TITLE PAGE

Full-length title: Decreased mortality associated with respiratory viral infections between December 2019 and March 2020 compared to previous year, Southeast France

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TEXT

Respiratory viruses are a major cause of mortality worldwide with an estimated 2.7 million deaths in 2015 [1]. In France, they are causing several thousands of deaths every year during colder months [2]. Since January 2020, the SARS-CoV-2 outbreak has generated much fear and countermeasures to stem the spread of this respiratory virus. This has been largely fueled by the tremendously extensive reporting of Covid-19-associated deaths. As of March 26, 2020, 492,603 people have been found infected worldwide of whom 22,184 (4.5%) died, four countries (Italy, China, Iran, Spain and France) being concerned by 83% of these deaths (https://coronavirus.jhu.edu/map.html). France identified 1,331 deaths for 25,233 infections (5.3%). The University Hospital Institute Méditerranée Infection performs real-time surveillance of all infections diagnosed in public hospitals of Marseille, Southeastern France [3;4]. This includes the count of the deaths associated with any diagnosed infection. Here, we compared the mortality associated with diagnoses of respiratory viruses during colder months overlapping 2018-2019 and 2019-2020.

Testing of respiratory samples was performed using FTD Respiratory pathogens 21 (Fast Track Diagnosis, Luxembourg) or Biofire FilmArray Respiratory panel 2 plus (Biomérieux, France) assays. Between week 47 of 2018 and week 11 of 2019, 72 patients died after being diagnosed with a respiratory virus (Table 1). They represented 0.16% of the 43,909 patients hospitalized during this period and 6.9% of the 1,042 who died. Deaths occurred in 38 of the patients diagnosed with Influenza A virus (1.7%), which was the respiratory virus associated with the highest number of deaths. In addition, deaths occurred in 19 of the patients diagnosed with rhinoviruses (1.8%), and in 13 of those diagnosed with respiratory syncytial virus (RSV) (1.1%). Respiratory samples had not been tested for coronaviruses and parainfluenza viruses in routine clinical practice, but all those tested retrospectively from dead patients were negative. In comparison, during the same period of

winter 2019-2020 (between week 47 of 2019 and week 11 of 2020), 44 patients died after being diagnosed with a common respiratory virus. They represented 0.11% of the 52,624 patients hospitalized during this period and 5.6% of the 985 who died. They included 6 of the patients diagnosed with influenza A virus (0.4%), 2 of those diagnosed with influenza B virus (0.2%), 7 of those diagnosed with RSV (0.7%), and 4, 2 and 1 of those diagnosed with human coronavirus-HKU1 (1.7%), NL63 (1.2%) and OC43 (1.0%), respectively (Table 1). Additionally, we tested since the 29th of January 13,089 patients for SARS-CoV-2 using a reverse transcription-PCR assay [5], and diagnosed 1,416 infections (11%). Of these infected patients, 11 (0.8%) died; 8 were ≥82 year-old and 5 were men. Overall, 55 patients died after being diagnosed with a respiratory virus during colder months of 2019-2020 so far, versus 72 the year before. The proportion of respiratory virus-associated deaths among hospitalized patients was thus significantly lower in 2019-2020 than in 2018-2019 (105 per 100,000 people vs 164 per 100,000 people; p= 0.007, Yates-corrected chi-square test). This proportion among patients who died of any cause at hospital was also lower, although not significantly (5.6% vs 6.9%; p= 0.13).

Hence, we observed 39% less deaths associated with common respiratory viruses during colder months of 2019-2020 compared to 2018-2019. This was essentially due to significant decreases of influenza A virus (-84%; $p<10^{-3}$) and RSV (-46%; p=0.055)-associated deaths, and was not compensated so far by SARS-CoV-2-related deaths. Excess mortality associated with influenza virus infections is estimated to be 5.9 per 100,000 people worldwide and 5.3 per 100,000 people in Europe [6]. In comparison, mean mortality associated with SARS-CoV-2 infections is estimated to be 0.3 per 100,000 people worldwide and 2.2 per 100,000 people in Western Europe (https://www.mediterranee-infection.com/covid-19/). These data and our findings allow putting into perspective the death burden of SARS-CoV-2 infections. Finally, we observed that fatality rate was ≈7 times lower in our center than for

whole France that has a very high fatality rate of 26.0 per 100,000.

Author contributions

Conceived and designed the review: DR. Contributed materials/analysis tools: AG, MTJ, CZ, LN, CB, JCL, BLS, HC, PC. Analyzed the data: AG, PC, DR. Wrote the paper: AG, PC, DR.

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Conflicts of interest

The authors have no conflicts of interest to declare. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Ethics

All data have been generated as part of the routine work at Assistance Publique-Hôpitaux de Marseille (Marseille university hospitals), and this study results from routine standard clinical management.

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TABLE

Table 1. Tests performed and positive for PCR detection of respiratory viruses, and associated deaths during same colder months overlapping years 2018-2019 and 2019-2020

Viruses	Tests		Positive patients				Deaths				P [a]
	2018-2019	2019-2020	2018-2019		2019-2020		2018-2019		2019-2020		
	Number	Number	Number	*%*	Number	*%*	Number	%	Number	*%*	
Adenovirus	11 004	13 462	439	*4,0*	426	*3,2*	2	*0,5*	4	*0,9*	
Coronavirus HKU1	-	7 461	-	-	236	*3,2*	-	-	4	*1,7*	
Coronavirus NL63	-	7 461	-	-	162	*2,2*	-	-	2	*1,2*	
Coronavirus OC43	-	7 461	-	-	102	*1,4*	-	-	1	*1,0*	
Coronavirus E229	-	7 461	-	-	57	*0,8*	-	-	0	*0,0*	
SARS-CoV-2 [b]	-	13 089	-	-	1 416	*10,8*	-	-	11	*0,8*	
Enterovirus	11 004	13 462	308	*2,8*	356	*2,6*	0	*0,0*	2	*0,6*	
Influenza A virus	11 004	13 462	2 277	*20,7*	1 516	*11,3*	38	*1,7*	6	*0,4*	$<10^{-3}$
Influenza B virus	11 004	13 462	13	*0,1*	1 220	*9,1*	0	*0,0*	2	*0,2*	
Metapneumovirus	11 004	13 462	306	*2,8*	449	*3,3*	0	*0,0*	2	*0,4*	
Parainfluenza virus 1	-	7 461	-	-	6	*0,1*	-	-	0	*0,0*	
Parainfluenza virus 2	-	7 461	-	-	6	*0,1*	-	-	0	*0,0*	
Parainfluenza virus 3	-	7 461	-	-	8	*0,1*	-	-	0	*0,0*	
Parainfluenza virus 4	-	7 461	-	-	22	*0,3*	-	-	0	*0,0*	
Rhinovirus	11 004	13 462	1 073	*9,8*	1 459	*10,8*	19	*1,8*	14	*1,0*	*0,055*
Syncytial respiratory virus	11 004	13 462	1 135	*10,3*	1 040	*7,7*	13	*1,1*	7	*0,7*	*0,177*

[a] Assessed for proportions of deaths among positive patients; Yates-corrected chi-square test; [b] until 25th of March, 2020