
Lymphopenia	94	26.33%
Thrombocytopenia	2	0.56%
Pancytopenia	1	0.28%

Neurological diseases and respiratory diseases were observed as the two most common underlying diseases among the admitted patients with a frequency of 10.64% and 10.08%, respectively (Table 5).

Table 5  
Prevalence of underlying disease in hospitalized patients with influenza.

<b>Underlying conditions</b>	<b>Number of patients</b>	<b>Percentage</b>
Neurological diseases	38 patients	10.64%
Respiratory diseases	36 patients	10.08%
Cardiovascular diseases	2 patients	0.56%
Renal diseases	3 patients	0.84%
Hematologic diseases	2 patients	0.56%
Endocrine diseases	4 patients	1.12%
Immunocompromised	2 patients	0.56%
Malignancies	2 patients	0.56%
Failure to thrive	1 patient	0.28%

## Discussion

In this study, we described the epidemiology of hospital admissions and the severe complications caused by influenza virus in children under 15 years of age in Hazrat Masoumeh Hospital in Qom. Our study was aimed to help physicians; especially in the Middle East, to achieve a more accurate approach while being aware of the common clinical signs, red flags, and the dangerous complications of the disease.

Severe infections that led to hospitalization were more common in males. Patients aged 13 months to 3 years were the most prevalent group of admitted patients. Fever and cough were considered as the most

common symptoms in hospitalized patients, in laboratory parameters, lymphopenia and leukopenia were the most common laboratory finding in patients. As expected, influenza caused complications in a significant portion of the patients. Complications such as pneumonia, otitis, and myositis were reported to be the most common complications caused by influenza that led to hospitalization. Neurological diseases and respiratory diseases were observed as the two most common underlying diseases among the admitted patients.

## **Comparison with other researches**

Male patients admitted with influenza related complications were higher in our study than female patients, a finding consistent with previous studies reported in influenza A (H1N1) pandemics, as well as studies in the United States (13) and Canada (14) and Japan (15) have confirmed this finding. Studies have also confirmed that respiratory diseases including asthma marks the most common PMH which leads to pneumonia in children. (16)

In a study conducted in Japan, the highest mortality was due to the encephalopathy caused by influenza (17). In our study, pneumonia caused by influenza led to the death of two of our patients (0.56%).

Also, in our study, the highest risk of hospitalization was estimated between the ages of 13 months and 3 years, but in a study conducted in Japan (2009-2010) and the United States, this age was reported to be between 0-1 years of age (12, 17). Another study conducted in the United Kingdom between 2001 and 2007, estimated the highest incidence of hospitalization to be among 6 months to 6 years of age. (10)

A systematic review stated that the H1N1 influenza pandemic had the highest hospitalization rates in children under 2 years of age, whereas in seasonal influenza epidemics this finding was reversed. They also reported that the actual mortality rate from influenza reported in hospitals and intensive care units was lower than the actual mortality rate in the society. [18]

## **Implication for clinicians and policymakers**

As we have been dealing with the COVID-19 pandemic for the last 2 years, we need to know that viral pandemics will put a heavy burden on the society and our health system. Therefore, we need to tackle the most common cause of these pandemics; the 'flu virus' to prevent unintended consequences.

Compensation is only possible by correctly understanding the common behavior and clinical signs and knowing the red flags and complications for dealing with it more aggressively. We must be aware that what actually causes hospitalization is not the virus itself but its complications such as respiratory involvement (pneumonia, sinusitis), neurological involvement (encephalitis, encephalopathy, febrile and non-febrile seizures), and otitis and myositis. (19) During the outbreak of influenza virus in 2009-2010, WHO and CDC (21) published guidelines for the management of the disease, in which the use of neuraminidase inhibitors in the first 48 hours prevented severe complications as well as the mortality of the disease. Cochrane reviews also reported that the use of oseltamivir significantly reduced the chances of developing secondary infections (5).

Previous studies have shown the effect of vaccination against influenza in preventing severe and dangerous complications. One of the best approaches to this disease is vaccinating children to prevent unwanted complications.

In our study, it is important to highlight that the presence of complications such as pneumonia, sinusitis, seizures, myositis and otitis along with symptoms such as fever, cough, severe vomiting, myalgia and diarrhea and the presence of laboratory parameters such as lymphopenia and Leukopenia in children with influenza should not be ignored. If any of these are present, more care should be taken to avoid side effects and death in children.

## **Strengths and weaknesses**

Our study has the ability to expand to larger communities by estimating the appropriate sample size. One of the main strengths of this study is to include only individuals with positive PCR test results in the study, which therefore states the real frequency of the complications caused by the influenza virus and prevents counting complications caused by other viruses that give flu-like symptoms.

limiting the age of patients to under 15 is also another factor in making it more accurate. Also, one of the most important points to note down is that the precious studies are mostly done in Western countries and it is possible that the results obtained in general and cannot be generalized to Asian countries and the Middle East. Conducting this study in an Asian country is an important action taken to extend the information to other Asian countries as well. However, one of the weaknesses of our study is that this study is limited to only one hospital and in order to obtain more accurate statistics and results it is necessary to conduct surveys in larger statistical communities.

## **Conclusions**

Complications of influenza was not uncommon in children and affect a fifth of the patients. The influenza epidemic of October 2019- February 2020 imposed a heavy burden on our hospital and children aged 13 months to 3 years were the most common group of admitted pediatric patients. Therefore, understanding the clinical presentations, laboratory findings, and consequences of influenza is vital for the diagnosis and management of the influenza virus infection and its consequences.

## **Declarations**

### **Funding:**

Qom University of Medical Sciences provided all the funding for this study to collect and analyze the data.

### **Conflicts of interest/Competing interests:**

The authors declare that they have no conflicts of interest.

### **Ethics approval:**

The study was approved by the Qom University of Medical Sciences biomedical research ethics committee (IR.MUQ.REC) with study number IR.MUQ.REC.1399.161.

### **Consent to participate**

All the participant gave consent to participate in the study.

### **Written Consent for publication:**

All the participants had consent for data publication.

### **Availability of data and material:**

All the data is available upon requested from the corresponding author.

### **Code availability:**

Not applicable.

### **Authors' contributions:**

Z.M: Conception and Data collection, S.D: Drafting manuscript, Z.A: Drafting manuscript, A.K: Drafting manuscript, S.A: Data analysis, H.B: Data collection, H.H: Conception and Manuscript revision

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