



A comparative study between the incidence and epidemiological features of Influenza-Like Illness and laboratory-confirmed COVID-19 cases in the Italian epicenter (Lombardy)

Francesca Grosso^{a,1}, Ambra Castrofino^{a,1}, Gabriele Del Castillo^{a,1}, Cristina Galli^a, Sandro Binda^a, Laura Pellegrinelli^a, Laura Bubba^a, Danilo Cereda^c, Marcello Tirani^c, Maria Gramegna^c, Antonino Bella^e, Silvana Castaldi^{a,d}, Elena Pariani^{a,b,*}

^a Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

^b Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy

^c DG Welfare, Regione Lombardia, Milan, Italy

^d Health Management Department, Fondazione IRCCS Ca' Granda OMP, Milan, Italy

^e Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

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ABSTRACT

Introduction: In Lombardy, the influenza surveillance system relies on sentinel physicians that weekly report data on the number of Influenza-Like Illness (ILI) and a part of them also collect nasopharyngeal samples for virologic analyses. This study aims at comparing the ILI incidence of 2019–2020 influenza season with the incidence of COVID-19 cases in order to better understand the current epidemic and to evaluate whether the implementation of ILI surveillance system could succeed in early detection and monitoring of COVID-19 diffusion.

Methods: The distribution of ILI cases in the seasons 2017–2018, 2018–2019 and 2019–2020 was taken in consideration and the curve trends were compared and analyzed according to geographical areas, age groups and time differences.

Results: The curve trends presented a similar pattern up to the 9th week; in fact, a reduction in the ILI incidence rate was observed in the 2017–2018 and 2018–2019 season but in the 2019–2020 an increase in the reported ILI emerged. The relation between the numbers reported by 2019–2020 ILI surveillance and those reported for COVID-19 is supported by the curve trends, the correspondence between age groups, the correspondence by geographical location, and also by the results of the nasopharyngeal swab tests performed.

Discussion: The influenza surveillance system is an effective tool for early detection of COVID-19. It may provide timely and high-quality data evaluating the SARS-CoV-2 burden among population with ILI. Implementation of the system has to be prioritized in order to identify any future novel respiratory pathogen with pandemic potential.

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Introduction

Following the first report of cases of acute respiratory syndrome in the Chinese Wuhan municipality at the end of December

2019 [1], a pneumonia outbreak caused by human-to-human transmission of a new coronavirus rapidly spread to become a global pandemic [2]. In February 2020, the World Health Organization (WHO) named the novel coronavirus SARS-CoV-2 and its associated spectrum of respiratory diseases COVID-19 [3].

In Europe, the first positive COVID-19 case was found in France on 24th January 2020 and a week later WHO declared COVID-19 as a public health emergency of international concern [4]. On 30th January the Italian Ministry of Health banned flights from and to China and implemented surveillance controls in the airports [5]. Despite these measures, Italy reported the first positive

* Corresponding author at: Department of Biomedical Sciences for Health, University of Milan, via C. Pascal, 36 - 20133 Milan, Italy.

E-mail addresses: antonio.bella@iss.it (A. Bella), elena.pariani@unimi.it (E. Pariani).

¹ These authors contributed equally to this work.

case of SARS-CoV-2 on February 20th in the city of Codogno, in the province of Lodi (Northern Italy), soon followed by an exponential growth of COVID-19 cases that initially involved almost exclusively the province of Lodi. This area was then referred to as “red zone” and restraint measures were applied to reduce the spread of the infection. Nevertheless, COVID-19 spread outside the “red zone”, reached all parts of Italy, and on March 8th, the Italian Government implemented extraordinary measures to limit viral transmission, including a national lockdown to minimize the SARS-CoV-2 transmission. Lombardy – a region in Northern Italy accounting for nearly 10 million inhabitants, equal to about 1/6 of the entire national population – has been, up to now, the core of COVID-19 epidemic in Italy [6]. Since February 20th, more than 239,410 people have been infected by SARS-CoV-2 in Italy, most of whom (39%) reside in the region of Lombardy, Italy’s COVID-19 epicenter [6].

As of April 9th, when COVID-19 had already taken on pandemic proportions and during the developing and drafting of this work, Italy recorded 136,110 positive cases, among which 19,375 were hospitalized with respiratory symptoms, 22.8% requiring admission at intensive care units (ICU) with a fatality rate of 12.2% [7].

Since SARS-CoV-2 has never circulated among humans in the past, we are all immunologically naïve to it and, thus, potentially susceptible to it. As COVID-19 is an emerging, rapidly evolving situation, at the time of this manuscript’s revision (January 2021), vaccine development was already on a fast track, including (i) mRNA, (ii) viral vector, (iii) protein-based and (iv) whole virus vaccines [8]. Nowadays, only two vaccines have been authorized and recommended by the Food and Drugs Administration (FDA) to prevent COVID-19: (i) BNT162b2 mRNA Covid-19 Vaccine and (ii) mRNA-1273 SARS-CoV-2 Vaccine, conferring respectively 95% and 94.1% efficacy in preventing COVID-19, as shown by ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial [9,10]. Both formulations are based on mRNA; BNT162b2 mRNA Covid-19 Vaccine is a lipid nanoparticle-formulated, nucleoside-modified RNA (modRNA) encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation whereas mRNA-1273 SARS-CoV-2 vaccine is a lipid-nanoparticle-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein and both formulations require two consecutive intramuscular injections to grant complete immunity against SARS-CoV-2 [9,10]. Given the worldwide limited supplies, a strategy of prioritization has been advocated and vaccines are firstly offered to those most at risk for SARS-CoV-2 exposure or COVID-19 complications and then to those that are progressively less at risk, following sequential prioritization steps, aiming at universal coverage [11].

To current knowledge about COVID-19, the clinical outcome of symptomatic SARS-CoV-2 not only includes viral pneumonia, but also milder illness overlapping with Influenza-Like Illness (ILI) [12] allowing the tracking of SARS-CoV-2 mild infection in the framework of influenza surveillance system [13,14].

InfluNet is the Italian national surveillance system for influenza. Coordinated by National Institute of Health (Istituto Superiore di Sanità) with the support of the Italian Ministry of Health, InfluNet is based on the voluntary participation of sentinel physicians who weekly report data on the number of ILI observed among their outpatients [15] and collect respiratory samples for virological analyses. Epidemiological and virological data are collected at regional level and then centralized by the National Institute of Health (Istituto Superiore di Sanità) in the framework of Global Influenza Surveillance and Response System (GISRS) [16].

This study aims at comparing the ILI incidence of 2017–2018, 2018–2019 and 2019–2020 influenza season with the incidence of COVID-19 cases in order to better understand the current epidemic and to evaluate whether the implementation of ILI surveillance sys-

tem could succeed in early detecting and monitoring SARS-CoV-2 diffusion.

Materials and methods

In Lombardy, influenza surveillance system relies on the voluntary participation of sentinel physicians (pediatricians and general practitioners) who survey about 2% of the general population seeking care in ambulatory facilities for ILI occurrence [15].

Sentinel physicians weekly report data on the number of ILI according to the ECDC case definition: an abrupt onset of fever ($>38^{\circ}\text{C}$) or feverishness, one or more respiratory symptoms (cough, sore throat and/or shortness of breath) and one or more systemic symptoms (myalgia, headache and/or malaise) [17]. A number of sentinel physicians is also in charge of collecting respiratory samples (nasal/throat swabs) from their outpatients from November to April of each season (i.e. from week 46 to week 17 of the following year) for virological analyses.

Since the beginning of the COVID-19 epidemic in Lombardy (week 8 of 2020), “Integrated COVID-19 Surveillance”, a regional database including laboratory-confirmed COVID-19 cases, was developed and updated daily [7]. This database collected data derived from (i) hospitals, reporting cases on inpatients (date of hospital admission, ICU admission, outcome), (ii) laboratories, reporting confirmed diagnosis on nasopharyngeal swabs, (iii) local health agencies, investigating individual cases and reporting epidemiologic characteristics (date of symptoms’ onset, comorbidities, symptoms’ severity, contacts), (iv) and from regional registry, on general and health related information.

The 2017–2018, 2018–2019, 2019–2020 influenza seasons and laboratory-confirmed COVID-19 epidemic curves were compared and analyzed according to geographical areas, time distribution and age-groups.

Results

At the beginning of 2019–2020 influenza season 170 sentinel physicians were recruited for epidemiological surveillance, thus covering a total of 218,696 people (2.2% of the total population of Lombardy). ILI incidence rates during the last three influenza seasons (from 2017–2018 to 2019–2020) increased since week 50–52 with peak in week 02–2018, 06–2019 and 06–2020, respectively (Fig. 1). The incidence of ILI cases in week 11–2020 (March 9th–15th) was 6.2 per 1,000 patients, in line with what observed during the two previous seasons (2017–2018, 2018–2019) (Fig. 1). The estimated number of ILI cases since the beginning of the 2019–2020 epidemiologic surveillance is 1,360,000. The contribution of sentinel doctors to the surveillance system in terms of number of doctors reporting ILI cases has been constant during the last two influenza seasons (2017–2018 and 2018–2019), with a reduction of 19% and 15% in the 11th week of 2019 and 2018, respectively. Out of the 170 sentinel doctors recruited for 2018–2019 season, 129 (75.9%), 105 (61.7%) and 68 (40%) doctors actively reported cases of ILI for the 9th, 10th and 11th week of 2019/2020 influenza surveillance, respectively. The greatest reduction in the number of doctors participating in the surveillance program was registered during the 11th week in the areas of Bergamo, Milan and Brescia; in these areas only 4, 19 and 7 sentinel doctors were active, corresponding to 23.5%, 34.5% and 38.9% of the total, respectively (Table 1).

Fig. 1 shows the distribution of ILI incidence rate by week for 2017–2018, 2018–2019 and 2019–2020 season. The distribution of ILI cases in the three seasons taken in consideration presented a similar trend up to the 9th week; since this time, a reduction in the ILI incidence rate was observed in the 2017–2018 and in the

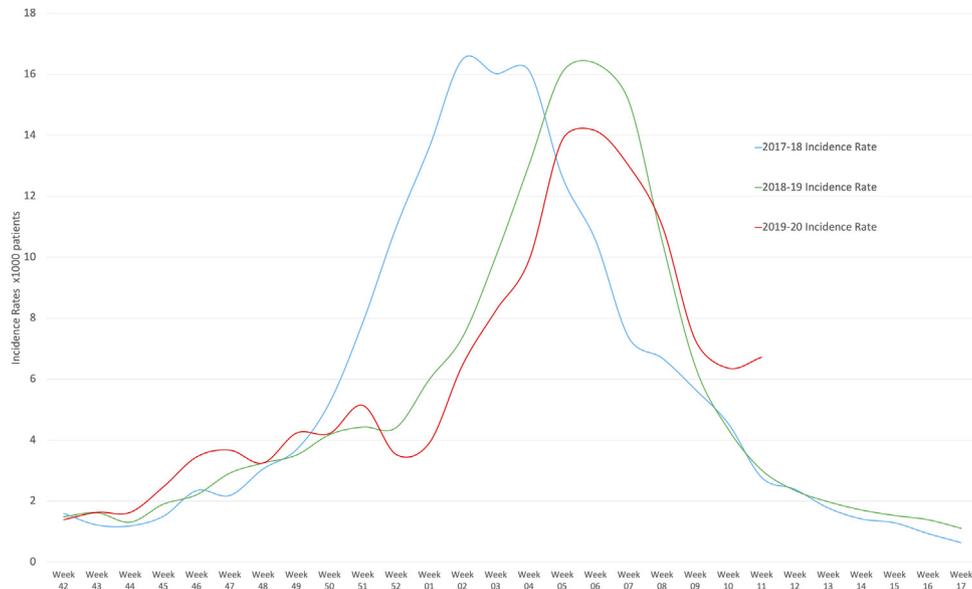


Fig. 1. Temporal distribution of the ILI incidence rates during the last three Influenza Seasons (from 2017–2018 to 2019–2020).

Table 1

Number of active sentinel doctors in the 9th, 10th and 11th weeks per regional area during the 2019–2020 influenza season (Lombardy region).

Regional area	9th Week			10th Week			11th Week		
	Active	Total	% Reduction	Active	Total	% Reduction	Active	Total	% Reduction
Insubria	21	25	84.0	17	25	68.0	10	25	40.0
Brianza	12	16	75.0	9	16	56.3	7	16	43.8
Milan	43	55	78.2	31	55	56.4	19	55	34.5
Mountains	5	7	71.4	4	7	57.1	3	7	42.9
Valpadana	19	22	86.4	19	22	86.4	11	22	50.0
Bergamo	10	17	58.8	9	17	52.9	4	17	23.5
Brescia	10	18	55.6	9	18	50.0	7	18	38.9
Pavia	9	10	90.0	7	10	70.0	7	10	70.0

2018–2019 season but in the 2019–2020 an increase in the reported ILI (Fig. 1). Analyzing in detail the distribution of the ILI cases per week during the 2019–2020 season, three major characteristics stand out: (i) at the beginning of COVID-19 epidemic, when the first case of SARS-CoV-2 infection was identified (7th to 9th week) there was a reduced steepness of the part of the curve with incidence varying from 13 cases per 1,000 individuals to 7.29 per 1,000 individuals; (ii) during the recognition of the COVID-19 outbreak (9th to 10th week) a plateau phase in the number of reported ILI cases was identified with 6.36 cases per 1,000 individuals; (iii) during the spread of COVID-19 (10th to 11th week) an unexpected increase of 6.72 cases per 1,000 individuals resulting in the steepness of the curve was observed.

In Fig. 2 incidence rates curve for 2019–2020 season and the number of laboratory-confirmed SARS-CoV-2 cases [2] are shown together; data on symptoms development, retrieved from the COVID-19 database, are shown in terms of week of symptoms onset. The peak in this curve matches the increased cases of ILI reported by sentinel doctors contributing to the influenza surveillance system in Lombardy (Fig. 2).

The analysis of respiratory cases (ILI and laboratory-confirmed COVID-19 cases) by age group show that the incidence rate of reported ILI among the adults (15–64 years) and the elderly over 65 years increased from the 9th to 11th week concurring to the determination of the observed curve plateau, while that of the pediatric age group (0–4 and 5–14 years) decreased. Comparing the ILI incidence rate curve related to individuals over 65 years with the curve of laboratory-confirmed COVID-19 cases, in the week from 9th to 11th and corresponding with the spread of COVID-19, the two

curves share the same trend (Fig. 3). The adult age group (15–64 years) was split into three age subgroups (15–24 years, 25–44 years, 45–64 years, respectively) so as to carry out a more detailed analysis. From 9th to 11th week, the ILI incidence rate in the 15–24 age group was lower than those of the other two; ILI incidence rate in the 25–44 age group instead exceeded that of the 45–64 age group (Table 2). Since the mostly affected by the increment of reported ILI cases, the 25–44 years and the 45–64 years age groups were compared from a geographical area standpoint in terms of the ILI incidence rate, and the trend was confirmed for every area, except for Bergamo.

The geographical distribution of reported ILI cases in Lombardy in the 2019–2020 season shows an increased incidence rate in four main areas: Bergamo, Brescia, Pavia and Mountain area (Fig. 4). In particular: the incidence rate in Bergamo area reached a peak of 7.63 cases per 1,000 patients in 10th week and then decreased to 1.45 in 11th week; the incidence rate in Brescia area was 2.97 cases per 1,000 patients at the 10th week and 3.94 in 11th week; Pavia area had an incidence rate of 3.98 cases per 1,000 and 7.05 in 10th and 11th week, respectively; Mountain area, which comprehends several areas scattered in the northern part of the region, had an incidence rate of 3.75 cases per 1,000 and 6.98 in 10th and 11th week, respectively (Fig. 4A). The same consideration can be made by geographical distribution of laboratory-confirmed COVID-19 cases, with the exception of Mountain area. In particular, Fig. 4B shows the distribution of the date of symptom onset (expressed as the corresponding week of the year) for the provinces of Bergamo, Brescia, Pavia and Lodi.

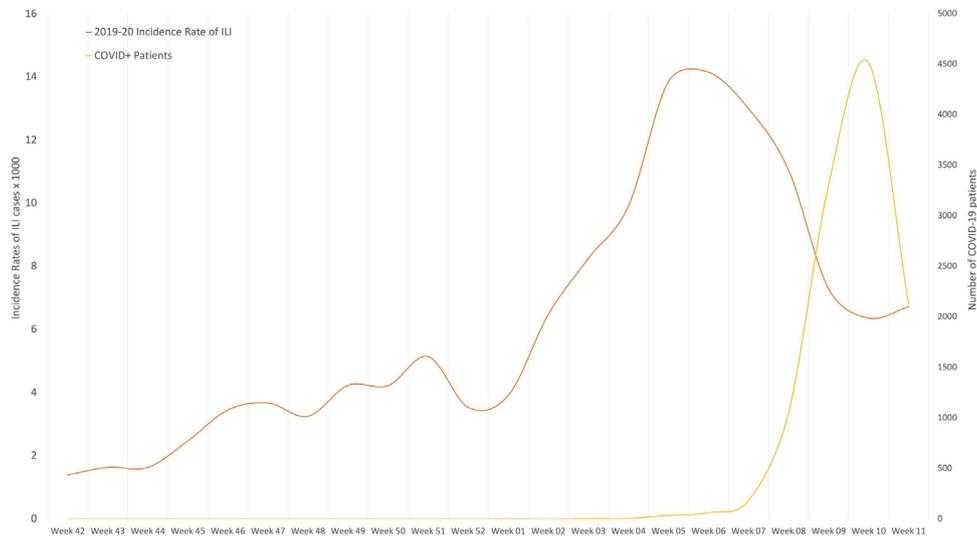


Fig. 2. Temporal distribution of the ILI incidence rates in the 2019–2020 influenza season and temporal distribution of the symptom onset of patients with COVID-19 identified by the Integrated COVID-19 Surveillance.

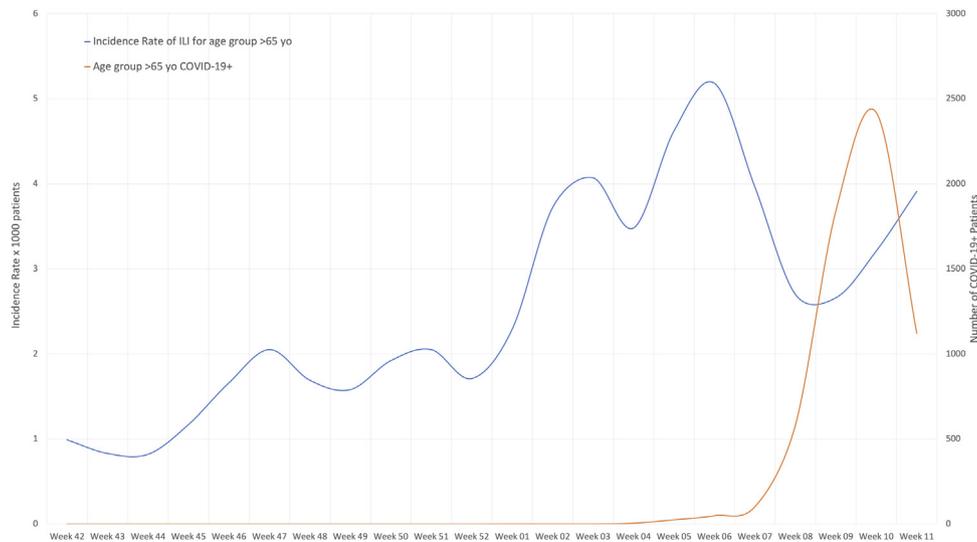


Fig. 3. Comparison between incidence rates of ILI cases and COVID-19 patients' symptom onset in individuals >65 years.

Table 2

Trend of the incidence rates of ILI cases per 1000 patients in each considered age group in week 9th, 10th and 11th during the 2019–2020 influenza season (Lombardy region). In bold the age group and the week with an increase in ILI incidence rate.

Number of week	0–4 years		5–14 years		15–24 years		25–44 years		45–54 years		>65 years	
9	14.91	/	8.68	/	6.1	/	8.6	/	7.3	/	2.7	/
10	6.55	–56%	2.82	–68%	4.7	–23%	10.0	+16%	9.9	+36%	3.2	+19%
11	2.58	–61%	1.65	–41%	5.5	+17%	12.6	+26%	10.6	+7%	3.9	+22%

Data of symptom onset derive from epidemiological investigations carried out by public health operators on laboratory-confirmed COVID-19 cases and are constantly updated even if the date of symptom onset was not available for 29% of the total population included in the analysis, that consisted of 15,716 positive patients on March 15th. The relation between the numbers reported by 2019–2020 ILI surveillance and those reported for COVID-19 is supported not only by their curve trends, the correspondence between age groups and the correspondence by geographical location.

Discussion

The signs and symptoms of SARS-CoV-2 overlap with those of many other viral respiratory tract infections, including influenza viruses. Beside “Integrated COVID-19 surveillance” purposely establish to burden and track COVID-19, influenza surveillance may provide timely and high-quality data evaluating the SARS-CoV-2 burden among population with mild respiratory symptoms [18]. Moreover, influenza surveillance can work as a global alert mechanism for the emergence of viruses with pandemic potential [16].

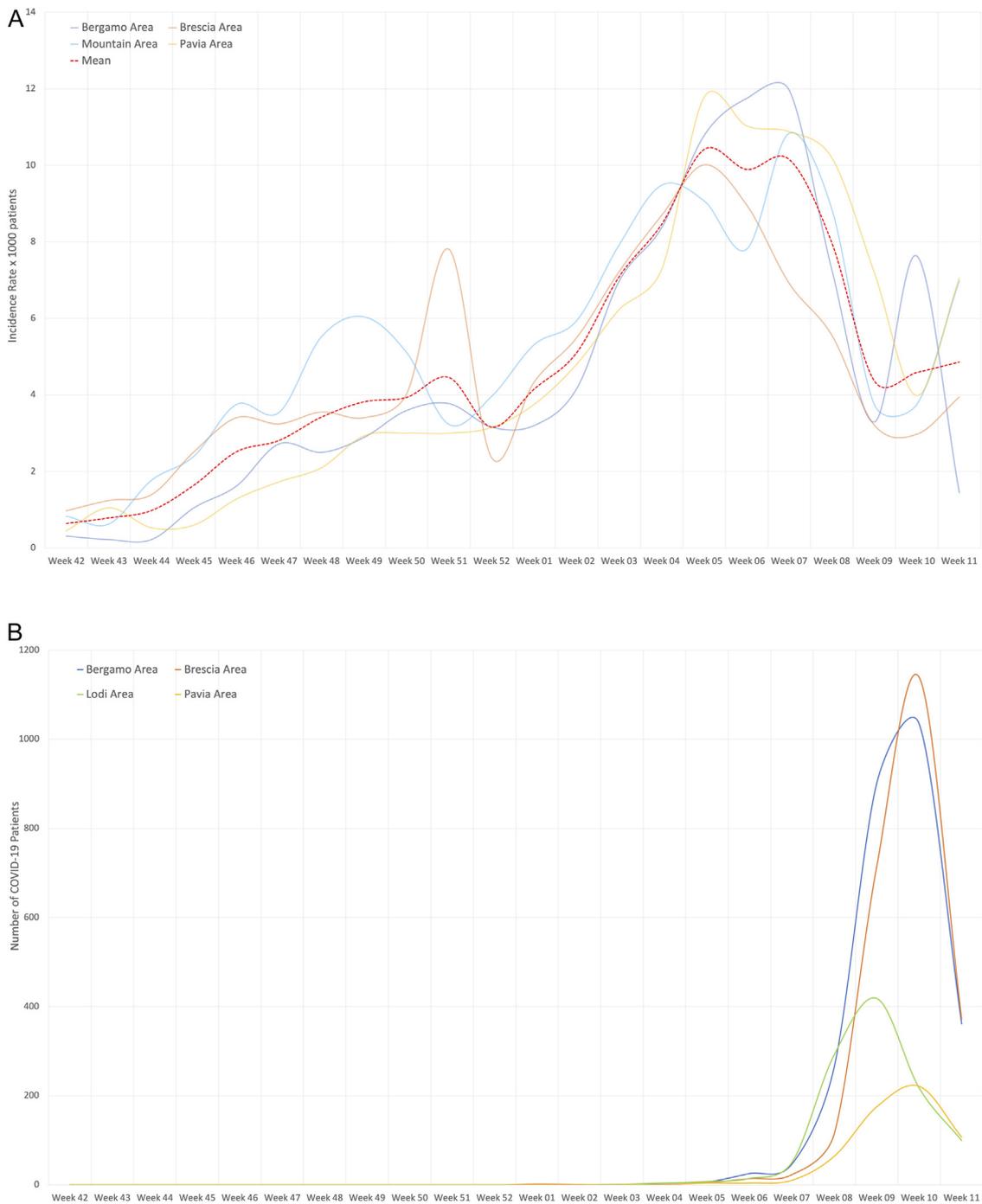


Fig. 4. (A) Incidence Rates of ILI cases for 2019–2020 influenza season detail on Bergamo, Brescia, Pavia and Mountains Areas. (B) Distribution of the COVID-19 patients in provinces of Bergamo, Brescia, Pavia and Lodi.

In Europe, influenza surveillance relies mainly on sentinel general practitioners in charge of recording the number of ILI cases per week and collecting respiratory specimens from their patients for laboratory tests [19]. In Italy, the influenza epidemiological and virological surveillance network (InfluNet) [15] consists surveys approximately 2% of the general population; epidemiological data are collected from week 42 to week 17 of the following year, while virological surveillance begins on week 46 and ends on week 17 of the following year. Epidemiological and virological data are collected at a regional level and are aggregated subsequently at a national level on a weekly basis [20]. In the Lombardy region, at

the beginning of 2019–2020 influenza season, 170 sentinel physicians were recruited for epidemiological surveillance thus covering a total of 218,696 people (2.2% of the total population of Lombardy).

The distribution of ILI cases in the three seasons taken in consideration presented a similar pattern up to the 9th week; since then, a reduction in ILI incidence rate was observed in the 2017–2018 and the 2018–2019 season but in the 2019–2020 an increase in the reported ILI emerged. The trend of ILI epidemic in 2019–2020 season in Lombardy was characterised by the introduction of SARS-CoV-2 since the 7th week with peak in the 11th week (6.72 cases per 1,000 individuals); from an epidemiological

point of view, comparing the ILI incidence with the distribution of laboratory-confirmed COVID-19 cases symptom onset in the week from 9th to 11th and corresponding with the spread of COVID-19, the two epidemic curves related to individuals over 65 years share the same trend, supporting the findings that COVID-19 most affected elderly, as reported elsewhere [6,7,12]. Nevertheless, during the 2019–2020 influenza season the epidemic curve of ILI and laboratory-confirmed COVID-19 overlapped in elderly, the increase of the incidence rate of ILI in this age group resulted with a lower value than that observed in the younger; this finding may be explained by the fact that elderly affected by SARS-CoV-2 manifest severe forms of the illness [21] so as to call the emergency department rather than the general practitioner, would instead be the reference doctor for the youngest population, as confirmed by data from the Italian “Integrated COVID-19 Surveillance” [22].

The introduction of an emerging virus with pandemic potential resulted in a reduction of the number of sentinel physicians active in the 2019–2020 influenza surveillance in Lombardy, with a more impressive consequence during the spread of SARS-CoV-2 in the 10th and 11th week and across the most affected by COVID-19 such as area of Bergamo, Brescia and Milan. In fact, these provinces reported the ILI cases that contributed to the abnormal shape of the 2019–2020 curve, confirmed the widespread of SARS-CoV-2 circulation in these geographical areas. These results support the idea that COVID-19 outbreak played a role in the absence of several sentinel doctors. An assumption regarding how the epidemic affected those physicians can be made: patients with any suggestive symptom were either prevented from going to their own general practitioners due to restrictive measures taken by the Government, or were accessing emergency care, and therefore the number of ILI cases reported by sentinel doctors decreased.

We have to consider that the reduction of the number of active sentinel doctors notifying ILI cases to the surveillance system in the 11th week may concur to generate an inaccurate estimate of ILI incidence rates and that it has not been possible to collect complete information for every patient from “Integrated COVID-19 Surveillance”; in particular, the date of symptom onset was not available for 29% of the total population included in the analysis, that consisted of 15,716 positive patients on March 15th.

With the availability and introduction of SARS-CoV-2 vaccine, another parameter of ILI surveillance should be the assessment of SARS-CoV-2 vaccine effectiveness as referred to laboratory-confirmed cases, that may present due to the presence of circulating viral strains different from the one of the vaccine.

One of the limitations of this study was the limited number of sentinel physicians involved in the network, affecting the number of notified ILI during the SARS-CoV-2 epidemic; nevertheless, the influenza surveillance system in 2019–2020 enabled us to detect the introduction and distribution of SARS-CoV-2.

Conclusions

Implementation of the ILI surveillance system has to be prioritized in order to early identify viral respiratory outbreaks and any future novel respiratory pathogens with pandemic potential. To this end, sentinel physicians homogeneously allocated in the country should survey at least 4% instead of 2% of the general population seeking care in ambulatory facilities for ILI occurrence. This would empower this syndromic surveillance and strengthen the network. Furthermore, an increase in appointed doctors collecting respiratory swabs should also be endorsed to improve the virological surveillance. In fact, both individuals and health system take advantage from an early virological diagnosis: individuals with ILI can benefit from adequate treatments and can see reduced their probability of viral-related complication, positively impacting the

health system in reduce the emerging room and hospitals access, particularly during influenza seasons.

Authors' contributions

EP and DC designed the study. FG, AC, GDC, LP and CG collected the data. FG, AC, GDC and DC analyzed the data. AB, EP, LP, CG and SB contributed data on incidence. CG, SB, LP and EP characterised viruses. FG, AC and GDC drafted the manuscript. MG, MC and LB contributed to the manuscript. DC, EP, SC, AB reviewed the manuscript. All authors approved the last version.

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Competing interests

None declared.

Ethical approval

Not required.

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