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Short communication

Reduced risk of severe COVID-19 in more than 1.4 million elderly people aged 75 years and older vaccinated with mRNA-based vaccines

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ABSTRACT

Randomized clinical trials have shown mRNA-based vaccines to be 92–95% effective to prevent COVID-19 in adults. We aimed to estimate the impact of vaccination on the risk of severe COVID-19 (requiring hospitalization) in elderly people. Each 1,422,461 vaccinated subject aged 75 or older was matched to two unvaccinated subjects of same age, sex, administrative region, and type of residence. They were followed from date of first injection between 27 December 2020 and 24 February 2021 to 20 March 2021 for COVID-19 hospitalization. Mean age was 82.4 years (SD, 5.7) and median follow-up was 38 days [IQR, 17–54]. Adjusted Hazard Ratio for COVID-19 hospitalization from day 7 after the second dose was estimated at 0.14 (95% confidence interval, 0.11–0.17), i.e. an estimated 86% risk reduction in people aged 75 and older, highlighting the major impact of mRNA vaccination on reducing the risk of COVID-19 among elderly people.

Vaccination campaigns were initiated in Europe immediately following EMA approval of mRNA-based vaccines. Randomized clinical trials have shown mRNA-based vaccines to be 92–95% effective to prevent coronavirus disease 2019 (COVID-19) in persons 16 years of age or older [1,2]. However, these trials were conducted under highly controlled conditions and included limited numbers of elderly subjects. Real-world studies are crucial to evaluate the effectiveness of COVID-19 vaccines in the elderly population, which has been shown to be the population most vulnerable to COVID-19 and which may present a suboptimal immune response to vaccination due to the weakened immune system.

A first Israeli post-marketing study showed that the BNT162b2 mRNA vaccine was 87% (95 %CI, 55–100) effective in reducing hospitalization at 7 or more days after the second dose [3]. More specifically, in about 80,000 vaccinated subjects aged 70 years or older, the effectiveness of vaccination on symptomatic illness was estimated to be 98% (90–100). In a US study, adjusted vaccine effectiveness against COVID-19-associated hospitalization among adults aged 65 years or older was estimated to be 94% (95% confidence interval [CI] = 49%–99%) for full vaccination [4]. To date, other studies reported estimation of high effectiveness (87–98%) of mRNA-based vaccines on severe-COVID-19 in fully vaccinated elderly people in the 1–6 months following vaccination [5–8], reporting the results with different age limits. Data from other settings in large datasets are useful to refine this findings and evaluate whether the estimates are consistent across diverse populations.

In France, COVID-19 vaccination started on 27 December 2020, initially targeting elderly people living in long-term nursing homes and retirement homes, followed by people aged 75 or older and people at high risk of severe forms of COVID-19 starting from 18 January 2021. mRNA-based vaccines were mainly used and two doses were required.

In this study, we aimed to estimate the impact of vaccination on the risk of severe COVID-19 in more than 1.4 million elderly people vaccinated during the first two months of the vaccination campaign in France, using data of the French National Health Data System [9] (SNDS, Système National des Données de Santé) linked to the national COVID-19 vaccination database called VAC-SI.

We constructed a cohort of subjects aged 75 or older vaccinated between 27 December 2020 and 24 February 2021 (i.e. the 60 first days of vaccination campaign). Each vaccinated subject was matched to two unvaccinated subjects of the same age (same year of birth), sex, administrative region, and type of residence (i.e. personal home or Residential Care Homes for dependent elderly persons, with or without a pharmacy), and the trios formed in this

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Table 1
Characteristics of vaccinated and unvaccinated subjects. Controls who were subsequently vaccinated are included only in the control group. Comorbidities were assessed during the previous year.

	Unvaccinated		Vaccinated	
	N = 2,023,680	%	**N = 1,095,820**	%
Age (years), mean (SD)	82.3 (5.6)		82.4 (5.7)	
Women, N (%)	1,190,456	58.8%	636,509	58.1%
Region, N (%)				
Ile de France	274,146	13.5%	152,648	13.9%
Grand Est	172,894	8.5%	92,706	8.5%
Hauts-de-France	135,076	6.7%	72,311	6.6%
Auvergne-Rhône-Alpes	252,970	12.5%	136,493	12.5%
Bourgogne-Franche-Comté	111,725	5.5%	60,613	5.5%
Centre-Val-de-Loire	93,383	4.6%	50,144	4.6%
Provence-Alpes-Côte d'Azur	176,627	8.7%	95,962	8.8%
Occitanie	211,269	10.4%	114,237	10.4%
Nouvelle-Aquitaine	227,696	11.3%	123,002	11.2%
Normandie	107,791	5.3%	57,932	5.3%
Pays de la Loire	115,900	5.7%	61,524	5.6%
Bretagne	115,544	5.7%	62,048	5.7%
Corse	13,876	0.7%	8,011	0.7%
Guadeloupe	1,619	0.1%	883	0.1%
Martinique	2,228	0.1%	1,222	0.1%
Guyane	644	0.0%	407	0.0%
La Réunion	10,080	0.5%	5,521	0.5%
Mayotte	212	0.0%	156	0.0%
Social deprivation index (quintiles), N (%)				
1 (least deprived)	355,610	17.6%	225,394	20.6%
2	364,060	18.0%	199,219	18.2%
3	411,554	20.3%	221,690	20.2%
4	429,223	21.2%	222,951	20.3%
5 (most deprived)	412,827	20.4%	197,313	18.0%
Unknown	50,406	2.5%	29,253	2.7%
Population, N (%)				
At home	1,839,767	90.9%	1,001,184	91.4%
Retirement home without pharmacy	159,771	7.9%	80,440	7.3%
Retirement home with pharmacy	24,142	1.2%	14,196	1.3%
Lifestyle habits, N (%)				
Smoking	40,334	2.0%	19,615	1.8%
Alcohol use disorders	14,073	0.7%	5,607	0.5%
Comorbidities, N (%)				
Cardiorespiratory				
Obesity	14,903	0.7%	7,459	0.7%
Diabetes	376,903	18.6%	171,454	15.6%
Dyslipidaemia and lipid-lowering drugs	707,826	35.0%	400,993	36.6%
Hereditary metabolic diseases or amyloidosis	6,446	0.3%	3,612	0.3%
Hypertension	1,328,352	65.6%	707,776	64.6%
Coronary heart disease	251,139	12.4%	145,237	13.3%
Peripheral arterial disease	83,537	4.1%	42,998	3.9%
Cardiac arrhythmias or conduction disorders	267,850	13.2%	148,682	13.6%
Heart failure	126,865	6.3%	60,947	5.6%
Valvular heart disease	112,941	5.6%	61,565	5.6%
Stroke	120,860	6.0%	63,307	5.8%
Pulmonary embolism	19,692	1.0%	10,968	1.0%
Chronic respiratory diseases (excluding cystic fibrosis)	209,423	10.3%	108,205	9.9%
Cancers				
Female breast cancer (active)	12,959	0.6%	7,481	0.7%
Female breast cancer (under surveillance)	50,574	2.5%	30,100	2.7%
Colorectal cancer (active)	12,125	0.6%	6,151	0.6%
Colorectal cancer (under surveillance)	31,838	1.6%	17,332	1.6%
Lung cancer (active)	4,914	0.2%	2,708	0.2%
Lung cancer (under surveillance)	5,463	0.3%	3,406	0.3%
Prostate cancer (active)	24,608	1.2%	14,718	1.3%
Prostate cancer (under surveillance)	50,994	2.5%	32,514	3.0%
Other cancers (active)	70,917	3.5%	42,834	3.9%
Other cancers (under surveillance)	107,148	5.3%	64,671	5.9%
Inflammatory and skin diseases				
Chronic inflammatory bowel diseases	7,321	0.4%	4,154	0.4%
Rheumatoid arthritis and related diseases	25,979	1.3%	13,560	1.2%
Ankylosing spondylitis and related diseases	7,486	0.4%	4,259	0.4%
Psoriasis	14,754	0.7%	7,921	0.7%
Psychological and neurodegenerative diseases				
Neurotic and mood disorders, use of antidepressants	314,547	15.5%	175,681	16.0%
Psychotic disorders, use of neuroleptics	45,463	2.2%	23,342	2.1%
Epilepsy	15,744	0.8%	7,961	0.7%
Multiple sclerosis	2,163	0.1%	979	0.1%
Dementia (including Alzheimer's disease)	156,580	7.7%	92,267	8.4%

(*continued on next page*)

Table 1 (*continued*)

	Unvaccinated		Vaccinated	
	N = 2,023,680	%	**N = 1,095,820**	%
Other diseases				
HIV infection	1,411	0.1%	772	0.1%
Liver diseases	18,579	0.9%	8,852	0.8%
Chronic dialysis / Renal transplant	5,845	0.3%	8,018	0.7%

way were followed from the date of the first vaccine injection of the vaccinated subject (index date). Unvaccinated subjects (controls) could only be matched to one vaccinated person. If a control subject was vaccinated during follow-up, follow-up was stopped for the whole trio, and the subject was then eligible to be included again in the cohort as a vaccinated subject.

The endpoint of interest was hospitalization for COVID-19 during follow-up. Each subject was followed from the index date until hospitalization for COVID-19, death, or the end of follow-up on 20 March 2021, whichever occurred first. Different time windows were considered: from the first dose of vaccine until the end of follow-up, from first dose until day 13, from day 14 until the second dose, from the second dose until the end of follow-up, and from day 7 after the second dose until the end of follow-up. For the analysis from day 14 to the second dose, vaccinated subjects who did not receive the second injection after 6 weeks (42 days) were censored at that date.

The COVID-19 hospitalization rate in vaccinated subjects was compared to that in unvaccinated controls by Cox models adjusted for individual comorbidities [10] (see Table 1) using inverse probability of treatment weighting (IPTW) and taking matched variables into account. Social deprivation index and lifestyle habits (i.e. smoking and alcohol use disorders) were also included in calculation of the propensity score. Risk reduction was defined as the percent reduction in risk, calculated as 1 minus the Hazard Ratio (HR).

A total of 1,422,461 vaccinated persons (i.e. 89% of the total number of vaccinated persons recorded over the study period in France) and 2,631,108 controls were included and followed for a median of 40 days [Interquartile range, IQR, 19–55] and 38 days [IQR, 17–54], respectively. Median follow-up from day 7 after the second dose was 18 days [IQR, 9–28] and 17 days [IQR, 9–28], respectively, with a maximum of 66 days. Ninety-two percent of vaccinated people had received the Pfizer/BioNTech vaccine and 8% had received the Moderna vaccine. The median interval between doses among subjects who had received two doses was 28 days [IQR, 26–30].

Matched vaccinated and unvaccinated subjects were fairly similar in terms of comorbidities and lifestyle habits (Table 1, in this table controls who were subsequently vaccinated were only included in the control group). Over the follow-up from day 7 after the second dose, 113 and 1406 events were recorded respectively. In adjusted Cox models using IPTW, vaccinated subjects compared to unvaccinated subjects had a HR for hospitalization for COVID-19 between day 7 after the second dose and the end of follow-up of 0.14 (95% confidence interval, 0.11–0.17) (Table 2), i.e. a risk reduction (1-HR) of 86% (95 %CI = 83%–89%). The risk difference was greater among people aged 75–84 years compared to those aged 85 years and older (HR = 0.10; 0.07–0.13 *versus* HR = 0.19; 0.15–0.25) (Table 3). The results remained unchanged (HR = 0.14; 0.12–0.17) when the analysis was restricted to subjects vaccinated with the Pfizer / BioNTech vaccine. The risk of death from COVID-19 more than 7 days after the second dose was also reduced by 91% [87%–93%] in the vaccinated group.

The early 55% risk reduction observed during the first two weeks after the first dose could not be due to the vaccination by itself, but probably to the higher risk of infection (and then the higher risk of COVID-19 hospitalization) for unvaccinated subjects compared to vaccinated subjects because people with warning

Table 2
Hazard ratio (HR) and 95% confidence interval (95 %CI) between vaccination and the risk of hospitalization for COVID-19 and the related risk reduction by windows of follow-up. Adjustment for age, sex, region, type of residence by matching and for other variables of Table 1 (including comorbidities) using inverse probability of treatment weighting.

Population	Unvaccinated	Vaccinated
Follow-up after the 1st dose		
Number of events/at-risk population	6,580/2,631,108	1,463/1,422,461
Median follow-up and interquartile range (days)	38 [17–54]	40 [19–55]
HR (95 %CI)	1	0.40 (0.38–0.42)
Risk reduction (95 %CI)		60% (58%–62%)
Follow-up from 1st dose to day 13		
Number of events/at-risk population	2,795/2,631,108	685/1,422,461
Median follow-up and interquartile range (days)	14 [14–14]	14 [14–14]
HR (95 %CI)	1	0.45 (0.41–0.49)
Risk reduction (95 %CI)		55% (51% – 59%)
Follow-up from day 14 after the 1st dose to the 2nd dose		
Number of events/at-risk population	1,616/2,091,749	594/1,145,854
Median follow-up and interquartile range (days)	12 [7–13]	12 [7–13]
HR (95 %CI)	1	0.66 (0.60–0.72)
Risk reduction (95 %CI)		34% (28%–40%)
Follow-up after the 2nd dose		
Number of events/at-risk population	2,142/1,692,867	175/935,987
Median follow-up and interquartile range (days)	22 [12–34]	22 [12–34]
HR (95 %CI)	1	0.14 (0.12–0.17)
Risk reduction (95 %CI)		86% (83%–88%)
Follow-up from day 7 after the 2nd dose		
Number of events/at-risk population	1,406/1,511,628	113/840,546
Median of follow-up and interquartile range (days)	17 [9–28]	18 [9–28]
HR (95 %CI)	1	0.14 (0.11–0.17)
Risk reduction (95 %CI)		86% (83%–89%)

Table 3
Hazard ratio (HR) and 95% confidence interval (95 %CI) between vaccination and the risk of hospitalization for COVID-19 and related risk reduction by windows of follow-up, stratified by age and sex. Adjustment for region, type of residence and other variables of Table 1 (including comorbidities) using inverse probability of treatment weighting.

Age	**Less than 85 years**		**85 years or older**	
Population	**Unvaccinated**	**Vaccinated**	**Unvaccinated**	**Vaccinated**
Follow-up after the 1st dose				
Number of events/at-risk population	3,604/1,781,722	667/949,480	2,976/849,386	796/472,981
HR (95 %CI)	1	0.34 (0.32–0.37)	1	0.47 (0.43–0.50)
Follow-up from 1st dose to day 13				
Number of events/at-risk population	1,440/1,781,722	324/949,480	1,355/849,386	361/472,981
HR (95 %CI)	1	0.42 (0.37–0.47)	1	0.48 (0.42–0.54)
Follow-up from day 14 after the 1st dose to the 2nd dose				
Number of events/at-risk population	942/1,467,684	281/788,082	674/624,065	313/357,772
HR (95 %CI)	1	0.55 (0.48–0.63)	1	0.81 (0.70–0.92)
Follow-up after the 2nd dose				
Number of events/at-risk population	1213/1,191,877	58/644,505	929/500,990	117/291,482
HR (95 %CI)	1	0.09 (0.07–0.11)	1	0.21 (0.17–0.25)
Follow-up from day 7 after the 2nd dose				
Number of events/at-risk population	797/1,062,152	42/576,800	609/449,476	71/263,746
HR (95 %CI)	1	0.10 (0.07–0.13)	1	0.19 (0.15–0.25)
Sex	**Women**		**Men**	
Population	**Unvaccinated**	**Vaccinated**	**Unvaccinated**	**Vaccinated**
Follow-up after the 1st dose				
Number of events/at-risk population	3,230/1,537,209	693/820,274	3,350/1,093,899	770/602,187
HR (95 %CI)	1	0.39 (0.36–0.43)	1	0.41 (0.37–0.44)
Follow-up from 1st dose to day 13				
Number of events/at-risk population	1,400/1,537,209	317/820,274	1,395/1,093,899	368/602,187
HR (95 %CI)	1	0.42 (0.37–0.48)	1	0.48 (0.42–0.53)
Follow-up from day 14 after the 1st dose to the 2nd dose				
Number of events/at-risk population	754/1,207,043	295/652,050	862/884,706	299/493,804
HR (95 %CI)	1	0.71 (0.62–0.81)	1	0.61 (0.54–0.70)
Follow-up after the 2nd dose				
Number of events/at-risk population	1057/977,385	76/532,282	1085/715,482	99/403,705
HR (95 %CI)	1	0.13 (0.10–0.16)	1	0.15 (0.12–0.19)
Follow-up from day 7 after the 2nd dose				
Number of events/at-risk population	696/855,009	48/468,481	710/624,069	65/354,859
HR (95 %CI)	1	0.12 (0.09–0.16)	1	0.16 (0.12–0.20)

symptoms (at higher risk for severe COVID-19) were less likely to be instantly vaccinated.

This is among the first time that risk reduction of COVID-19 hospitalization after mRNA vaccination has been measured on such a large population of elderly people. This study provides evidence supporting the high level of effectiveness of vaccination in people aged 75 years or older, with an overall efficacy of 86% and 90% in the 75–84 year age-group. Evidence from both clinical trials and real-world studies now accumulates on the high effectiveness of mRNA-based vaccine in elderly people. Longer follow-up will allow determination of the longer-term impact of vaccination on the risk of severe forms of COVID-19.

In conclusion, with an estimated 86% risk reduction based on data from more than 1.4 million vaccinated people aged 75 or older in France, these results highlight the major impact of mRNA vaccination on reducing the risk of severe forms of COVID-19 requiring hospitalization among elderly people.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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