Estimation of influenza-attributable burden in primary care from season 2014/2015 to 2018/2019, France

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Abstract

Purpose

Influenza viruses cause seasonal epidemics whose intensity varies according to the circulating virus type and subtype. We aim to estimate influenza-like illness (ILI) incidence attributable to influenza viruses in France from October 2014 to May 2019.

Methods

Physicians participating in the French Sentinelles network reported the number of patients with ILI seen in consultation and performed nasopharyngeal swabs in a sample of these patients. The swabs were tested by RT-PCR for the presence of influenza viruses. These clinical and virological data were combined to estimate ILI incidence attributable to influenza viruses by subtypes and age groups.

Results

Influenza incidence rates over seasons ranged from 1.9% (95% CI, 1.9; 2.0) to 3.4% (95% CI, 3.2; 3.6) of the population. Each season, more than half of ILI cases were attributable to influenza. Children under 15 years were the most affected, with influenza incidence rates ranging from 3.0% (95% CI, 2.8;3.3) to 5.7% (95% CI, 5.3;6.1). Co-circulation of several (sub)types of influenza viruses was observed each year, except in 2016/17 where A(H3N2) viruses accounted for 98.0% of the influenza cases. Weekly ILI incidences attributable to each influenza virus (sub)type were mostly synchronized with ILI incidence, except in 2014/15 and 2017/18, where incidence attributable to type B viruses peaked few weeks later.

Conclusion

The burden of medically-attended influenza among patients with ILI is significant in France, varying considerably across years and age groups. These results show the importance of influenza surveillance in primary care combining clinical and virological data.

Keywords: influenza, primary care, influenza-like illness (ILI), surveillance

Declarations

Funding: No funding was received for this study.

Conflict of Interest: The authors declared no competing interests for this work.

Ethics approval: The protocol was conducted in agreement with the Helsinki declaration. We obtained authorization from the French Data Protection Agency (CNIL, registration number #471393) and the French ethical research committee (Comité de protection des personnes).

Authors contribution: SvDW, BL, DLB, SBS, TB, TH, CT and CS participed to the conception of the study. CT performed the statistical analysis. MP, CT, CS contributed to interpretation of data. SvDW, BL, DLB, SBS, TB, TH, SM, NV, CG, MV, SB, AF contributed to the data collection. MP and CS drafted and wrote the manuscript. All authors read and approved the final manuscript.

Data availability: Incidence of influenza-like illness are available in the Sentinelles network website, https://www.sentiweb.fr/france/fr/?page=table. The virological data analysed during the current study are available from the corresponding author on reasonable request.

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Introduction

Influenza is a common infectious disease of varying severity, ranging from mild to more severe forms with impact on morbidity and mortality [1,2]. Seasonal influenza epidemics lead to significant absenteeism from school or work and has serious economic consequences, even for mild forms [3].

Influenza surveillance generally relies on networks at the primary care level, with a sample of physicians reporting the number of patients with influenza-like illness (ILI) seeking medical attention [4]. These data are used to estimate ILI incidence in order to follow up influenza spread in time and space.

However, ILI might be caused by other respiratory viruses. Only virological analysis can confirm the diagnosis of influenza, which is not feasible in routine by physicians for all patients with ILI. In practice, only a sample of the patients presenting with ILI is swabbed by the physicians, allowing to characterize circulating respiratory viruses.

The contribution of influenza viruses to ILI could be estimated by combining clinical and virological surveillance data [5,6]. This allowed to assess the burden of influenza along with the contribution of each virus types and subtypes.

Since 2014, in France, the Sentinelles network is monitoring influenza surveillance in primary care based on clinical and virological data. We aimed to investigate the variation in ILI incidence attributable to influenza observed in primary care over five seasons from 2014/15 to 2018/19.

Methods

Data Sources

Data were obtained from the Sentinelles network, a nationwide epidemiological surveillance system based on about 500 voluntary general practitioners (GP) and 100 paediatricians in France [7]. Sentinel GPs reported throughout the year the number of their patients presenting with ILI using the following definition: “sudden onset of fever >39°C (102°F) with respiratory signs and myalgia” [8].

Along with this clinical surveillance, about half of the GPs and the paediatricians participated in virological surveillance of respiratory viruses between week 40 (end of September) and week 15 (mid-April) of the following year - called season thereafter. Physicians collected nasopharyngeal swabs in a systematic sample of their patients presenting with ILI (same definition as above) [9]. The sample consisted of the first two patients of the week presenting with ILI and consenting to provide a nasopharyngeal specimen (restricted to the first patient of the week from the 2017/18 season). Virological analyses were performed by the National Reference Centre (CNR) for respiratory viruses (Paris and Lyon) and the Laboratory of virology at the University of Corsica. The laboratories performed real-time RT-PCR tests for the detection of influenza viruses, (sub)typing and determination of the influenza B virus lineage.

The study period covered five surveillance seasons from 2014/15 to 2018/19. Because of the late 2015/16 influenza epidemic, we considered that this season lasted from week 2015w40 to week 2016w16.

Incidence computation

ILI incidences were estimated from data reported by the sentinel GPs using a method described elsewhere [8]. To sum up, the mean number of reported patients presenting with ILI per sentinel GP for a given week is multiplied by the total number of French GPs. ILI incidence rates were estimated by dividing incidences by yearly population size (census data).

Weekly ILI incidence attributable to influenza viruses (or influenza virus subtypes) was estimated by multiplying the ILI incidence rate by the influenza (or influenza subtypes) positivity rate of a given week. Estimations were stratified by age group to take into account variations in influenza attack rate according to age. A 95% confidence interval was computed using a subsampling approach as described by Politis & Romano [10]. This approach consisted in re-estimating the ILI incidence attributable to influenza viruses (or influenza subtypes) using random subsamples of data. Here, we used 50 000 subsamples consisting in a random selection of 64% of sentinel physicians each week.

To estimate yearly burden of influenza, cumulative ILI incidence attributable to influenza were computed over surveillance seasons. No estimations were computed for viral subtypes with a positivity rate of less than 1% over the season.

All statistical analyses were performed using the R software version 3.6.3 (R Foundation, Vienna, Austria).

Results

Over the five seasons studied, between 411 (in 2014/15) and 468 (in 2018/19) GPs participated in ILI surveillance. They reported between 10,820 (in 2016/17) and 16,154 (in 2014/15) patients with ILI per season. The physicians collected from 2,610 (in 2014/15) to 3,982 (in 2015/16) respiratory specimens of which 48.3% (n=1,437/2,973 in 2016/17) to 57.9% (n=1,670/2,886 in 2017/15) were positive to at least one influenza virus.

The burden of ILI attributable to influenza ranged from 1,949 (95% CI, 1,852; 2,045) cases per 100,000 population in 2016/17 to 3,414 (95% CI, 3,261; 3,568) cases per 100,000 population in 2014/15 (Table 1). The average annual rate was estimated to 2,516 (95% CI, 2,397; 2,635) cases per 100.00 population (Table 2). Each season, more than half of ILI cases were attributable to influenza, with proportions ranging from 55.9% for 2016/17 to 64.0% for 2018/19. The rate attributable to influenza at ILI peak incidence ranged from 62% for 2016/17 to 80% for 2018/19 (Figure 1).

Over each of the five seasons studied, incidences attributable to influenza resulted from co-circulation of different subtypes of influenza viruses, except in 2016/17 where the influenza burden was almost only due to A(H3N2) viruses accounting for 98.0% of the influenza attributable cases (Table 1). This subtype also represented the majority of the influenza burden in 2014/15 and 2018/19 (59.1% and 64.9% of the influenza-attributable incidence respectively). A low circulation of A(H3N2) viruses was also observed in 2017/18, accounting for 8.5% of the total influenza burden during this season. The highest incidence attributable to A(H3N2) viruses was estimated in 2014/15 at 2,018 (95% CI, 1,897; 2,139) cases per 100,000 population.

Burden of influenza A(H1N1)pdm09 viruses was estimated for all seasons except in 2016/17. The highest incidence attributable to A(H1N1)pdm09 viruses was estimated in 2017/18 at 1,170 (95% CI, 1,085;1,255) cases per 100 000 population representing 47.0% of the influenza burden of this season.

Incidences attributable to influenza B viruses were estimated for three of the five seasons studied (2014/15, 2015/16 and 2017/18). During the 2015/16 season, 71.0% of the influenza incidence was due to influenza B viruses corresponding to 1,820 (95% CI, 1,722; 1,917) cases per 100,000 population.

Throughout each season, weekly incidences attributable to each influenza virus subtypes were mostly synchronized with a peak of ILI incidence identified on the same week (Figure 1). However, during seasons 2014/15 and 2017/18, incidence attributable to type B viruses peaked later (delay of two and eight weeks respectively) while incidence attributable to type A viruses peaked earlier, the same week as ILI incidence.

Among age groups, the highest cumulative influenza incidence rate was always estimated for the youngest (<15 years), ranging from 3,048 (95% CI, 2,832; 3,264) cases per 100,000 population in 2016/17 to 5,943 (95% CI, 5,604; 6,283) cases per 100,000 population in 2015/16 (Table 1). Those from 65 years and above had the lowest cumulative influenza incidence rates, ranging from 487 (95% CI, 381; 592) cases per 100,000 population in 2015/16 to 1,716 (95% CI, 1,520; 1,912) cases per 100,000 population in 2014/15. Whatever the influenza type/subtype, incidences rates were always highest among the youngest (<15 years) (Table 1, Table 2, Figure 2). Influenza incidence was between 2.8 (in 2016/17) and 12.2 (in 2015/16) times higher in the youngest (<15 years) than in the elderly (Table 1, Figure 2). This ratio was lower for seasons dominated by A(H3N2) (2.8 in 2016/17 and 3.3 in 2014/15) than for seasons (co)dominated by other subtypes (12.2 in 2015/16, 4.7 in 2017/18 and 6.1 in 2018/19).

Discussion

The burden of medically-attended influenza in outpatient care in France from 2014/15 to 2018/19 represented between 1.9% and 3.4% of the French population each season. This burden varies across season, age group, and dominant viral subtype(s).

The Sentinelles network is the only nationally system in France monitoring medically-attended influenza in primary care through clinical and virological data collection using the same protocol since 2014, allowing comparisons over time [11]. This surveillance system allows the estimation of influenza disease burden using an original method, based on subsamples to estimates the confidence intervals of incidence estimates. This method could be applied to other respiratory viruses circulating in the community and identifiable in nasopharyngeal swabs.

We estimated that an average of 2.5% of the population seek medical attention in outpatient care for a symptomatic laboratory confirmed influenza infection each winter season in France, in line with previous studies conducted in temperate climate countries. The yearly average burden of ILI attributable to influenza has been estimated at 0.8% in the USA (from 2009/10 to 2012/13), 1.5% in the UK (from 1995/96 to 2008/09), 2.4% in Spain (from 2010/11 to 2015/16) and 3.4% in Germany (from 2001/02 to 2014/15) [5,6,12,13]. Differences between countries may be related to surveillance protocols or ILI cases definition, but also differences in the organization of health care systems. ILI can be caused by others respiratory viruses such as respiratory syncitial virus, metapneumovirus, rhinovirus, etc. [9]. However, it appeared that more than half of the swabbed patients with ILI were infected by influenza viruses over the surveillance period. The peak of weekly ILI incidence was always synchronized with the peak of the incidence attributable to influenza. These observations reinforced the use of this ILI case definition for influenza monitoring.

The incidence attributable to each subtype of influenza virus allowed to compare their burden and study their diffusion overtime. Over the study period, the highest burden was estimated for A(H3N2) viruses, as commonly reported [14]. During season with co-circulation of several influenza (sub)types, we observed that incidences attributable to each subtype were generally synchronous, except in 2017/18 and, to a lesser extent in 2014/15. During the season 2017/18, A(H1N1)pdm09 and B viruses were co-dominant with close estimated burden (1,170 (95% CI, 1,085; 1,255) for A(H1N1)pdm09 and 1,100 (95% CI, 1,026; 1,174) for B). However, their dynamics over time were different: A(H1N1)pdm09 viruses lead to a high and early peak (week 52) and decreased quickly whereas B viruses circulation reached a plateau during nine weeks. A delay between influenza A and influenza B peaks was already reported in seasons with co-circulation of type A and B [13,15]. This epidemiological dynamic could only be observed when studying incidence attributable to influenza combining influenza positivity rates and ILI incidences.

The influenza burden varied widely according to age group. The highest cumulative incidence rates of influenza were observed among those under 15 years of age and the lowest among those from 65 years and above. This is consistent with what is commonly described in the literature [12,13,16]. This may be partly explained by previous exposure to influenza viruses which confers partial immunity and a better vaccination coverage of those over 65 years, compared to other age groups [17]. Moreover, we observed that patients over 65 years of age seems to be more affected when seasons were dominated by A(H3N2) viruses (2014/15 and 2016/17) compared to other seasons. During these two seasons, relatively high influenza-related mortality was observed in France, with significant impact on the elderly [18,19]. Previous studies showed that circulation of A(H3N2) viruses is associated with higher morbidity and more severe illness in elderly compared to others subtypes [5,20,21].

The main limitation of this study is that we considered only patients with ILI seen in primary care. This underestimated the burden of influenza as we did not consider patients who did not consult a GP and patients with other clinical presentation. Moreover, we used a febrile ILI definition that could underestimate the burden of influenza, especially among elderly who had more frequently lower symptoms. However, the stability in ILI definition and data collection protocol makes comparison of influenza activity and epidemiology possible over the five seasons studied.

Conclusion

These results give us a better understanding of influenza epidemics in France. The large proportion of ILI attributable to influenza, as well as the variation in the circulation of the different dominant viral type(s) and subtypes, confirm the need for surveillance programs based on clinical and virological monitoring.

Table 1. Cumulative incidence per 100,000 population of influenza-like illness attributable to influenza by age group, seasons 2014/15 to 2018/19, France

Season	Age group (years)	Cumulative incidence per 100,000 population (95% CI)					Dominant or co-dominant virus(es)*
		Influenza-like illness	Influenza	A(H1N1)pdm09	A(H3N2)	B	
2014/15	<15	8,596 [8,200;8,992]	5,724 [5,326;6,121]	780 [576;983]	3,895 [3,514;4,276]	1,088 [869;1,308]	A(H3N2)
	15 – 64	5,502 [5,330;5,674]	3,225 [3,064;3,386]	749 [663;835]	1,720 [1,597;1,844]	755 [672;837]	
	≥65	2,643 [2,420;2,867]	1,716 [1,520;1,912]	263 [151;376]	1,149 [967;1,330]	322 [210;435]	
	Overall	5,559 [5,421;5,696]	3,414 [3,261;3,568]	667 [594;740]	2,018 [1,897;2,139]	738 [667;810]	
2015/16	<15	9,223 [8,816;9,629]	5,943 [5,604;6,283]	1,176 [1,030;1,323]	-**	4,753 [4,448;5,059]	B
	15 – 64	3,785 [3,643;3,928]	2,182 [2,063;2,302]	750 [677;822]	-**	1,407 [1,308;1,506]	
	≥65	1,074 [933;1,216]	487 [381;592]	180 [104;256]	-**	303 [215;390]	
	Overall	4,287 [4,168;4,407]	2,563 [2,442;2,683]	723 [665;782]	-**	1,820 [1,722;1,917]	
2016/17	<15	5,566 [5,249;5,883]	3,048 [2,832;3,264]	-**	3,004 [2,788;3,219]	-**	A(H3N2)
	15 – 64	3,400 [3,264;3,536]	1,885 [1,777;1,994]	-**	1,844 [1,736;1,952]	-**	
	≥65	1,750 [1,572;1,928]	1,092 [961;1,222]	-**	1,068 [938;1,198]	-**	
	Overall	3,486 [3,377;3,595]	1,949 [1,852;2,045]	-**	1,910 [1,815;2,006]	-**	
2017/18	<15	7,117 [6,780;7,454]	4,334 [4,047;4,622]	2,459 [2,226;2,691]	283 [201;365]	1,583 [1,405;1,761]	A(H1N1)pdm09, B
	15 – 64	3,916 [3,780;4,052]	2,429 [2,308;2,550]	1,073 [979;1,167]	206 [165;247]	1,136 [1,048;1,223]	
	≥65	1,507 [1,352;1,663]	931 [762;1,101]	254 [122;385]	157 [74;240]	521 [383;658]	
	Overall	4,041 [3,932;4,150]	2,492 [2,376;2,607]	1,170 [1,085;1,255]	211 [176;246]	1,100 [1,026;1,174]	
2018/19	<15	6,429 [6,128;6,730]	4,356 [4,070;4,643]	1,137 [954;1,320]	3,208 [2,943;3,474]	-**	A(H1N1)pdm09, A(H3N2)
	15 – 64	3,200 [3,084;3,315]	1,976 [1,871;2,080]	795 [720;871]	1,147 [1,058;1,236]	-**	
	≥65	1,112 [990;1,234]	716 [618;813]	164 [88;240]	540 [440;641]	-**	
	Overall	3,379 [3,285;3,472]	2,162 [2,061;2,263]	734 [673;796]	1,403 [1,318;1,487]	-**	

* Source : https://www.sentiweb.fr/france/en/?page=epidemics

** Incidence were not estimated for subtypes with a positivity rate of less than 1% over the season

Table 2. Average cumulative incidence per 100,000 population of influenza-like illness attributable to influenza by age group, seasons 2014/15 to 2018/19, France

Age group (years)	Cumulative incidence per 100,000 population (95% CI)				
	Influenza-like illness	**Influenza**	**A(H1N1)pdm09**	**A(H3N2)**	**B**
<15	7,386 [7,032;7740]	4,681 [4,370;4,992]	1,118 [944;1,291]	2,084 [1,852;2,316]	1,486 [1,300;1,672]
15 – 64	3,961 [3,819;4102]	2,339 [2,215;2,462]	676 [602;750]	989 [903;1,075]	661 [591;731]
≥65	1,617 [1,450;1,785]	988 [844;1,133]	172 [81;263]	583 [467;699]	229 [141;318]
Overall	4,150 [4,036;4,265]	2,516 [2,397;2,635]	662 [599;725]	1,113 [1,033;1,193]	733 [669;796]

Figures

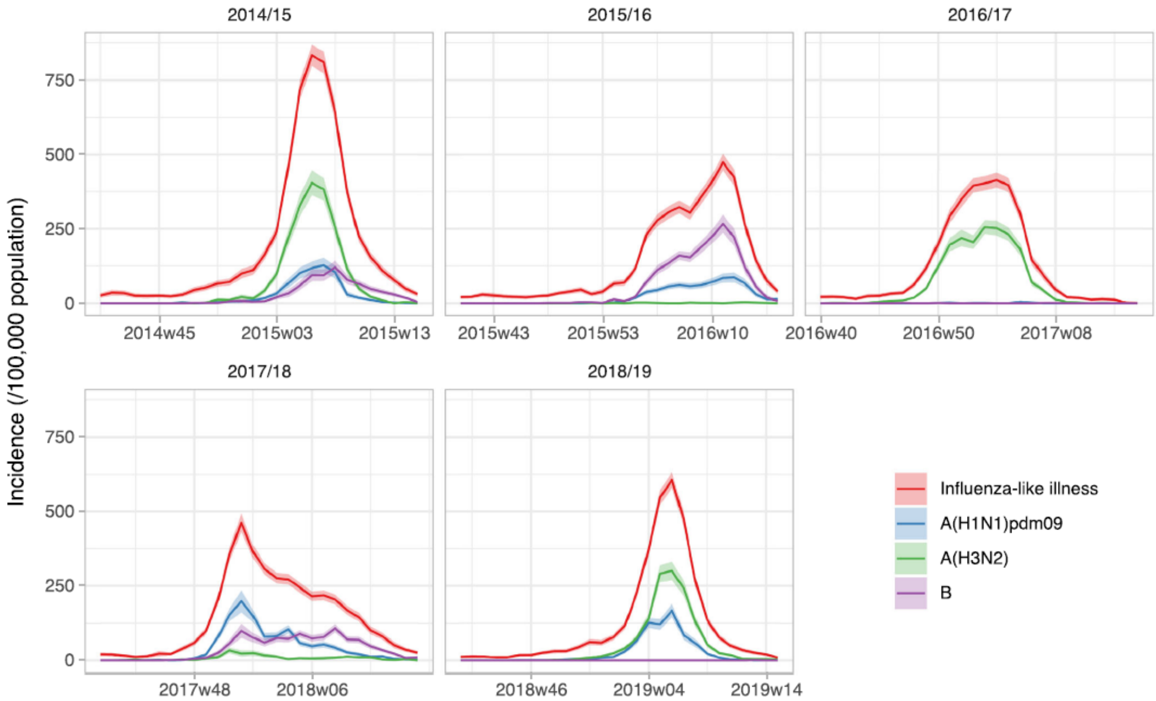

Figure 1. Influenza-like illness incidence and influenza-like illness incidence attributable to influenza by subtype (and 95% confidence intervals) per 100,000 population, seasons 2014/15 to 2018/19, France

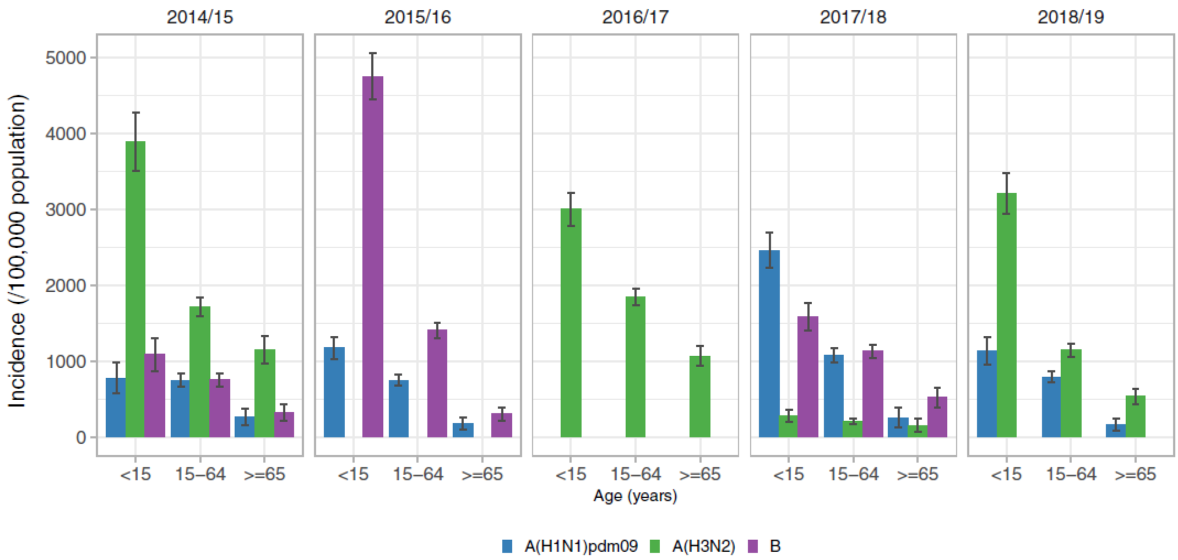

Figure 2. Influenza-like illness incidence attributable to influenza (and 95% confidence intervals) per 100,000 population by age group and subtype, seasons 2014/15 to 2018/19, France

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