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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.

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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 these 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...
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.

| Characteristic                                      | Unvaccinated | Vaccinated |
|-----------------------------------------------------|--------------|------------|
| **Age (years), mean (SD)**                          | N = 2,023,680| N = 1,095,820|
| **Women, N (%)**                                    | 1,190,456    | 58.8%      |
| **Region, N (%)**                                   |              |            |
| Ile de France                                       | 274,146      | 13.5%      |
| Grand Est                                           | 172,894      | 8.5%       |
| Hauts-de-France                                     | 135,076      | 6.7%       |
| Auvergne-Rhône-Alpes                                | 252,970      | 12.5%      |
| Bourgogne-Franche-Comté                             | 111,725      | 5.5%       |
| Centre-Val-de-Loire                                 | 93,383       | 4.6%       |
| Provence-Alpes-Côte d'Azur                          | 176,627      | 8.7%       |
| Corse                                               | 211,269      | 10.4%      |
| Nouvelle-Aquitaine                                  | 227,696      | 11.3%      |
| Normandie                                           | 107,791      | 5.3%       |
| Pays de la Loire                                    | 115,900      | 5.7%       |
| Bretagne                                            | 115,544      | 5.7%       |
| Corse                                               | 13,876       | 0.7%       |
| Guadeloupe                                          | 1,619        | 0.1%       |
| Martinique                                          | 2,228        | 0.1%       |
| Guyane                                              | 644          | 0.0%       |
| La Réunion                                          | 10,080       | 0.5%       |
| Mayotte                                             | 212          | 0.0%       |
| **Social deprivation index (quintiles), N (%)**     |              |            |
| 1 (least deprived)                                  | 355,610      | 17.6%      |
| 2                                                   | 364,060      | 18.0%      |
| 3                                                   | 411,554      | 20.3%      |
| 4                                                   | 429,223      | 21.2%      |
| 5 (most deprived)                                   | 412,827      | 20.4%      |
| Unknown                                             | 50,406       | 2.5%       |
| **Population, N (%)**                               |              |            |
| At home                                             | 1,839,767    | 90.9%      |
| Retirement home without pharmacy                    | 159,771      | 7.9%       |
| Retirement home with pharmacy                       | 24,142       | 1.2%       |
| **Lifestyle habits, N (%)**                         |              |            |
| Smoking                                             | 40,334       | 2.0%       |
| Alcohol use disorders                               | 14,073       | 0.7%       |
| **Comorbidities, N (%)**                            |              |            |
| Obesity                                             | 14,903       | 0.7%       |
| Diabetes                                            | 376,903      | 18.6%      |
| Dyslipidaemia and lipid-lowering drugs              | 707,826      | 35.0%      |
| Hereditary metabolic diseases or amyloidosis        | 6,446        | 0.3%       |
| Hypertension                                        | 1,328,352    | 65.6%      |
| Coronary heart disease                              | 251,139      | 12.4%      |
| Peripheral arterial disease                         | 83,537       | 4.1%       |
| Cardiac arrhythmias or conduction disorders         | 267,850      | 13.2%      |
| Heart failure                                       | 126,865      | 6.3%       |
| Valvular heart disease                              | 112,941      | 5.6%       |
| Stroke                                              | 120,860      | 6.0%       |
| Pulmonary embolism                                  | 19,692       | 1.0%       |
| Chronic respiratory diseases (excluding cystic fibrosis) | 209,423     | 10.3%      |
| **Cancers**                                         |              |            |
| Female breast cancer (active)                       | 12,959       | 0.6%       |
| Female breast cancer (under surveillance)           | 50,574       | 2.5%       |
| Colorectal cancer (active)                          | 12,125       | 0.6%       |
| Colorectal cancer (under surveillance)              | 31,838       | 1.6%       |
| Lung cancer (active)                                | 4,914        | 0.2%       |
| Lung cancer (under surveillance)                    | 5,463        | 0.3%       |
| Prostate cancer (active)                            | 24,608       | 1.2%       |
| Prostate cancer (under surveillance)                | 50,994       | 2.5%       |
| Other cancers (active)                              | 70,917       | 3.5%       |
| Other cancers (under surveillance)                  | 107,148      | 5.3%       |
| **Inflammatory and skin diseases**                  |              |            |
| Chronic inflammatory bowel diseases                 | 7,321        | 0.4%       |
| Rheumatoid arthritis and related diseases           | 25,979       | 1.3%       |
| Ankylosing spondylitis and related diseases         | 7,486        | 0.4%       |
| Psoriasis                                           | 14,754       | 0.7%       |
| **Psychological and neurodegenerative diseases**    |              |            |
| Neurotic and mood disorders, use of antidepressants | 314,547      | 15.5%      |
| Psychotic disorders, use of neuroleptics            | 45,463       | 2.2%       |
| Epilepsy                                            | 15,744       | 0.8%       |
| Multiple sclerosis                                  | 2,163        | 0.1%       |
| Dementia (including Alzheimer's disease)            | 156,580      | 7.7%       |

(continued on next page)
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 1 (continued)

| Other diseases                                      | Unvaccinated | %   | Vaccinated | %   |
|-----------------------------------------------------|--------------|-----|------------|-----|
| 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%|

### Table 2

| 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            | 0.65 (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 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%) |             |
symptoms (at higher risk for severe COVID-19) were less likely to be hospitalised among elderly people.

In conclusion, with an estimated 86% risk reduction based on real-world studies now accumulates on the high effectiveness of the 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.

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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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