

RESEARCH ARTICLE

Epidemiological and virological surveillance of Severe Acute Respiratory Infections in the 2019/2020 season in Siena, Tuscany, Italy

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Keywords

Influenza A and B viruses • Severe Acute Respiratory Infections • Epidemiological and virological surveillance

Summary

Background. Influenza is a major public health issue. Indeed, in Italy there were 7.6 million symptomatic cases of influenza in the 2019/2020 influenza season (from October 2019 to April 2020). The aim of this study is to analyse the circulation of influenza A and B viruses in hospitalized adult and elderly patients with Severe Acute Respiratory Infections (SARI) at Le Scotte University Hospital in Siena.

Methods. Oropharyngeal swabs were taken from SARI patients, who also completed a questionnaire recording their underlying diseases and vaccination status. Total RNA was extracted from each respiratory swab by means of the QIAamp Viral RNA Mini kit, and RT-PCR was carried out. All statistical analyses were performed by means of GraphPad Prism 6 software and STATA.

Results. In this study we collected 68 swabs. The average age of subjects was 79.4 years (C.I.: 76.6-82.3) and 52.9% were female. The subjects had fever (89.7%), fatigue (77%), headache (47%), cough (75%), sore throat (70.5%), and breathlessness (63.2%). We found that 20% of the 68 subjects were positive (13% for A H3N2 and 7% for A H1N1). Of the 68 subjects, 25% had received a seasonal influenza vaccine (91.6% trivalent and 8.4% quadrivalent).

Conclusions. Our study is important in order to determine the timing and spread of influenza viruses and track changes in circulating influenza viruses, so as to inform seasonal influenza vaccine composition. Seasonal vaccination is considered the most effective way to prevent influenza and its complications.

Introduction

Influenza is a major public health problem, causing an estimated 3 to 5 million cases of serious illness and 290,000 to 650,000 deaths due to respiratory infections per year worldwide [1]. There are four types of influenza viruses: A, B, C and D. Influenza A and B viruses cause seasonal epidemics of influenza disease; influenza type A viruses, unlike type B viruses, can also cause influenza pandemics, as their reservoir of infection is not only humans but also animal species. Influenza A viruses are further classified into subtypes according to the combinations of their two surface proteins, haemagglutinin (HA) and neuraminidase (NA), which are responsible for the infectious cycle of the influenza virus. Currently circulating in humans are subtypes A(H1N1) and A(H3N2) [2, 3]. A(H1N1) is also called A(H1N1)pdm09, as it caused a pandemic in 2009 and subsequently replaced the seasonal influenza A(H1N1) virus which had circulated prior to 2009. Influenza B viruses are not classified into subtypes, but can be broken down into lineages. Currently circulating influenza type B viruses belong to either

the B/Yamagata or the B/Victoria lineage. Influenza C virus is detected less frequently and usually causes mild infections; it does not therefore arouse public health concern. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people [1, 4]. At the global level, influenza surveillance is conducted by the Global Influenza Surveillance and Response System (GISRS), which is coordinated by the WHO [1]. The virological surveillance of influenza is an important means of determining the timing and spread of influenza viruses, tracking changes in circulating influenza viruses and informing seasonal influenza vaccine composition [5]. In Siena, the epidemiological surveillance of influenza has been carried out since the 1980s [6, 7].

Only during the 2009 influenza pandemic did the need for more global data on severe influenza disease starkly emerge, promoting the World Health Organization to recommend conducting surveillance for severe acute respiratory infection in hospitalised patients; indeed, before 2011 a global surveillance case-definition of Severe Acute Respiratory Infections (SARI) did not exist. The proposed clinical case-definition of

SARI in all age-groups therefore became “an acute respiratory illness with a history of fever or measured fever of $\geq 38^{\circ}\text{C}$ and cough, with onset within the past 10 days, requiring hospitalization”. To simplify the implementation process, the same criterion, i.e. “onset within the past 10 days”, was subsequently used in the case-definitions of both ILI (Influenza-like illness) and SARI [8-10].

Since the 2009/2010 pandemic season, Italy has been monitoring the evolution of severe and complicated forms of seasonal influenza. This surveillance aims to collect information on severe forms and deaths, in order to better understand the epidemiology of severe forms in the country, also in terms of possible risk factors and viral mutations during influenza epidemics [11].

In Italy, the virological and epidemiological surveillance of influenza is carried out by InFluNet [12]. This national surveillance system is based on a network of sentinel doctors made up of general practitioners and paediatricians, recruited by the Regional health authorities, who report cases of influenza-like syndrome (ILI) observed among their patients. Sentinel doctors and other doctors working in the territory and in hospitals also collaborate in the collection of biological samples for the identification of circulating viruses.

The collection and processing of disease reports is carried out by the Public Health Institute (ISS), which processes them at the national level and produces a weekly report that is published on the Ministry of Health website. The InFluNet network is integrated by FluNews, which collects the results of several influenza surveillance systems (Sismg, InFluWeb, InFluNet-Epi, InFluNet-Vir) [13]. Influenza severity measurements proposed by the WHO vary by influenza epidemic and cannot be deduced from ILI surveillance alone, thus emphasizing the potential use of and the necessity for prospective SARI surveillance, in order to assess the burden of seasonal influenza [14, 15].

The Italian Ministry of Health recommends that the monitoring of SARI be widely implemented in the intensive care units of local hospitals, and has requested their compliance [16]. Seasonal (or inter-pandemic) influenza surveillance generates information that can be used to plan appropriate measures of control and intervention (including vaccination), allocate health resources, and make recommendations for influenza case management [17].

All these surveillance systems are essential to the creation of a comprehensive representation of influenza from both the epidemiological and virological standpoints. Moreover, the reporting of SARI in a patient with chronic diseases ensures that the complications of influenza are not underestimated [18]. The consequences of influenza infection can be severe both for individuals and for the healthcare system. The severity of the infection depends on the type/subtype of the virus and the characteristics of the patient, including age (infants < 1 year and over 65 years) and the presence of cardiovascular, respiratory,

or immunodeficiency diseases. SARI caused by the influenza virus can result in hospitalisation [19-21]. Influenza vaccination is the most effective measure to prevent influenza disease. The WHO and EU countries, including Italy, recommend routine seasonal influenza vaccination for the elderly and individuals at increased risk of influenza complications, and have set a target of 95% influenza vaccine coverage for the elderly. In Italy, the three objectives of the seasonal vaccination campaign are: to reduce the individual's risk of disease, hospitalization and death, to reduce the risk of transmission to subjects at risk of other complications or at risk of hospitalization, and to reduce the costs associated with the morbidity and mortality of the disease [22].

The 2017/2018 season saw the launch of the Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project [23]. This project is a public-private partnership aimed at building the capacity for yearly estimation of brand-specific influenza vaccine effectiveness (IVE) in Europe. DRIVE is a five-year project funded by the IMI (Innovative Medicines Initiative) and our study is part of this project. It was initiated as a response to the guidelines on influenza vaccines issued by the EMA (European Medicines Agency), which advised vaccine manufacturers to work with public health institutes to set up a joint IVE study platform [23]. The data generated through DRIVE are expected to increase the understanding of influenza vaccine effectiveness, lead to enhanced monitoring of influenza vaccine performance by public health institutes and allow manufacturers to fulfil regulatory requirements [24]. In this study, we analysed the circulation of influenza viruses in the hospital setting in adult and elderly patients with SARI during the 2019/2020 season.

Materials and Methods

STUDY DESIGN

Oropharyngeal swabs were collected at the Unit of Emergency Medicine and Internal Medicine II of Le Scotte University Hospital in Siena, Italy, in the 2019/2020 influenza season. In Italy, the influenza season lasts from 47/2019 to 17/2020 weeks. The study is an observational case-control study in which SARI cases confirmed for influenza and controls will be identified as such after the test has been performed cases confirmed for influenza and controls will be identified as such following laboratory testing laboratory test. The study is multicentre (see setting section), non-commercial and will be conducted during the influenza season from 18 November 2019 and will end on 26 April 2020.

Sample collection was conducted in the context of the project DRIVE. The study was approved by the Ethics Committee of Area Vasta Sud Est Tuscany: approval Report n. 16344 of 16th December, 2019. Written

consent was obtained from all patients enrolled in the study.

The study population is made up of all non-institutionalized subjects hospitalized for SARI, who do not present contraindications to flu vaccination.

Patients enrolled in the study presented symptoms (at least one systemic sign and symptom and one respiratory sign and symptom) and/or deterioration of their general condition at the time of hospital admission or within 48 hours after admission. The symptoms considered were: fever, headache, myalgia, generalized malaise, cough, sore throat and breathing difficulties. During interviews, patients were asked about their vaccination status; each patient's general practitioner was then asked to confirm the vaccination status and the type of vaccine (trivalent or quadrivalent). Patients were included if they had been vaccinated more than 14 days before the onset of SARI symptoms. The information was collected through a standardized questionnaire in which socio-demographic data and any underlying conditions were recorded. The swabs were collected by the ward doctor, stored at + 4°C and transported to the Molecular Epidemiology laboratory of the University of Siena and processed within 24 hours.

LABORATORY ANALYSIS

Total RNA was extracted from swabs by means of the QIAamp Viral RNA Mini kit (Qiagen, Hilden, Germany).

One-step real time RT-PCR was performed in a final volume of 25 µl with 0.8 µM forward and reverse primers, 0.2 µM probe and 5 µl of extracted RNA, in accordance with the manufacturer's instructions for the use of the One-Step RT-PCR Kit (SuperScript III Platinum One-Step qRT-PCR Kit, Thermo Fisher Scientific, Waltham, MA, USA): Cycling conditions were 50°C for 30 minutes, 95°C for 2 minutes and 45 cycles of 15 seconds at 95°C and 30 seconds at 55°C. Fluorescence was measured during the 55°C annealing/extension step.

STATISTICAL ANALYSIS

The average ages of the study population and positive subjects were calculated. Frequencies, Standard Deviation (SD) and Confidence Interval (CI) were calculated. All statistical analyses were performed by means of GraphPad Prism 6 software and STATA.

Results

Sixty-eight oropharyngeal swabs were taken from patients with SARI. The first swab was collected on December 15, 2019, and the last swab was collected on March 15, 2020. Their average age was 79.4 years (SD:1.44; C.I.: 76.6-82.3). The median age was 82 and 52.9% were female.

The patients had fever (89.7%), fatigue (77%), headache (47%), cough (75%), sore throat (70.5%), and breathlessness (63.2%). Of the 68 patients, 25% had

received a seasonal influenza vaccine (91.6% trivalent and 8.4% quadrivalent); 23.5% had not undergone anti-pneumococcal vaccination, while 76.5% whether they had or not. We found that 20% of the 68 subjects were positive (13% for A H3N2 and 7% for A H1N1). The median age of the positive subjects was 79.5 years and 57.1% were male. There were 12 positives among the unvaccinated, only 2 positives among the vaccinated were hospitalised. The positive subjects mostly had fever (100%), fatigue (71.4%), headache (28.6%), myalgia (35.7%), cough (78.6%), sore throat (57.1%), and breathlessness (50%) (Tab. I).

Tab. I. Symptoms of positive subjects: number of subjects (N) and frequency (%).

Symptoms	(N)	%	C.I.
Fever	14	100	0
Fatigue	10	71.4	0.01 - 0.55
Headache	4	28.6	0.44-0.98
Myalgia	6	42.9	0.27-0.86
Cough	11	78.6	-0.03-0.46
Sore throat	8	57.1	0.13-0.72
Breathlessness	7	50.0	0.20-0.79

Positive subjects had a mean of 2.2 underlying conditions. The most common underlying diseases found in the positive subjects were: obesity (100%), cardiovascular diseases (50%), hypertension (50%), renal diseases (50%), lung diseases (42.8%), diabetes (35.7%), and cancer (35%). Other underlying conditions found in positive subjects were: haemopoietic organ diseases (14.3%), acquired immunosuppression (14.3%), liver disease/cirrhosis (7.1%), dementia (7.1%), stroke (7.1%), leukaemia or lymphomas (7.1%), and rheumatic diseases (7.1%) (Tab. II).

Tab. II. The most frequent underlying condition in positive subjects

Underlying Conditions	Freq.	%	C.I.
Cardiovascular diseases	7	50.0	0.20-0.79
Hypertension	7	50.0	0.20-0.79
Lung diseases	6	42.9	0.27-0.86
Diabetes	5	35.7	0.35-0.92
Renal diseases	7	50.0	0.20-0.79
Haemopoietic organ disease	2	14.3	0.64-1.06
Cancer	5	35.7	0.35-0.92
Liver disease/cirrhosis	1	7.1	0.77-1.08
Immunosuppression	2	14.3	0.64-1.06
Obesity	14	100	1

Among the positive subjects, 2 were smokers, 5 were ex-smokers, 4 had never smoked and 3 did not answer (Tab. III).

Tab. III. Smoking among positive subjects

Smoker	Freq.	%
No	4	28.6
Yes	2	14.3
Ex	5	35.7
no answer	3	21.4
Total	14	100.0

Tab. IV. Positive patients: number of subjects (N) and type of influenza virus.

	A/H1N1 (N.)	A/H3N2 (N.)
Positive subjects	5	9
No Vaccination	4	8
Cardiovascular diseases	2	5
Hypertension	2	5
Lung diseases	1	6
Diabetes	1	4
Renal diseases	1	6
Haemopoietic organ disease	0	2
Cancer	3	2
Liver disease/cirrhosis	0	1
Immunosuppression	1	1
Fever	5	9
Fatigue	3	7
Headache	1	3
Myalgia	1	5
Cough	3	8
Sore throat	4	4
Breathlessness	1	6

Two of the positive subjects had been vaccinated with trivalent vaccine; in a 90-year-old woman, influenza virus A(H3N2) was identified, and in an 86-year-old woman, influenza virus A (H1N1)pdm09 was identified. Both women had fever and cough. The 86-year-old also had muscle pain and breathlessness. Table IV shows positive patients based on the type of influenza virus, symptoms, underlying conditions and vaccination status.

Discussion

In this study, we found that 20.5% of 68 subjects hospitalized in Siena, Tuscany with SARI symptoms were positive for influenza virus infection. Most of the infections were sustained by type A viruses, especially A (H3N2) viruses, which accounted for two-thirds of infections in our study. These values are in line with the trend reported by virological surveillance in Italy and in Europe [13,25-27]. In Europe, the first detections during the 2019-2020 season indicated co-circulation of influenza types A (71%) and B (29%) viruses in the WHO European Region. All four influenza subtypes and lineages circulated. Of the types A and B viruses detected, the A(H3N2) subtype and B/Victoria lineage were dominant in north-western Europe and Central Asia, respectively [26]. In Italy, from a virological

point of view, the season was characterised by the predominant circulation of type A viruses (68%); 32% of viruses were of type B, and were isolated by InfluenzaNet laboratories. Of the type A viruses, 54% belonged to the A(H3N2) subtype, 39% belonged to the A(H1N1)pdm09 subtype, and 7% were not subtyped [25]. In particular, the most frequently identified subtype was A(H1N1)pdm09 at the sites in Finland, France and Spain (range 71.7% to 91.3%), and A(H3N2) at the sites in Austria, Italy and Romania[28].

In Italy, influenza vaccination coverage in the 2019/2020 season was 54.6% in subjects aged over 65 years and 16.8% in the general population [29]. In Tuscany instead, influenza vaccination coverage in the 2019/2020 season was 54.6% in subjects aged over 65 years[29]. In support of the importance of vaccination coverage, our study shows that of the hospitalised patients only two were vaccinated, all the others who tested positive had not been vaccinated.

The WHO recommended that quadrivalent vaccines for the 2019/2020 season should contain: an A/Brisbane/02/2018 (H1N1)pdm09-like virus; an A/Kansas/14/2017 (H3N2)-like virus, and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) [30]. In the case of trivalent vaccines, the WHO recommended the insertion of the B/Washington/02/2019-like virus strain (lineage B/Victoria), in addition to the two types of A strain mentioned above.

During the 2019/2020 season, mismatch between the circulating A(H3N2) virus and the vaccine strain prompted the WHO to modify the composition of the vaccine for the 2020/2021 season [31, 32].

Following the first report of cases of acute respiratory syndrome in the Chinese municipality of Wuhan at the end of December 2019 [33], a pneumonia outbreak caused by human-to-human transmission of a new coronavirus rapidly spread, becoming a global pandemic [34]. In February 2020, the World Health Organization (WHO) named the novel coronavirus “SARS-CoV-2” and its associated spectrum of respiratory diseases “COVID-19” [35].

The signs and symptoms of SARS-CoV-2 infection overlap with those of many other viral respiratory tract infections, including those caused by influenza viruses. Beside “integrated COVID-19 surveillance”, which is specifically designed to track COVID-19 disease and to assess its burden, influenza surveillance can provide timely, high-quality data that can help to evaluate the SARS-CoV2 burden among populations with mild respiratory symptoms [36, 37]. The COVID-19 outbreak impacted influenza surveillance; thus, the study period of the main analysis was truncated. Indeed, the pandemic and the subsequent lockdown measures curbed the already modest circulation of influenza and impacted data collection within DRIVE study sites [24]. Several DRIVE study sites implemented a different triage protocol in response to the SARS-CoV-2 emergency, whereby all SARI patients arriving at hospitals were first tested for SARS-CoV-2; if the

results were negative, tests were performed for other respiratory viruses, such as influenza. This new triage strategy was not expected to significantly reduce the number of influenza cases captured in the DRIVE dataset in 2019/2020, as very few cases of co-infection of influenza/SARS-CoV-2 were reported at the DRIVE sites that did test swabs for both viruses; this was due to the minimal overlap between the influenza season and the emergence of the SARS-CoV-2 pandemic [24]. Moreover, during the pandemic, the implementation of strict public health measures (e.g. working from home, school closures, limiting social gatherings, increased hygiene measures, wearing masks etc.) to reduce SARS-CoV-2 transmission also reduced the circulation of other respiratory viruses. This was reflected by an all-time low level of influenza activity in the southern hemisphere and elsewhere in 2020 [38].

After consultation with the EMA and IMI in April 2020, the DRIVE consortium decided to take COVID-19 into account in its study documents (protocols, SAP, etc.) and operational procedures for the 2020/2021 season. Since then, DRIVE has closely tracked the evolution of the pandemic and has liaised with study sites in order to adapt rapidly to this ever-changing situation [24].

In the WHO European Region, unusually late and low-level influenza activity was predicted for the 2020/21 winter; these predictions were based on the low numbers of specimens testing positive for influenza virus that were detected in the summer months by sentinel and non-sentinel surveillance, despite substantial testing for influenza viruses during the COVID-19 pandemic [26,38]. Moreover, influenza surveillance can act as a global alert mechanism for the emergence of viruses with pandemic potential [1, 37].

The importance of influenza vaccination, especially for at-risk groups, remains a priority, as a higher influenza vaccination coverage rate in people aged 65 and over is associated with a reduced spread and a less severe clinical expression of COVID-19 [39]. The WHO recommends reconsidering the priority of risk groups for influenza vaccination during the COVID-19 pandemic for the following reasons: to ensure optimal influenza control among groups at high risk of severe COVID-19 disease and influenza; to reduce emergency room admissions and hospitalisations for influenza; and to ensure optimal management and use of potentially limited seasonal influenza vaccines worldwide [22, 39, 40].

Our study has some limitations. First, as the sample size was limited by the overall availability of swabs collected, it may not have been fully representative of the population. The hospital where the study was conducted is a 2nd level hospital with about 700 beds and the specific catchment area of the hospital has around 120,000 inhabitants as a reference for basic activities but only two departments participated in the study. In addition, many patients were not able to provide adequate answers regarding their medical history and vaccination status. In the future we will try to increase the sample by involving other units of the Le Scotte University Hospital in Siena.

Conclusions

Overall, our data support the importance of seasonal influenza vaccination in subjects with chronic diseases, in order to reduce hospitalisations and mortality, and highlight the key role of epidemiological and virological surveillance as an essential tool for monitoring circulating viruses, identifying possible mismatches with seasonal vaccine strains, and providing information that can be used to improve the composition of influenza vaccines.

The virological surveillance of influenza is important, in order to determine the timing and spread of influenza viruses, to track changes in circulating influenza viruses and to inform seasonal influenza vaccine composition. Seasonal vaccination is considered the most effective way to prevent influenza and its complications. During the COVID-19 pandemic, influenza vaccination is an essential supplement for people at risk.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

E.C.: conceptualisation, writing original draft, data curation, formal analysis, supervision. E.M.: review and editing. A.C.: resources, review and editing. G.B.: resources, review and editing. P.L.C.: resources, review and editing. A.M.: resources, review and editing. N.N.: review and editing. I.M.: conceptualisation, investigation, writing-review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

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