



ORIGINAL ARTICLE

The burden of severe cases of Influenza disease: the Friuli Venezia Giulia Region experience

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Keywords

Influenza • Vaccination • Neuraminidase • Pneumonia • Respiratory illness

Summary

Introduction. Influenza is a matter of serious concern for clinicians, in both outpatient and in-hospital settings. Worldwide, the 2017-18 epidemic proved to be the most severe since 2003-04. We report a real-world experience regarding the management of patients with influenza admitted to a large teaching hospital in the Friuli Venezia Giulia region during the 2017-2018 influenza season. We also provide a practical guide for the management of hospitalized influenza patients.

Methods. A retrospective observational analysis was conducted among all influenza patients requiring admission to our center during the 2017-18 season.

Results. Overall, 29 patients were admitted to the University Hospital of Udine during the 2017-18 season with a diagnosis of influenza. B virus was responsible for the majority of cases. More than 65.5% of the subjects presented with a complication. We estimated that 41.4% of the patients admitted were affected by

a "severe form". All these cases required admission to the Intensive Care Unit, with 27.6% and 10.3% needing Orotracheal Intubation and Extracorporeal Membrane Oxygenation, respectively. The fatality rate was 24.1%. Notably, only 9 subjects in our cohort had been vaccinated. Based on the experience acquired during the past season, we propose a practical guide to the management of influenza cases in everyday hospital practice.

Conclusion. The cornerstones of the management of all hospitalized influenza patients are the rapid identification and treatment of severe forms. Timely and strict adherence to contact and respiratory precautions are also fundamental to reducing the risk of intra-hospital outbreaks. Despite improvements in antiviral therapies and supportive measures, influenza-related morbidity and mortality remain high. In our opinion, a universal vaccination program is the only safe and effective method of filling the gap.

Introduction

Influenza is still a matter of serious concern for clinicians, in both outpatient and in-hospital settings. Indeed, worldwide, the 2017-18 epidemic proved to be the most severe since 2003-04.

The "influenza season" is generally defined as the period of the year during which more than 80% of influenza cases occur. The usual length of the influenza season is of 8-12 weeks, from late autumn to early spring [1]. However this time-frame is arbitrary, as the definition varies widely across surveillance studies. Some authors, for example, regard the "influenza season" as the period when more than 10% of sentinel specimens prove positive for influenza virus; conversely, other experts consider the "influenza season" to be the interval between the diagnosis of the first case, or the week in which the vaccination campaign begins, and the week after the diagnosis of the last Influenza case [2].

The World Health Organization (WHO) estimates that influenza affects almost 10-20% of the world's population every year and causes between 250,000 and 500,000

deaths and 3-5 million hospitalizations [3, 4]. In Europe, it is estimated that approximately 10 to 30% of the population become infected with seasonal influenza every year, with several hospitalizations [5].

Epidemiological data on influenza circulation and influenza-related illness are provided by Flunet, an online database of the WHO Global Influenza Surveillance Network, which releases weekly reports of influenza virus circulation and influenza-related illness. Data are provided by the National Influenza Centers of the Global Influenza Surveillance and Response System (GISRS), local laboratories, and WHO regional databases [6]. Since 1999, in Italy a nationwide sentinel system (InfluenNet) coordinated by the Ministry of Health regularly provides national and regional surveillance data on the influenza season. InfluenNet depends on a group of sentinel practitioners and pediatricians, who cover up to 2% of the general population. Their reports are also uploaded to the European Centre for Disease Prevention and Control (ECDC) database [7].

According to the intensity thresholds currently approved by the CDC to classify influenza seasonal severity, the

2017-18 season in Europe was the first to be classified as a “highly severe” across all age-groups since 2003-2004 [1].

Compared with recent seasons, the 2017-2018 epidemic was characterized by a higher level of circulation of the B virus. Indeed, B viruses were responsible for the majority of severe cases in 2017–2018, most of which occurred in patients aged over 39 years. Moreover, in people aged 65 years and older, an excess in all-causes mortality was reported by the majority of sentinel countries.

Comparable characteristics were also observed for the 2017-2018 influenza season in Italy. According to the Italian surveillance system, since the beginning of the surveillance, in September 2017, 764 patients with laboratory-confirmed influenza were admitted to intensive care units (ICUs). Of these, 173 died [9].

The clinical pattern of seasonal influenza infection is extremely heterogeneous, ranging from mild disease to lethal forms.

The acute clinical presentation is similar to that of other influenza-like illnesses (ILI), consisting of abrupt onset of fever, sore throat, headache, cough and myalgia. The majority of cases resolve spontaneously within 1-2 weeks, without complications. Nevertheless, some patients undergo a more serious clinical course, which may be complicated by respiratory and extra-respiratory disorders [10]. Among these patients, elderly people, younger children, pregnant women and patients with underlying chronic diseases are at high risk of developing severe forms and influenza-related complications, such as bacterial pneumonia and extra-pulmonary influenza-related disease [1].

Patients admitted to ICUs and those hospitalized because of influenza are defined as “severe cases”. It has been estimated that their risk of death due to influenza and influenza-related respiratory complications is 3.6-4.8-fold higher than that of the remaining population infected with seasonal influenza [11, 12].

Despite the availability of antiviral drugs for both therapeutic and prophylactic purposes, the only effective method of preventing influenza and influenza-related complications is vaccination [13].

Currently, two main types of influenza vaccines are available. Trivalent vaccines protect against three flu viruses: influenza A (H1N1) virus, influenza A (H3N2) virus and influenza B virus. Quadrivalent vaccines protect against the same viruses as the trivalent ones, plus an additional B virus.

Different formulations of influenza vaccines exist: inactivated, live attenuated and recombinant vaccines. Inactivated influenza vaccines (IIV) are egg-based compounds, which may contain the whole inactivated virus, split virion or subunits, and induce specific antibodies against the hemagglutinin (HA) component. IIVs are licensed for use in adults and children. IIVs also exist as adjuvanted vaccines (with the inclusion oil-in-water emulsions, such as MF59) and as high-dose vaccines, which have been licensed for use in the elderly. A type of cell-based IIV has been licensed in the United States

(US) and in some European countries [14]. A live attenuated influenza vaccine (LAIV) is available in the US and Canada for use in adults and children, and in Europe for use in children and adolescents. LAIV contains four influenza strains (H1N1, H3N2 and the two prevalent B strains) and is administered intranasally. The attenuated influenza virus replicates in the upper respiratory airways and stimulates the production of specific antibodies in serum as well as in the respiratory mucosa. The effectiveness of LAIV against influenza A(H3N2) and Influenza B viruses is similar to that of IIVs. Nevertheless, LAIV is poorly active against influenza A(H1N1) pdm09 viruses [15]. A Recombinant Vaccine (RV) has also been developed. This is made up of a purified HA subunit and is expressed in insect cells through baculovirus vectors. The RV is currently licensed for adults and destined for use in subjects who cannot receive other formulations. One major advantage of this vaccine is the short manufacturing process. It could therefore be useful during a pandemic season [16, 17].

Twice a year, the WHO organizes consultations of experts to formulate recommendations concerning the composition of the influenza vaccines for the following influenza season [18].

With regard to the 2017-18 influenza season, the trivalent vaccine included an A/Michigan/45/2015 (H1N1) pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brasília/60/2008-like (B/Victoria lineage) virus. The quadrivalent vaccine also included a B/Phuket/3073/2013-like (B/Yamagata lineage) virus [19].

Overall, the effectiveness of influenza immunization is estimated to be around 40-60%. Effectiveness varies considerably according to the circulating seasonal viruses, being good against A(H1N1)pdm09, moderate against influenza B virus, and poor against influenza A(H3N2) [20].

The WHO states that influenza vaccines should be directed to protecting the whole population, with particular attention to individuals most at risk for severe forms of influenza and influenza-related complications. These “priority groups” were originally designed by the WHO Strategic Advisory Group of Experts on immunization (SAGE) in 2012, and include the elderly, children, people with chronic conditions, pregnant women, and healthcare workers. In Italy, these recommendations are reported in the National Immunization Plan and confirmed every year in the influenza vaccination program by the Ministry of Health. According to the international recommendations, in Italy the minimum objective of influenza vaccine coverage in patients considered at risk is 75%, while the optimal coverage target is 95% [21, 22]. In this context, our study aimed to provide real-world data on patients with severe influenza admitted to a large teaching hospital in the Friuli Venezia Giulia region during the 2017-2018 influenza season. Based on our experience, we propose a practical guide for the management of hospitalized patients with influenza.

Methods

STUDY POPULATION

We evaluated all patients admitted to the University Hospital of Udine (UHU) from October 1, 2017, to April 1, 2018. Individuals diagnosed with Influenza were enrolled in this retrospective analysis. UHU is part of the Azienda Sanitaria Universitaria Integrata di Udine, and is located in the Friuli Venezia Giulia region, in north-eastern Italy. UHU has 1,000 beds and serves a population of almost 250,000 inhabitants.

DATA SOURCES

Information on the patients admitted to UHU was collected from the hospital discharge records and the Regional surveillance data forms provided by the Department of Prevention of Udine [23].

DATA COLLECTION AND DEFINITIONS

The following information was collected: the patient's demographic characteristics (date of birth, gender, place of residence), clinical history (anamnesis of comorbidities, previous hospital admissions), history of previous vaccinations. The presence of at least one comorbidity was used to classify patients as "comorbid".

Influenza-like illness (ILI) and severe acute respiratory infections (SARI) were diagnosed according to the "WHO surveillance case definitions for ILI and SARI" [24].

The diagnosis of influenza was based on the detection of influenza viral RNA by means of molecular assays performed on either nasopharyngeal swabs or bronchoalveolar lavage fluid. Disease severity was defined according to the "WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and Other Influenza Viruses" [25].

Influenza related-complications were diagnosed according to the ICD-10-CM diagnostic codes.

Influenza season was defined according to the time-frame proposed by Smetana et al. [1].

See Table I for a complete list of definitions.

STATISTICAL ANALYSIS

Data were analyzed by means of the software package SPSS Statistics v.20.0 (SPSS Inc., Chicago, IL). Baseline characteristics of the population enrolled were described through descriptive statistics. Quantitative variables were presented as median and range, and categorical variables as absolute numbers.

Results

Overall, during the 2017-18 season, 29 patients admitted to UHU received a diagnosis of Influenza. The characteristics of the study population are summarized in Table II. The median age of the patients admitted was 48 years (range 0-87 years); there was an equal distribution

of genders (51.7% men, 48.3% women). Two women were pregnant: one in the first trimester and one in the second.

In 65.5% of cases, a B virus was isolated, in 24.1% an A/unsubtypized virus, in 6.9% an A H1N1 and in 3.4% another A virus subtype.

The seasonal peak was reached in the first two months of 2018, with 68.9% of all severe cases notified between January and February.

It was estimated that an antiviral treatment was administered (a neuroaminidase inhibitor, Oseltamivir) in 58% of cases. The median duration of antiviral therapy was 7 days.

Overall, 65.5% of the subjects developed a complication (see Tab. I for details of the definition of "complication"). The majority of these had respiratory syndromes: 44.8% complicated with bacterial pneumonia, 17.2% developed a severe acute respiratory infection (SARI) and 27.6% an acute respiratory distress syndrome (ARDS); 6.8 % developed myocarditis. A case of encephalitis was also observed in a patient with Influenza B/Yamagata strain isolated from a nasopharyngeal swab.

The cases classified as "severe" accounted for 41.4% of those admitted to UHU (see Tab. I for details of the definition of "severe case"). The median age of this population was 59.5 years (range 0-84), and the gender distribution was almost equal (46.5% were males). The majority of patients (70%) had at least one comorbidity, with a predominance of cardiovascular diseases (48.3%). See Tab. II for details of "comorbidity" definition.

All patients with severe forms were admitted to the ICU. Of this group, 27.6% required Orotracheal Intubation (OTI) and 10.3% needed to be placed on Extracorporeal Membrane Oxygenation (ECMO).

Seven patients (24.1%) died; 4 had Influenza B virus isolated from respiratory samples. Overall, 3 deaths were recorded in subjects younger than 50 years old. Of these, one presented with an influenza-related myocarditis and developed cardiogenic shock; in the other two cases, the final diagnosis was multi-organ failure. None of the 3 patients aged under 50 years had been vaccinated.

Overall, 70% of the fatal cases developed pneumonia, ARDS was diagnosed in 4 cases, acute heart failure in 2 cases, and myocarditis in 1 case.

Regarding vaccination coverage, only 9 (31%) of the UHU cohort had been vaccinated. Six vaccinated subjects were older than 65 years old, 5 of whom were males. All the vaccinated patients were pluricomorbid and two of them suffered from a type of immunodeficiency. Information on the type of influenza vaccine is not available.

Details of the clinical presentation and vaccination status of patients admitted to UHU are summarized in Table III.

On the basis of the experience acquired during the 2017-18 season, we elaborated a checklist with the aim of facilitating early diagnosis and implementing a meticulous clinical approach, starting from admission.

We suggest that every patient presenting with symptoms compatible with respiratory or systemic illness (e.g.

Tab. I. Terms and definitions.

Term	Definitions
Influenza season	The period of the year during which more than 80% of influenza cases occur. The usual time-frame of the influenza season is of 8-12 weeks, from late autumn to early spring
ILI	An acute respiratory infection with: measured body temperature of $\geq 38^{\circ}\text{C}$ + cough; with onset within the last 10 days
SARI	An acute respiratory infection with: history of fever or measured body temperature of $\geq 38^{\circ}\text{C}$ + cough; with onset within the last 10 days, and requiring hospitalization
Severe flu	Influenza presenting as SARI, requiring ICU admission and/or ECMO Influenza presenting with ARDS, requiring ICU admission and/or ECMO Influenza initially presenting as non-severe disease, and subsequently developing any of the signs and symptoms of progressive disease: shortness of breath, tachypnea, cyanosis, bloody or colored sputum, chest pain, hypotension, central nervous system complications (altered mental state, confusion, unconsciousness, drowsiness, seizures, weakness, or paralysis), evidence of sustained virus replication or invasive secondary bacterial infection
Influenza-related complications	Acute respiratory failure, pneumonia, ARDS, febrile seizure, encephalitis/encephalopathy, renal failure, multi-organ failure, septic shock, rhabdomyolysis, myocarditis, exacerbation of underlying chronic disease, including asthma, COPD, chronic hepatic or renal insufficiency, diabetes, cardiovascular conditions

ILI: influenza like illness; SARI: severe acute respiratory infections; ARDS: Acute respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease

Tab. II. The demographic characteristics, seasonal distribution and outcome of patients admitted to Udine Hospital for Influenza and Influenza-related complications during the 2017-18 season.

Study population	
Total (n, %)	29 (100)
Age (median and range, years)	48.3 (0-87)
Male gender (n, %)	15 (51.7)
Female gender (n, %)	14 (48.3)
Pregnancy (n, %)	2 (6.9)
Subjects who had received seasonal Influenza vaccination (n, %)	9 (31)
Comorbidities (n, %)	18 (62)
• Cancer	2 (6.9)
• Diabetes mellitus	4 (13.8)
• Cardiovascular disease	14 (48.3)
• Immunocompromised*	4 (16)
• Chronic respiratory conditions	5 (17.2)
• Chronic kidney disease	7 (24.1)
• Metabolic conditions°	1 (3.4)
• Obesity	4 (13.7)
Seasonal distribution (n, %)	
• November	1 (3)
• December	2 (7)
• January	10 (35)
• February	10 (35)
• March	3 (10)
Virological distribution (n, %)	
• A non-subtyped virus	7 (24.1)
• A H1N1 virus	2 (6.9)
• A, other subtype	1 (3.4)
• B virus	19 (65.5)

* Immunocompromised cases included: 1 patient affected by Common Variable Immunodeficiency (CVID), 1 allogeneic hematopoietic stem cell transplant recipient, and 2 solid organ transplant recipients; ° metabolic conditions included: obesity, malnutrition, chronic liver disease (including cirrhosis and alcoholic liver disease), alcoholism, dyslipidemia, and glucose intolerance

cough, fever, coryza, arthromyalgia during the Influenza season should undergo the following work-up:

- For patients without any risk factor for severe Influenza forms: no routine testing nor routine antiviral

treatment, unless no spontaneous improvement in 1 week.

- For patients with one or more risk factors for severe Influenza forms:

- Naropharyngeal swabs for the detection of major respiratory viruses (e.g. Influenza, Respiratory Syncytial Virus, Metapneumovirus, Rhinovirus, Coronavirus) and major interstitial bacterial pneumonia (*Legionella*, *Chlamydia* and *Mycoplasma*).
- Legionella* and Pneumococcal urinary antigens.
- Nasal and cutaneous swabs to check for Methicillin-Resistant *Staphylococcus aureus* colonization.
- Sputum collection for gram stain and culture.
- Blood cultures.
- Chest X-ray.
- Computerized tomography (CT) thoracic scan and bronchoscopy should be offered to every patient with imaging abnormalities and no results from the previous tests, and to every critically ill patient.

Regarding treatment:

- In order to provide an adequate diagnosis, no antibiotic or antiviral should be started before preliminary sample collection, unless the patient presents serious instability.
- Support care must be provided for every patient (oxygen administration, non-invasive or invasive ventilation, vasopressors, intravenous fluids, etc.).
- Antivirals should be promptly administered to: critically ill people, patients affected by or at high risk of severe influenza forms, immunocompromised people, elderly and in-hospital patients. The antiviral should be started within 48 hours of symptom onset. We suggest using a neuraminidase inhibitor, such as Oseltamivir, Zanamivir, and Peramivir.

Empiric antibiotic treatment should be considered in cases of suspected superinfection and in cases at risk of complications with secondary infections. An adequate treatment for community-acquired pneumonia should be

Tab. III. Clinical presentation of patients admitted to Udine Hospital for Influenza and Influenza-related complications during the 2017-18 season.

Clinical presentation	
Admitted (n, %)	29 (100)
Admitted to ICU (n, %)	12 (41.4)
Admitted to Infectious Disease Department (n, %)	4 (13.8)
Admitted to other departments (n, %)	13 (44.8)
Requiring OTI (n, %)	8 (27.6)
Requiring ECMO (n, %)	3 (10.3%)
Receiving antiviral therapy (n, %)	17 (58.6)
Treatment duration (median days)	6.7
Severe cases (n, %)	12 (41.4)
Complications (n, %)	19 (65.5)
• Pneumoniae	13 (44.8)
• SARI	5 (17.2)
• ARDS	8 (27.6)
Outcome	
• Deaths	7 (24.1%)
• Cured	22 (75.9%)

ICU: intensive Care Unit; OTI: Orotracheal Intubation; ECMO: Extracorporeal Membrane Oxygenation; SARI: Severe Acute Respiratory Infection; ARDS: Acute respiratory distress syndrome

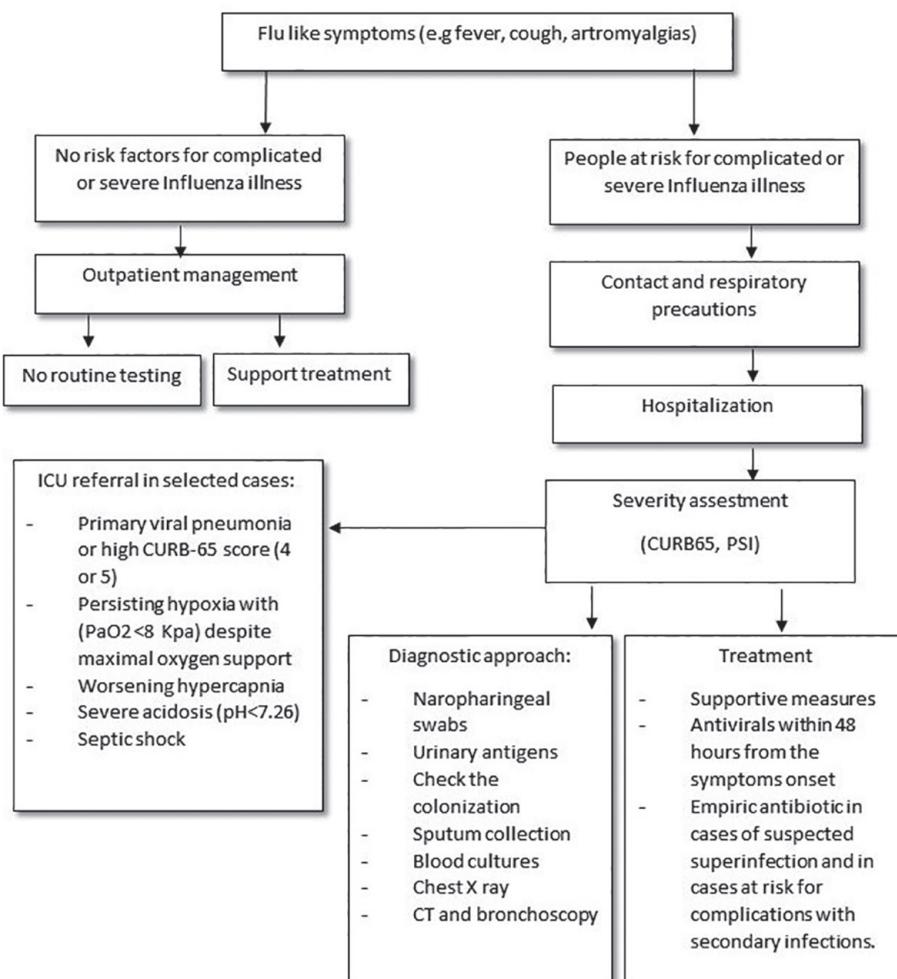
selected. Oral antibiotics are the preferred choice; parenteral treatment should be selected in the case of severe pneumonia. The duration of the treatment should be decided according to clinical evolution. Generally, standard antibiotic duration for community-acquired pneumonia is adequate. Antibiotic escalation should be considered in the case of insufficient improvement within 72 hours. An algorithm to guide the management of Influenza cases is reported in Figure 1.

Discussion

The 2017-18 epidemic was the most severe in all age-groups since 2003-04. Globally, lethality rates reached 22.6%, a disproportionate burden even in comparison with the 2014-15 season, when the “Fluad case” determined the lowest vaccination coverage in recent seasons [26, 27].

During the 2017-18 season, in Italy a total of 764 cases were classified as severe. For the first time since 2009-

Fig. 1. Algorithm to guide the management of influenza cases.



10, during the past season every Italian region (except Molise) reported one or more severe cases of Influenza. The majority of cases were reported in the north of the country, with highest incidence in the Lombardy and Emilia Romagna regions [28].

Among patients with severe forms, there was a slight predominance of males over females (58% national data vs 51% in our population). The median age of these patients was 60 years, and almost 84% presented at least one pre-existing risk factor for developing a severe illness (diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, immunosuppression). Fifteen severe cases involved pregnant women. Only 13 of the patients affected by a severe form presented no predisposing condition [9, 27].

Influenza-attributed deaths in Italy were 173, accounting for 22.6% of severe forms (versus 24.1% of our cohort); 90% of the deaths occurred in adults, 2 of whom were pregnant women. All (100%) patients with severe disease needed to be admitted to the ICU, 8.5 % required ECMO and 41% needed OTI [9].

In our cohort, too, the majority of severe forms were recorded in adults, and all required admission to the ICU. The rate of comorbidity among UHU patients who developed a severe form was slightly lower than that reported in the rest of Italy (70%).

Nearly half of the patients with severe disease, both in our cohort and in the national and global surveillance data, were affected by a cardiovascular disease. This finding highlights the relationship between influenza infection and poor outcomes due to underlying cardiovascular disease. In particular, a strong association with increased rates of hospitalization for cardiovascular events and a higher risk of acute ischemic events have been reported [29, 30].

Concerning the time-distribution, the 2017-18 season started early in Italy. A and B viruses co-circulated in the first few weeks; subsequently, after week 48, influenza B largely dominated over other subtypes, being responsible for 66% of cases (97% involved the B/Yamagata subtype) [31].

The cumulative rate of hospitalization due to influenza during the 2017-18 epidemic was the highest documented since 2005-2006 in all age-groups. Overall, in the 2017-18 season, a total of 30,453 influenza-related hospitalizations were reported. The majority of the hospitalized patients were ≥ 65 years old [27].

Although B viruses are traditionally known to cause less severe disease than A subtypes, during the 2017-18 season the predominant circulation of B/Yamagata virus (60% of the total viruses) in Italy was responsible for severe disease in most age-classes [9].

It has been estimated that 52% (308) of the severe cases reported in Italy were attributable to influenza A/H1N1pdm09 virus, 37% to influenza B virus, 9% to a non-subtyped A strain, and 2% to A/H3N2 virus. Of the cases requiring hospitalization, 72.3% were attributed to influenza A, 27% to influenza B, 0.4 % to influenza A and B co-infections, and 0.3% to a nontyped influenza virus. Of the patients who died, 84 (49%) were infected

with virus A/H1N1pdm09, 76 (44%) with B virus, and 13 (7%) with an unsubtyped influenza A virus [9, 27]. A similar distribution was also observed in our population. In UHU, B virus predominated throughout the season, with nearly 60% of the fatal cases infected with B strains.

The results of our analysis reflected the global and national epidemiology in the 2017-18 influenza season. In particular, we highlighted the necessity to strengthen the influenza surveillance system and vaccine prevention as a strategy for reducing the burden of influenza-related poor outcomes.

Our study presents several limits. First of all, we conducted a purely descriptive analysis of a small sample. Thus, no generalization of the results can be proposed. Furthermore, the retrospective design of the study makes it impossible to rule out external factors that might have interfered with the outcomes and compliance. Nevertheless, it should be underlined that Italian national and regional data are strongly influenced by the very low adherence to surveillance in some areas of the country.

Conclusions

Early recognition and prompt appropriate treatment are the cornerstones of the management of severe influenza forms. In our experience, a risk-stratified system of management is a useful strategy for the implementation of a cost-effective approach.

Every person who develops respiratory illness during the period from late autumn to early spring should be suspected of having been infected with influenza.

Patients with suspected Influenza and no risk of complicated infection should be candidates for outpatient management. The illness can be expected to resolve in 7-10 days. During recovery, the patient should be advised to stay at home and to avoid contact with vulnerable subjects. In selected cases (e.g. people at risk of developing complications due to Influenza), an antiviral should be prescribed. If no improvement is seen within 7 days, we strongly recommend that the microbiological diagnosis be confirmed through nasopharyngeal swabbing. Moreover, the virological confirmation of influenza cases contributes to epidemiological monitoring and enables the patient's contacts to be traced.

High-risk subjects and those with serious respiratory or systemic symptoms should be hospitalized and managed according to the best practice. We believe that currently approved pneumonia risk scores (e.g. CURB-65, PSI) should be used for initial evaluation. However, an individualized approach is mandatory.

In cases in which high severity criteria are met, the patient should be hospitalized in a medical or an intensive ward, according to the level of clinical complexity and general condition.

As a general rule, any patient who meets the following criteria should be considered for ICU admission:

- Primary viral pneumonia or high CURB-65 score (4 or 5).

Tab. IV. Influenza prevention strategy.

How to prevent Influenza	
Hygiene rules	Universal vaccination
Hand washing	Mandatory
Healthcare workers must use personal protection devices and respect good practice: use of surgical masks and gloves, hand washing, adherence to isolation rules	Immunodepressed Healthcare workers Pregnant women Children Residents in long-term facilities
Isolation of index cases	Strongly recommended
Respiratory good practices	Everyone

- Persistent hypoxia ($\text{PaO}_2 < 8 \text{ Kpa}$) despite maximal oxygen support.
- Worsening hypercapnia.
- Severe acidosis ($\text{pH} < 7.26$).
- Septic shock.

A key point in the management of hospitalized Influenza cases (whether proven or suspected) is the need for strict adherence to contact and respiratory precautions. A well-trained team plays a fundamental role in avoiding in-hospital outbreaks. The recommendations are summarized in Table IV.

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Conflicts of interest statement

Matteo Bassetti serves on scientific advisory boards for Angelini, AstraZeneca, Bayer, Cubist, Pfizer, Menarini, MSD, Nabriva, Paratek, Roche, Shionogi, Tetraphase, The Medicine Company and Astellas Pharma Inc.; has received funding for travel or speaker honoraria from Algorithm, Angelini, Astellas Pharma Inc., AstraZeneca, Cubist, Pfizer MSD, Gilead Sciences, Menarini, Novartis, Ranbaxy, Teva.

Authors' contributions

MB conceived the draft of the article and supervised the manuscript. NC collected clinical data and performed a review of the literature. TG, CP, PDA, AS, and RC provided epidemiological and surveillance data. MP and EG were involved in writing discussion and conclusions. All authors read and approved the manuscript.

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