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ESTIMATION DE L'EFFICACITE VACCINALE CONTRE LES FORMES GRAVES DE COVID-19 PAR LA METHODE DU TEST NEGATIF

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Résumé

L'année 2021 et le début de l'année 2021 ont été marqués par plusieurs vagues de l'épidémie de Covid-19, chacune associée à un ou plusieurs variants préoccupants, et la vaccination progressive et massive de la population française. Nous mobilisons l'appariement des bases de surveillance nationale liées à la Covid-19 : SI-VIC (hospitalisations), SI-DEP (tests) et VAC-SI (vaccination) afin d'étudier l'efficacité de la vaccination contre les formes symptomatiques et sévères de la Covid-19 en France. Nous utilisons la méthode dite du « test négatif » afin d'estimer l'efficacité contre les formes symptomatiques de Covid-19, une approche issue de la littérature épidémiologique visant historiquement à estimer l'efficacité des vaccins contre la grippe saisonnière en recrutant des cas et des témoins parmi les personnes ayant recours au système de soin suite à des symptômes évocateurs. Nous la combinons avec un modèle de Cox visant à estimer la réduction de risque additionnelle sur la progression de la maladie vers des formes graves nécessitant une hospitalisation. Une première analyse étudie la population des personnes de 50 ans et plus au cours de l'année 2021, avant l'émergence du variant Omicron. La deuxième analyse actualise ces résultats sur la période allant du 13 décembre 2021 au 31 janvier 2022 en comparant les variants Omicron et Delta, sur l'ensemble de la population de 18 ans et plus, en distinguant la protection conférée par une infection passée et vaccination. Ces deux analyses sont détaillées en langue anglaise, cependant, une version antérieure de ces travaux est disponible sous la forme du Dossier de la Drees 90. La dernière version de l'analyse portant sur les données du 13 décembre 2021 au 31 janvier 2022 a été publiée par la revue Eurosurveillance.

Suarez Castillo Milena, Khaoua Hamid, Courtejoie Noémie. Vaccine-induced and naturally-acquired protection against Omicron and Delta symptomatic infection and severe COVID-19 outcomes, France, December 2021 to January 2022. Euro Surveill. 2022;27(16):pii=2200250. https://doi.org/10.2807/1560-7917.ES.2022.27.16.2200250

Abstract 1

SARS-CoV-2 continues to spread despite fast vaccine rollout, which could be attributed to waning immunity or to a reduced protection against some variants. A thorough characterization of vaccine protection and its duration in time is needed to inform vaccination policies and enhance public trust. We matched three national databases with exhaustive information on screening, vaccination and hospitalizations in France over the year 2021. We performed a two-step analysis to estimate vaccine effectiveness against severe forms of Covid-19 in people aged 50 years or over, combining: *(i)* a test-negative case–control design to assess vaccine effectiveness against symptomatic infections; and *(ii)* a survival analysis to assess the additional protection against severe outcomes (hospitalizations and inpatient deaths) in infected individuals. We found a high vaccine effectiveness in people aged 50 years or more, reaching 82% against symptomatic infections and 94% against severe outcomes, after a full vaccination scheme. Vaccine effectiveness against symptomatic infections strongly decreased over time, dropping to 53% after six months, but remained high against severe forms (90% after six months). The booster dose allowed restoring high protection levels. Vaccine protection and its evolution in time, showed little difference against the variants that circulated prior to December 2021 in France, including the Delta variant. Though vaccine immunity decreases over time, vaccination remains crucial to provide individual protection against severe diseases. This decline can be reversed by the injection of a booster dose.

Abstract 2

The Omicron variant was detected in France in early December and spread more quickly than any previous SARS-CoV-2 variant, in individuals that had already been largely vaccinated or infected. We investigated the impact of vaccination against Covid-19 (primary vaccination scheme and booster dose), and of previous SARS-CoV-2 infection, at the individual level, on the risk of Covid-19 symptomatic infections, inpatient admissions, ICU admissions and deaths attributable to the Omicron variant. We analyzed the matching at the individual level of three nationwide French surveillance databases recording testing (SI-DEP), hospitalizations (SI-VIC), and vaccination (VAC-SI) from the 13th of December 2022 to the 31th of January 2022 for persons aged 18 years and older. First, we used a test-negative design case-control analysis to derive estimates of the different acquired immunity schemes against symptomatic infections. Second, we used a cox proportional hazard model to estimate the additional protection against severe outcomes in individuals with symptomatic infections. As a benchmark, the same analysis was conducted for the Delta variant. The vaccine-induced or naturally acquired protection against symptomatic infections was systematically lower against Omicron as compared to Delta, 15-30 days after the second injection, and 15-30 days after the booster dose. The vaccine-induced protection against Omicron waned at higher speed, with the time following the second injection, as well as the booster injection. Against Delta symptomatic infections, the naturally-acquired protection (in people that had been infected but not vaccinated) was similar to hybrid immunity (in people that had been both vaccinated and infected), whereas against Omicron the latter conferred a significantly 40 p.p. higher protection. In symptomatic individuals, the differences between variants were significantly less marked in vaccine-induced or naturally acquired protection against disease progression to severe inpatient outcomes. Overall, the protection against Omicron-induced severe outcomes remained above 70 % for naturally-infected unvaccinated persons, above 80 % for persons with hybrid immunity and at levels above 90 % after the booster dose with no additional difference in case of past infection. .

Vaccine effectiveness and duration of protection against symptomatic and severe Covid-19 during the first year of vaccination in France

1. Introduction

Vaccination against Covid-19 began in late December 2020 in France. By the end of 2021, the full vaccination coverage reached 77% overall (datavaccin), and 91% for people aged 18 and over. Meanwhile, the French territory was hit by three epidemic waves, defined by an acceleration of infections and hospitalizations related to severe forms of the disease, each one of them being attributed to a distinct dominant SARS-CoV-2 variant strain: the Alpha variant for the wave that peaked in March-April 2021, the Delta variant for the one that peaked in August 2021, and the Omicron variant for the one that peaked in early 2022. The latter was detected in France in early December 2021 and spread more quickly than any previous SARS-CoV-2 variant. Despite the gradual vaccine rollout, the burden of Covid-19 in France remained heavy in 2021. While vaccine coverage reached high level, part of the population remained reluctant to get the vaccine. In this context, it is essential to get reliable evidence on the protection provided by vaccines against symptomatic infections, hospitalizations and inpatient deaths related to Covid-19, on the evolution of this protection over time and after the booster dose, and on the relative effectiveness of vaccines against the different variants of concern.

At first, due to limited availability of vaccine doses, vaccines were administered in priority to healthcare workers and those most likely to develop severe forms of the disease, in particular to people aged 75 years and over, those living in retirement homes, and long-term care units. Vaccination was extended to all caregivers, and progressively to all age groups, starting with those with comorbidities, with a decreasing lower age limit for vaccine eligibility: 50 years, 18, 12 and five years (Appendix 1). Four different Covid-19 vaccine brands were used: Moderna, Pfizer/BioNTech, AstraZeneca and Janssen. A vaccination scheme was initially considered complete after two doses (or one dose for those infected by SARS-CoV-2), except for the Janssen vaccine, for which one dose was deemed sufficient. A full vaccination cycle became a sufficient condition required to get a French health pass that came into effect in June, and was first required to access events and places gathering many people. From August, the health pass was extended to grant entry into all museums, bars, restaurants, trains and other public spaces (irrespective of the number of people). The injection of a booster dose started in early September. First limited to the most fragile people and people aged 65 years or over, it became available to all professionals caring for these vulnerable people, and to all adults. This booster became mandatory for the health pass to remain valid as of December 15, 2021, and January 15, 2022, for those aged respectively 65 years or over, and 18 years or over.

Vaccination coverage progressed at unprecedented speed worldwide, providing growing evidence on vaccine effectiveness against the risk of symptomatic infections and severe forms of Covid-19 in the real world. The early estimates showed a good effectiveness of the first vaccine dose against the Alpha variant, with 61% (CI95%: 51-69) protection against symptomatic infections in people over 70 years of age, one month after the first dose of the

Pfizer/BioNTech and AstraZenecca vaccines (Lopez Bernal et al., 2021a). In people aged 80 years or over, vaccinated with Pfizer/BioNTech (resp. AstraZenecca), an additional reduction in the risk of hospitalization of 43% (33-52) (resp. 37%; 3-59) was observed; thus resulting in an effectiveness against the risk of hospitalization of about 80% after a single dose of one of the two vaccines. The protection provided by vaccination against the Alpha variant, increased after the second vaccine dose, reaching 89% (85-93) protection against symptomatic infections in people 80 years or older, with the Pfizer/BioNTech vaccine (Lopez Bernal et al., 2021a). Two weeks after the second dose, vaccination provided a reduction in the risk of severe forms of Covid-19 of 92% (91; 93) for vaccination with the Pfizer/BioNTech vaccine, 96% (94- 97) with the Moderna vaccine, and 96% (65-99) with the AstraZeneca vaccine, in people aged 75 years or older in France (Botton et al., 2021). However, this protection seemed lower against the Delta variant (84%; 75-90) (EPI-PHARE, 2021). Vaccine effectiveness against symptomatic cases in individuals aged 16 years was lower by 12 to 19% with the Delta variant as compared with the Alpha variant, after one vaccine dose. Yet, these differences were smaller after two doses: 88% (85-90) with the Alpha variant and 80% (77- 82) with the Delta variant (Lopez Bernal et al., 2021b).

Evidence started pointing towards a significant decline over time in vaccine effectiveness against symptomatic infections, but to a lesser extent against severe cases (Thomas et al., 2021; Tartof et al., 2021; Goldberg et al., 2021). Vaccine effectiveness against symptomatic Delta variant infections dropped, 20 weeks after vaccination, to 47% (45–50) and 70% (69-71), for AstraZeneca and Pfizer/BioNTech vaccine respectively, with a stronger decline in those aged 65 years or older, but with a lower decline against hospitalizations (Andrews et al., 2021). However, studies find that the booster dose restores similar (or even better) levels of protection against symptomatic infections and severe cases than those prior to the waning of immunity (Bar-On, et al.; 2021; Andrews, et al., 2021b; Matiuzzi and Lippi, 2022).

This paper provides with complementary insights on vaccine effectiveness and its evolution over the year 2021 in the French context, using unprecedented data matching three National exhaustive databases containing exhaustive information on Covid-19 screening (SI-DEP), vaccination (VAC-SI) and hospitalizations (SI-VIC) in France. We used data from January 1st 2021 to December 12, 2021, thus stopping our analysis prior to the exponential growth of the Omicron variant. We focused on people aged 50 years or over, a population that concentrates the most severe forms of the disease and that became eligible for vaccination and then booster dose at an earlier stage (Appendix 1). We performed a two-step analysis of vaccine effectiveness against severe forms of Covid-19 and estimated: *(i)* vaccine effectiveness against symptomatic forms of Covid-19; *(ii)* vaccine protection against the risk of hospitalization and death in individuals with symptomatic forms of Covid-19. In particular, we studied the evolution of vaccine protection under the combined effect of the emergence of the Delta variant, and of the decrease in immunity over time after the completion of the primary vaccination scheme. We additionally estimated the contribution of the booster dose in restoring a significant level of protection.

2. Material and methods

2.1. Study design

We used a two-step analysis to estimate vaccine effectiveness against severe forms of Covid-19, defined as leading to hospitalizations, intensive care units (ICU) admissions, or inpatient deaths. First, we used a test-negative case–control design (Jackson and Nelson, 2013) to estimate vaccine effectiveness against symptomatic Covid-19 infections. This method, already used in the Covid-19 pandemic (Lopez Bernal et al., 2021a and 2021b; Stowe et al., 2021; Tenforde et al., 2021; Chung et al., 2021), relies on the comparison of vaccination statuses between cases (individuals with confirmed SARS-CoV 2 infection) and controls (individuals who do not test positive for SARS-CoV-2 infection), with cases and controls tested after reporting symptoms suggestive of Covid-19.

Then, we performed a survival analysis among individuals with symptomatic forms of Covid-19, to evaluate a possible additional risk reduction provided by vaccination against severe forms of the disease.

2.2. Data sources

Three National databases created to monitor the epidemic and the vaccination campaign were matched together. This study provides the first use of this matched dataset in an international peer-reviewed journal.

SI-VIC, the information system for monitoring victims of attacks and exceptional health situations, provides, for people infected with SARS-CoV-2, the daily number of hospitalizations in general wards and ICU, and the number of inpatient deaths. The diagnosis of infection relies on RT-PCR testing or thoracic CT scanning. This reporting system, maintained by the ANS (*Agence du Numérique en Santé*), is exhaustive and covers all healthcare structures (public and private) over the French territory.

SI-DEP, the screening information system, provides the daily number of tests performed (RT-PCR, serology and antigenic tests) for SARS-CoV-2 and the results of these tests. This database, maintained by the AP-HP (*Assistance Publique - Hôpitaux de Paris*), is exhaustive for all tests performed on the French territory (but self-tests). Since mid-2020, PCR testing was available to the population without prescription and covered by national health insurance (Appendix 1). As of January 2021, a molecular screening was performed on all RT-PCR positive samples: first to identify known variant strains (wild-type, alpha, beta, gamma); then, from June 2021, to identify some key mutations (E484K, E484Q, L452R). The presence or absence of symptoms in tested individuals should be systematically reported, but this information is missing for 20% of the RT-PCR tests performed in 2021.

VAC-SI, the Covid-19 vaccine information system, maintained by the CNAM, the French national Health Insurance (*Caisse Nationale d'Assurance Maladie*), provides the number of administrated vaccines and vaccinated persons on the French territory. This dataset covers nearly the entire French population (all those affiliated to the French Health Care System [Social security]), whether vaccinated or not, and all individuals vaccinated in France. This database contains information on vaccination (dates of injection, vaccine brand name), and information on vaccine priority populations (presence of comorbidities, healthcare professionals or social workers, retirement homes residents).

To match these databases, a pseudonym (non-meaningful character string identifying each person) was generated from the concatenation and encryption of identifying information (surname, first name, sex and date of birth). The pseudonym (but not the identifying information) is present in all the databases transmitted to the Statistics office of the French Ministry for Solidarity and Health (DREES) for statistical use, which allows the matching of data on screening, hospitalization and vaccination at the individual level. However, matching imperfections may remain (DREES, 2021; Appendix 5).

The deployment of these three databases was authorized by the French Data Protection Authority (*Commission Nationale Informatique et Libertés*). No consent of the patients is required, and the patients must be informed of their right to access, modify, rectify and delete any data concerning them. The French Ministry for Health is accountable to implement legal, technical and organizational measures to guarantee data protection.

2.3. Study period and study population

The data used were extracted on the 11th of January 2022, for observations from January 1st to December 12, 2021. In the last week of the study period, the Omicron variant represented less than 10% of the positive RT-PCR tests with molecular screening. We excluded the last weeks of December when the Omicron variant started its exponential growth, as more data is needed to estimate vaccine effectiveness against this emerging variant.

We included tests performed on individuals: *(i)* aged 50 years or over, a population that concentrates the most severe forms of the disease and that became eligible for vaccination at an earlier stage; *(ii)* tested by RT-PCR, to focus on recent infections for which the causative variant could be identified; *(iii)* reporting symptoms in the seven days prior to the time of screening. When several positive tests were associated with the same pseudonym, we considered those performed less than 15 days apart as part of the same infectious episode. We thus identified distinct infectious episodes, and we included in the analysis only one positive test per episode and per individual (in priority a test with molecular screening). For a given individual, we also excluded the negative tests that had been performed within 15 days of a confirmed infectious episode.

We included only individuals present in the VAC-SI register and with non-missing information about the presence or absence of comorbidities considered for prioritizing vaccine administration in the 2021 French vaccination campaign. For our analysis, we defined four vaccination statuses: unvaccinated, one dose (D1), full primary vaccination cycle without (D2) or with booster (DB). They were further refined according to the time since the injection and the vaccine brand. In particular, individuals vaccinated with the Janssen vaccine completed their primary vaccination scheme after only one dose. The vaccination status was estimated as of the date of RT-PCR screening. In France, a full primary vaccination status is also achieved after only one dose in case of a confirmed past infection in the three months preceding the first dose or in the month following that dose (set aside the Janssen vaccine). We excluded all individuals with a confirmed SARS-CoV-2 infection at least 60 days prior to the time of screening (in coherence with the European Surveillance System definition of *suspected cases* of SARS-CoV-2 *reinfection*), in order to estimate vaccine effectiveness in fully susceptible individuals. This choice implies that a full primary vaccination cycle only relates to the injection

of two doses. We excluded individuals with atypical vaccination schemes: those vaccinated with two doses from two different vaccines when one of them was the Janssen vaccine, and those who never received their second injection of a bi-dose vaccine (they were excluded 28 days after their first dose).

To study severe forms of Covid-19, we included the inpatients aged 50 years or over that were present in all three databases (SI-VIC, SI-DEP and VAC-SI). We applied the filters already listed above on data from vaccination and screening. In addition, we excluded inpatients: *(i)* infected by SARS-CoV-2 but whose admission was not attributable to Covid-19 (persons hospitalized for other conditions may have been systematically screened); and *(ii)* with no symptomatic positive RT-PCR test recorded within 15 days before hospital admission, or within two days after. In case of symptomatic positive RT-PCR test within two days after admission, inpatients are reclassified as tested on the day of admission to avoid negative durations in the survival analysis, and kept in the analysis.

2.4. Statistical analysis

We used a test-negative case-control design to estimate vaccine effectiveness against symptomatic Covid-19. Symptomatic positive individuals (respectively positive to a given variant for the analysis by variant) were randomly matched to controls (symptomatic negative individuals) on age (ten-year age brackets), sex, area of residence (NUTS-3 level), week of testing and presence or absence of a comorbidity qualifying for prioritization in the vaccination campaign. The odds ratios (OR) were estimated using a conditional logistic regression, and vaccine effectiveness ($VE(S+)$) was given by the following formula: $VE(S+) = 1 - OR$ (Bond et al., 2017).

We then estimated the risk of severe outcome (hospitalization, ICU admission, or death) among individuals with RT-PCR-confirmed SARS-CoV-2 symptomatic infection, according to their vaccination status. We fitted a Cox survival model on the time interval between the date of the test and the date of the hospital admission associated with the severe outcome, if any, or the end of the follow-up period. The latter was censored at 15 days post-test or at the end of the study period (December 12, 2021). A hazard ratio of hospitalization (respectively ICU admission or death) was then estimated according to the vaccination statuses ($HR(H|S+)$), controlling for the same variables as those used in the case-control study.

This two-step analysis allowed calculating the vaccine effectiveness against severe forms of Covid-19, $VE(H)$, $VE(ICU)$, $VE(D)$, for hospitalization, ICU admission and inpatient death respectively, considering that, in addition to the risk reduction against symptomatic forms, vaccination also provides a risk reduction in the development of severe disease in symptomatic individuals. Vaccine effectiveness against severe forms of Covid-19 was deduced from the following formula: $VE(i) = 1 - OR(S+) * HR(i|S+)$, where i refers to either hospitalization, ICU admission or inpatient death.

We estimated the evolution of vaccine effectiveness over time, according to the time elapsed since each vaccine dose. We provided estimates up to six months after the second dose, except for the variant-specific analysis, that we truncated three months after the second dose. Indeed, for all variants but the Delta one, the variant-specific incidence was very low when the population reached this duration after a full vaccination scheme.

3. Results

3.1. Description of the study population

Over the period from January 1st to December 12, 2021, 8 881 107 individuals were tested by RT-PCR and reported symptoms at the time of screening. 2 413 356 (27%) of them were aged 50 years or over and 2 024 773 (84%) of the latter were successfully linked to vaccination data with non-missing data on comorbidities. We excluded 44 604 individuals with unusual vaccination schemes, and 67 134 individuals with a known past infection prior to the time of screening. Of these remaining individuals, 437 694 (23%) were tested positive for SARS-CoV-2. The study population for the test-negative design analysis consisted of 432 117 positive cases (5 577 cases were excluded because of the lack of similar controls) and 864 234 controls (two matched controls for each case). Almost none of them was vaccinated at the beginning of the year 2021, 50% had received one dose by May, the 20th of 2021, and two doses by July, the 2nd of 2021. By the end of 2021, 86% of them had completed their primary vaccination cycle and 46% of them had received a booster dose. The distribution of vaccination statuses over time differed between cases and controls, with an earlier start of the primary vaccination scheme in the latter (Figure 1, Appendix 2).

Among the symptomatic positive cases in the sample, 67% had not yet been vaccinated when they got tested, 15% were older than 75 years, 52% were women, and 63% had a comorbidity (Appendix 2).

The study population for the survival analyses consisted of the 437 694 persons with confirmed SARS-CoV-2 symptomatic infection, among which there were 44 615 hospitalizations, 12 050 ICU admissions and 7 476 inpatient deaths recorded in SI-VIC. We did not consider the 4 813 hospitalizations that did not meet the criteria listed in the study population section.

3.2. Vaccine effectiveness of the primary vaccination cycle

Among those aged 50 years and over, vaccine effectiveness against symptomatic infection grew quickly even after only one dose and further increased after the completion of the primary vaccination cycle. It reached 26% (24-28) two weeks after the first dose and 45% (43 – 47) one month after, and it peaked at 82% (81 – 83) two weeks after the second dose (Figure 2). However, in the early days after the first dose, before protective immunity has been reached, we observe an increased risk of symptomatic infection in vaccinated persons versus comparable unvaccinated persons.

The risk of hospitalization, ICU admission, and inpatient death of infected symptomatic individuals decreased as the vaccination cycle progressed (Figure 3). Among them, vaccination provided more than 75% (72-77) risk reduction against hospitalizations and ICU admissions, and 54% (44-63) risk reduction against inpatient deaths, one month after the injection of the second dose.

We then combined the estimates of vaccine effectiveness against symptomatic infections with the additional protection provided by vaccination against severe forms of the disease in those experiencing symptomatic infections. We thus obtained a vaccine effectiveness that peaked at 94% (93 – 95) against hospitalizations, 96% (95 – 97) against ICU admissions and 89% (87 – 91) against inpatient deaths after a primary vaccination cycle (Figure 2).

3.3. Decline in vaccination effectiveness over time, before the booster shot

Among persons aged 50 years or over, the vaccine effectiveness against symptomatic infections peaked in the first month after the second dose, before declining sharply (Figure 2),

and falling to 53% (52–54) within six months. However, the additional risk reduction for ICU admissions and inpatient deaths among symptomatic individuals decreased only very little over time (Figure 3), and remained constant for hospitalizations. As a result, vaccine effectiveness against severe disease declined less and slower. It was still about 90% (89–91) against the risk of hospitalization, more than six months after the second injection.
The booster dose seemed very efficient in restoring vaccine effectiveness to levels even higher than ever: reaching 92% against symptomatic forms and 99% against hospitalizations.

3.4. Vaccination effectiveness by age and comorbidities

Vaccine effectiveness against symptomatic infections was similar at the beginning of the vaccination cycle and up to five months after two doses for people aged 50 years or over with comorbidities, but was six percentage points lower after six months (Appendix 3). When studying severe Covid-19 outcomes, the presence of comorbidity, independently of vaccination status, was associated with a higher risk of complications with a hazard ratio of 1·57 (1·54-1·61) for hospitalization, 1·72 (1·65-1·79) for ICU admission, and 1·35 (1·27-1·43) with inpatient death. However, the vaccine reduced the risk of severe outcome in a similar way for people with comorbidities than for all people aged 50 years or more. As a result, vaccine effectiveness against severe Covid-19 after a full vaccination scheme appeared very similar for people with comorbidities. The booster dose then restored similar and high protection levels in both categories.

Vaccine effectiveness against symptomatic infections and severe cases showed no significant differences between age groups (for people aged 50 years or over) right after the completion of the primary vaccination cycle. However, vaccine effectiveness against symptomatic cases, which significantly declined for all age groups, decreased stronger among the elderly. After six months, it dropped to 59% (57-60) in people aged 50 to 74, to 37% (32-41) in people aged 75 to 84, and to 27% (20-34) in those aged 85 and over. Vaccine effectiveness against hospitalizations declined moderately for all age groups but those aged 85 years or over, for whom it dropped to 70% (64-75) after six months. Again, high vaccine effectiveness in these frail and older populations was restored after the booster dose, up to levels comparable to those obtained in the younger age groups (97%; 96-98).

3.5. Vaccination effectiveness against different variants

Vaccine effectiveness did not differ significantly against the Alpha variant and the wild type SARS-CovCov-2, reaching 91% (90-92) and 92% (88 – 96) respectively, 15 days after the second injection (Figure 5 and Table 4 in Appendix 3). In comparison, vaccine effectiveness against the Beta/Gamma and Delta variants were lower against symptomatic infections, at all stages of the vaccination course, peaking respectively at 84% (78–90) and 79% (77–80), 15 days after the second injection. Point estimates suggest a lower effectiveness against the Beta/Gamma variants than against the Delta one after one month, but these differences are not significant. A decrease in vaccine effectiveness against symptomatic infections is observed over time for all variants (but the wild type). In contrast, vaccine effectiveness against hospitalization does not appear to decrease in the first three months, regardless of the variant. At the peak and from two to three months after the second dose, this effectiveness is significantly higher against the Alpha variant than against the Delta one by four percentage points.

4. Discussion

We have used three large and exhaustive datasets on Covid-19 screening, vaccination and hospitalizations in France to assess vaccine effectiveness over the year 2021. On the study population aged 50 years or more, we found a high vaccine effectiveness against symptomatic and severe forms of the disease, which increased as one progressed through the vaccination scheme. At its peak, the vaccine effectiveness of a primary vaccination cycle (without booster) reached 85% against symptomatic forms and 90% against severe forms, with little difference between age groups, and no difference for individuals with comorbidities.
Vaccine effectiveness against symptomatic forms then decreased over time after the completion of the primary vaccination cycle, dropping to 57% in those aged 50 years or over six months after completion of the vaccination cycle and to 39% in those aged 85 years or over. However, protection against severe forms declined much slower and vaccine effectiveness remained high (84% six months after completion of the vaccination course), except in the oldest age group where protection over time dropped stronger (70% after six months). These estimates are consistent with observational studies in other countries.
When the time elapsed since vaccination reached several months in the first vaccinated individuals, the Delta variant had become predominant. Our findings show that the drop in vaccine protection over time seems mainly due to a decline in vaccine protection, rather than to a greater capacity of the Delta variant to escape vaccine protection. Indeed, we found that vaccine effectiveness was only slightly lower against the Delta variant than against the wild type and Alpha variant. In addition, in the first three months after vaccination, a similar drop in vaccine effectiveness was observed for all variants, which suggests that immunity waning is not specific to the Delta variant. If the reduction in vaccine protection against the variants under study remains limited, our analyses were conducted prior to the rapid spread of the Omicron variant in France, for which vaccine escape may be of greater concern. Estimates on that matter, though still little documented to date, point towards very little (or no) protection against symptomatic infections (Buchan et al. 2022; Andrews et al. 2021c), but partially restored protection with a booster (Willet et al. 2022) and a limited protection against severe cases (Collie et al. 2021).
We showed that the highest levels of protection against both symptomatic and severe forms of the disease were obtained one week after receiving a booster dose, without distinction on age groups. This confirms that the booster dose is essential to restore a high level of protection. These real-world estimates are also consistent with laboratory analyses: although the amount of antibodies in vaccinated individuals decreases over time (Levin et al., 2021), memory B cells seem to remain numerous and capable of a better response (Goel et al., 2021), thus likely preventing severe cases. In addition, a rapid serological response was observed after the booster dose (Pfizer/BioNTech), with significantly higher antibody titers than those observed after the second dose (Ireland et al., 2022).

The exhaustiveness of the databases and the possibility to match them together to get information at an individual scale are the great strengths of this study. We thus provide evidence of vaccine effectiveness in real-world conditions over a long period. The large sample size allows us: *(i)* to provide reliable estimates of vaccine protection against severe Covid-19, which remain rare events; and *(ii)* to detail these estimates for several sub-populations and with a precise time elapsed since the injection of all vaccine doses, up to the booster dose. However, the observational nature of the data itself also brings about some limitations. We used a test-negative design in order to reduce selection biases that are difficult to measure

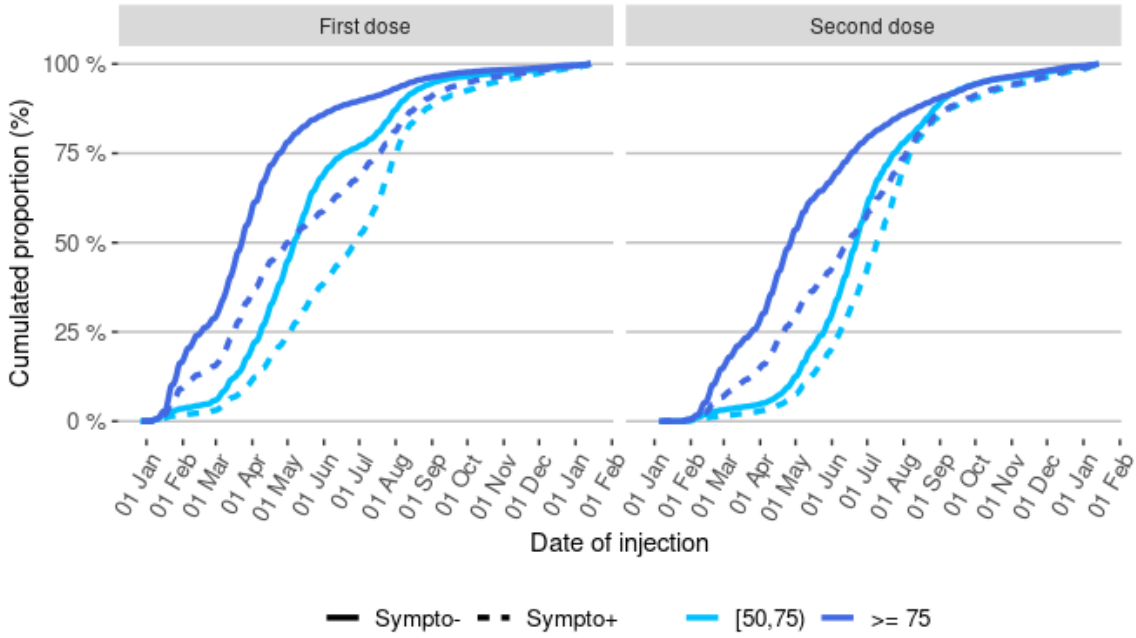
such as health-seeking behaviour, access to testing and case ascertainment. This method has been proven useful in our study context. In particular, it allowed limiting the effect of the evolution of screening policies on the propensity of getting tested (Appendix 1). Yet, test-negative designs rely on strong assumptions, the applicability of which is difficult to assess and may have varied over the study period (Jackson and Nelson, 2013; Dean et al, 2021). The control variables that are used to limit the selection bias in the use of vaccination may not be sufficient, as a given vaccination status at a given time may reflect unobserved factors. For example, among people aged 50 years or over, those vaccinated at the beginning of the study period are likely to be more vulnerable (persons in retirement homes or with comorbidities), whereas those unvaccinated at the end of the study period are likely to be special (persons for whom vaccination is contraindicated, or persons against vaccination). In our study, we observed an increased risk of infection in the first days after vaccination, before protective immunity has been reached. This finding, observed elsewhere (Lopez Bernal et al. 2021a; Chung et al. 2021), seems to be due to a higher baseline risk of infection among those who were initially prioritized to receive the vaccine, suggesting missing unobserved controls (Appendix 4). In addition, being vaccinated could affect: *(i)* the perception of the need to be screened in case of symptoms and *(ii)* the probability of exposure to the virus, if being vaccinated leads to an increase in social interactions or to a lesser application of barrier gestures.

Beyond the biases inherent to observational studies, some limitations are linked to the data and variables available. Even though we excluded individuals with a known past infection based on virological and serological tests performed prior to the first vaccination dose, some past infections remained undetected and the vaccine effectiveness of the first dose of vaccine may partially reflect the stimulation of pre-existing immunity. The matching between the three databases was not perfect, which led to sample restrictions that could affect the representativeness of the results obtained. However, the corrections made to improve the matching between databases have not resulted in significant revisions of the results. Our findings only relate to vaccine effectiveness against symptomatic infections, but these symptoms were self-reported, without medical advice. We did not attempt to distinguish results by type of vaccine, although the durability of vaccine protection and the ability to protect against different variants may differ (EPI-PHARE, 2021; Andrews et al., 2021).

Overall, we found high levels of vaccine effectiveness against symptomatic infections and severe diseases after a full primary vaccination cycle. The protection was high against all the variants that circulated in France prior to December 2021, including the Delta variant that did not show a strong capacity to escape vaccine immunity. The decline of effectiveness overtime -which is strong against symptomatic infections but remains limited against severe diseases-, is efficiently restored by a booster dose. Our findings underscore the importance of monitoring vaccine effectiveness over time, and of maximizing the vaccine uptake of the booster dose.

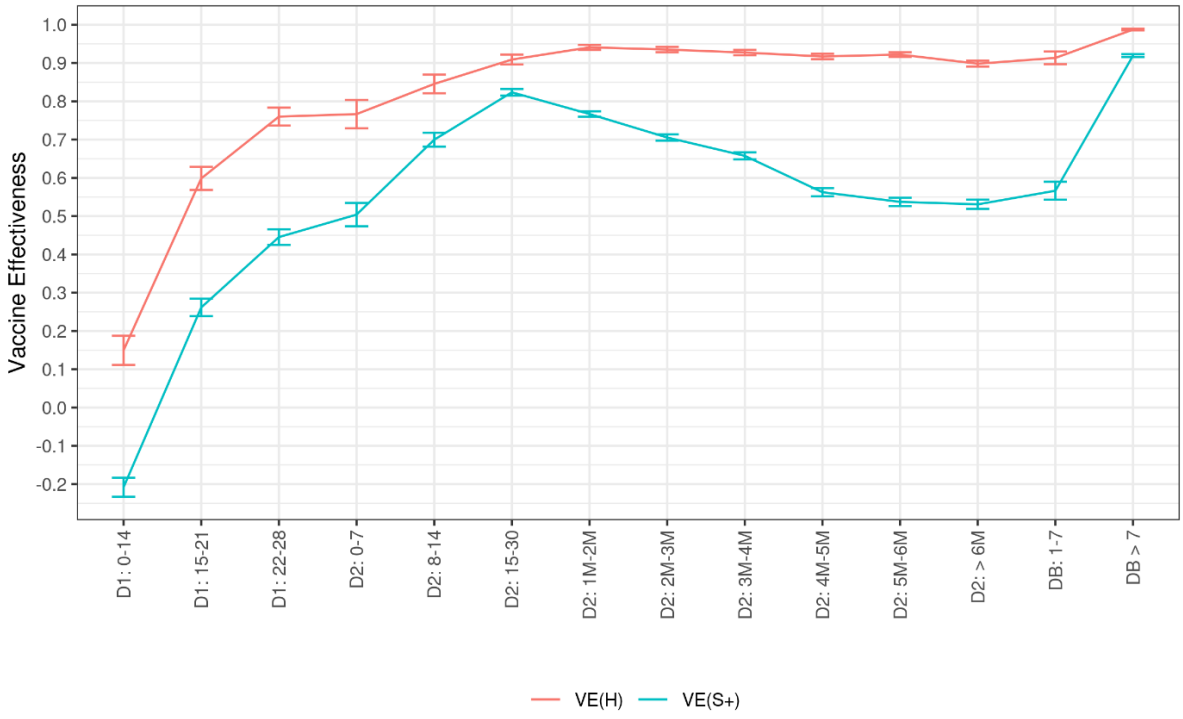
Figures

Figure 1 • Distribution of injection dates for the first and second vaccine doses in control and cases, by age-group



Abbreviations: Sympto+ (cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection (cases). Sympto- (controls): individuals with symptoms non-related to SARS-CoV-2 infection.

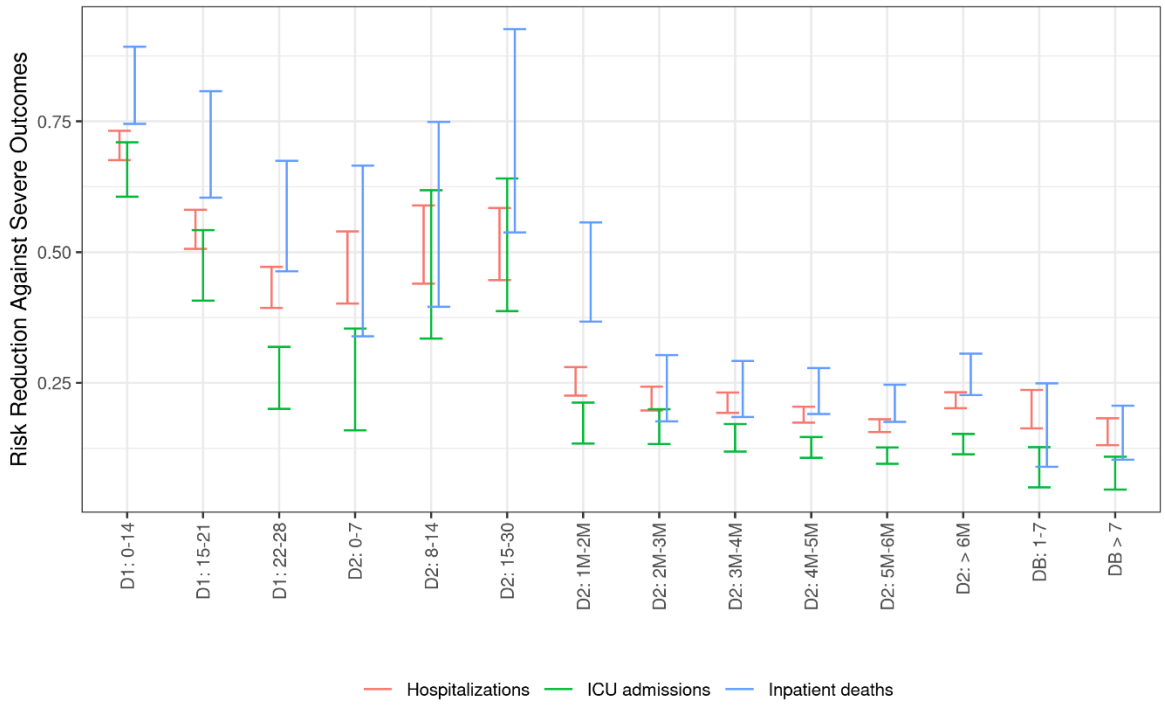
Figure 2 • Covid-19 vaccine effectiveness against symptomatic infections and hospitalizations among persons aged 50 years or over, according to the time elapsed since the injection of each vaccine dose, data collected from January 1st to December 12, 2021



Abbreviations: D1: first vaccine dose. D2: second vaccine dose. DB: booster dose. M: month. S+: symptomatic infection. H: hospitalization. VE: vaccine effectiveness. The numbers in the x-axis indicate the time (in days or months) elapsed since the injection of the dose of interest.

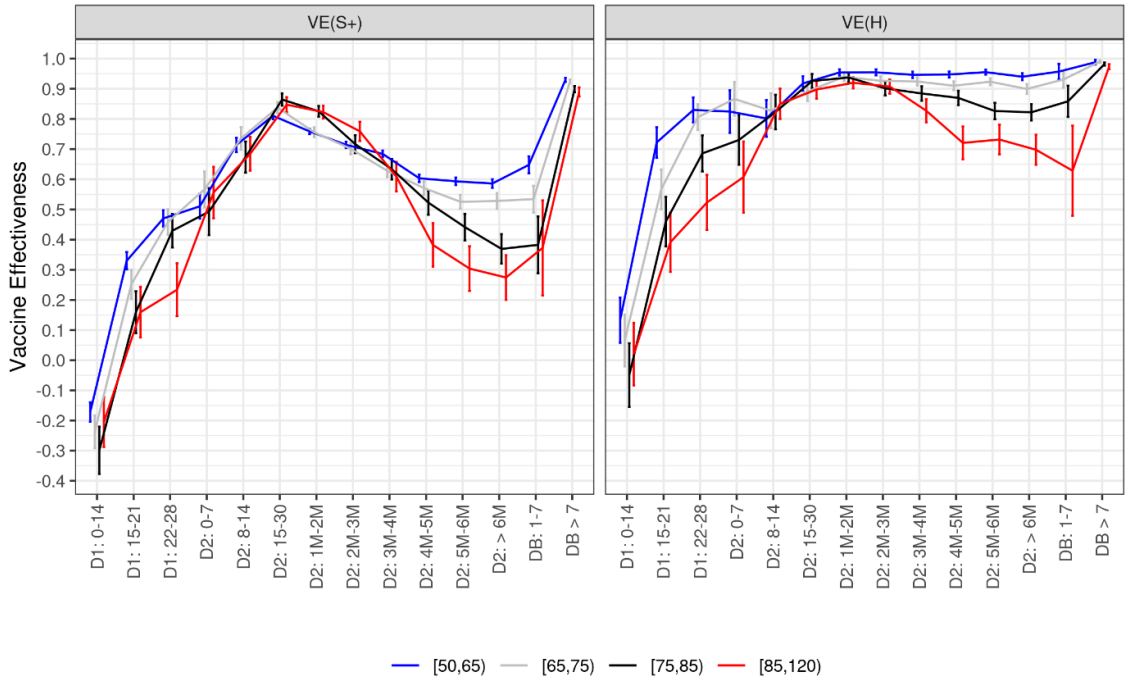
Figure 3 • Risk reduction against Covid-19 severe outcomes (hospitalizations, ICU admissions and inpatient deaths) among persons aged 50 years or over, according to the time elapsed since the injection of each vaccine

dose, data collected from January 1st to December 12, 2021



Abbreviations: D1: first vaccine dose. D2: second vaccine dose. DB: booster dose. M: month.
a The numbers in the x-axis indicate the time (in days or months) elapsed since the injection of the dose of interest.

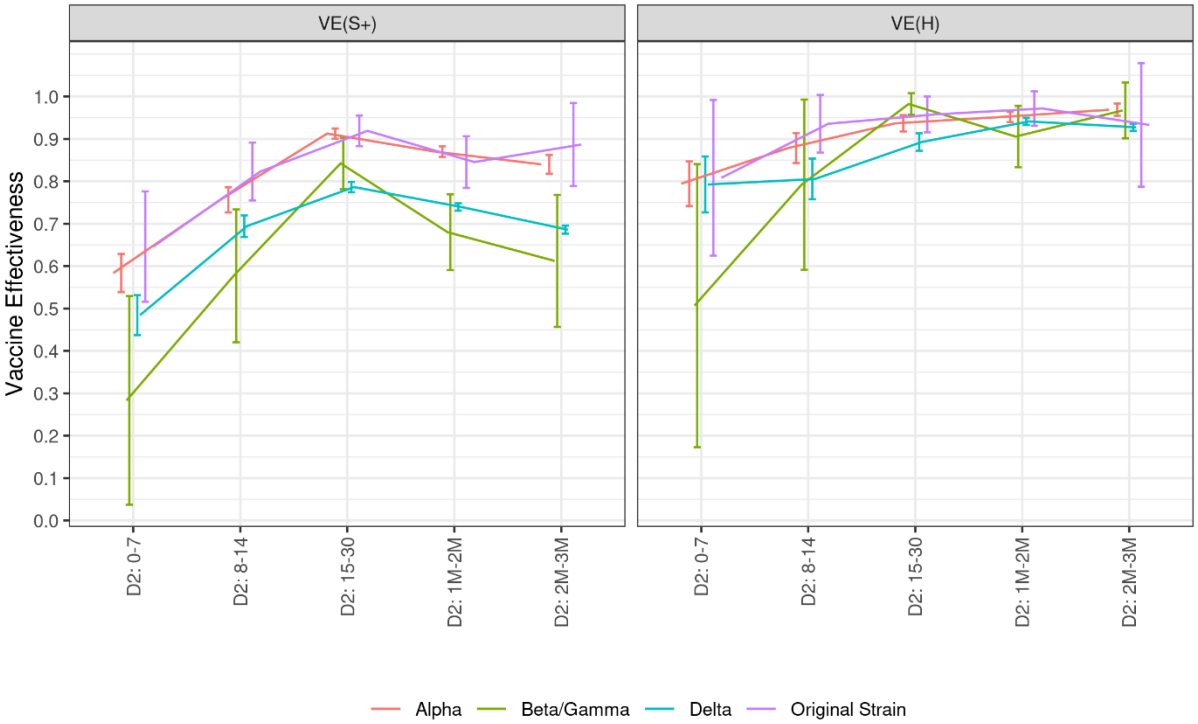
Figure 4 • Covid-19 vaccine effectiveness against symptomatic infections and hospitalizations by age, according to the time elapsed since the injection of each vaccine dose, data collected from January 1st to December 12, 2021



Abbreviations: D1: first vaccine dose. D2: second vaccine dose. DB: booster dose. M: month. S+: symptomatic infection. H: hospitalization. VE: vaccine effectiveness.
The numbers in the x-axis indicate the time (in days or months) elapsed since the injection of the dose of interest.

Figure 5 • Covid-19 vaccine effectiveness against symptomatic infections and hospitalizations related to various variants of concern, according to the time elapsed since the injection of each vaccine dose, data collected from

January 1st to December 12, 2021



Abbreviations: D1: first vaccine dose. D2: second vaccine dose. DB: booster dose. M: month. S+: symptomatic infection. H: hospitalization. VE: vaccine effectiveness. The numbers in the x-axis indicate the time (in days or months) elapsed since the injection of the dose of interest.

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Appendix. Supplementary materials

Appendix 1 • Milestones of the French sanitary crisis and its management

Context		
24/01/2020		First confirmed Covid-19 case in France
14/02/2020		First Covid-19 death in France
Lockdowns		
17/03/2020	10/05/2020	First lockdown
11/05/2020	01/06/2020	First phase of lifting of lockdown restrictions (gradual reopening according to local health situations)
02/06/2020	21/06/2020	Second phase of lifting of lockdown restrictions
17/10/2020	29/10/2020	Curfew in Île-de-France and in eight metropolitan areas between 9 p.m. and 6 a.m.
30/10/2020	14/12/2020	Second lockdown
15/12/2020	15/01/2021	Curfew between 8 p.m. and 6 a.m. throughout metropolitan France
16/01/2021	02/04/2021	Curfew between 6 p.m. and 6 a.m. throughout metropolitan France
03/04/2021	02/05/2021	Third lockdown
03/05/2021	29/06/2021	Gradual lifting of the lockdown restrictions, end of travel restrictions
03/05/2021	*18/05/2021*	*Curfew between 7 p.m. and 6 a.m.*
19/05/2021	*08/06/2021*	*Curfew between 9 p.m. and 6 a.m.*
09/06/2021	*29/06/2021*	*Curfew between 11 p.m. and 6 a.m.*
Schools closures		
16/03/2020	10/05/2020	Closure of all nurseries and schools
11/05/2020	02/06/2020	Gradual reopening of schools
05/04/2021	25/04/2021	Closure of schools
26/04/2021	02/05/2021	Closure of colleges and high schools
Activity restrictions		
29/02/2020		Prohibition of public gatherings of more than 5,000 people; in the most affected municipalities, all collective gatherings are prohibited, schools are closed and it is recommended to limit travel
14/03/2020		Closure of so-called “non-essential” businesses and establishments open to the public (restaurants, bars, cinemas, nightclubs, etc.)
17/03/2020		Ban on leaving the house, except for certain reasons requiring a daily covid travel certificate
17/03/2020		Closure of the external European Union borders
11/05/2020		Wearing a face mask is mandatory in public transport
01/07/2020		Gradual reopening of borders
20/07/2020		Wearing a face mask is mandatory in closed public places
27/08/2020		Wearing a face mask is mandatory in all closed places
30/10/2020		Ban on leaving the house, except for certain reasons requiring a daily covid travel certificate
30/10/2020		Closure of so-called “non-essential” businesses and establishments open to the public (restaurants, cafes, cinemas, nightclubs, etc.)
28/11/2020		Reopening of shops (except bars, restaurants and sports halls)
31/01/2021		Closure of the external European Union borders
03/04/2021		Limitation of travel to a radius of 10 kilometres
03/04/2021		Closure of so-called “non-essential” businesses
19/05/2021		Reopening of terraces (in cafes, bars and restaurants), shops and cultural and sports venues (with restrictions)
09/06/2021		Reopening of cafes, bars and restaurants, easing of restrictions
09/06/2021		Reopening of borders, subject to conditions depending on the country
Tests, vaccination, health pass		
27/01/2020		Development of a screening test (Pasteur)
06/04/2020		Beginning of screening of vulnerable people
12/05/2020		SI-DEP centralizes test results in a national database
28/05/2020		Test reimbursed by the French health insurance on prescription
25/07/2020		Test reimbursed by the French health insurance without medical prescription
17/10/2020		Deployment of rapid antigenic tests
27/12/2020		Beginning of the vaccination campaign (residents and staff of accommodation establishments for the elderly)
02/01/2021		Opening of vaccination to health workers, caregivers and firefighters caregivers aged 50 or over
18/01/2021		Opening of vaccination to persons aged 75 or over, then gradually to younger ages
06/02/2021		Opening of vaccination to health workers, caregivers and firefighters
19/02/2021		Opening of vaccination to persons aged 50 to 64 with comorbidities
02/03/2021		Opening of vaccination to persons aged 65 to 74 with comorbidities
27/03/2021		Opening of vaccination to persons aged 70 or over
12/04/2021		Opening of vaccination to persons aged 55 or over
01/05/2021		Opening of vaccination to all adults with comorbidities
10/05/2021		Opening of vaccination to persons aged 50 or over
31/05/2021		Opening of vaccination to all adults without condition
09/06/2021		Health pass is mandatory for public gatherings of more than 1,000 people

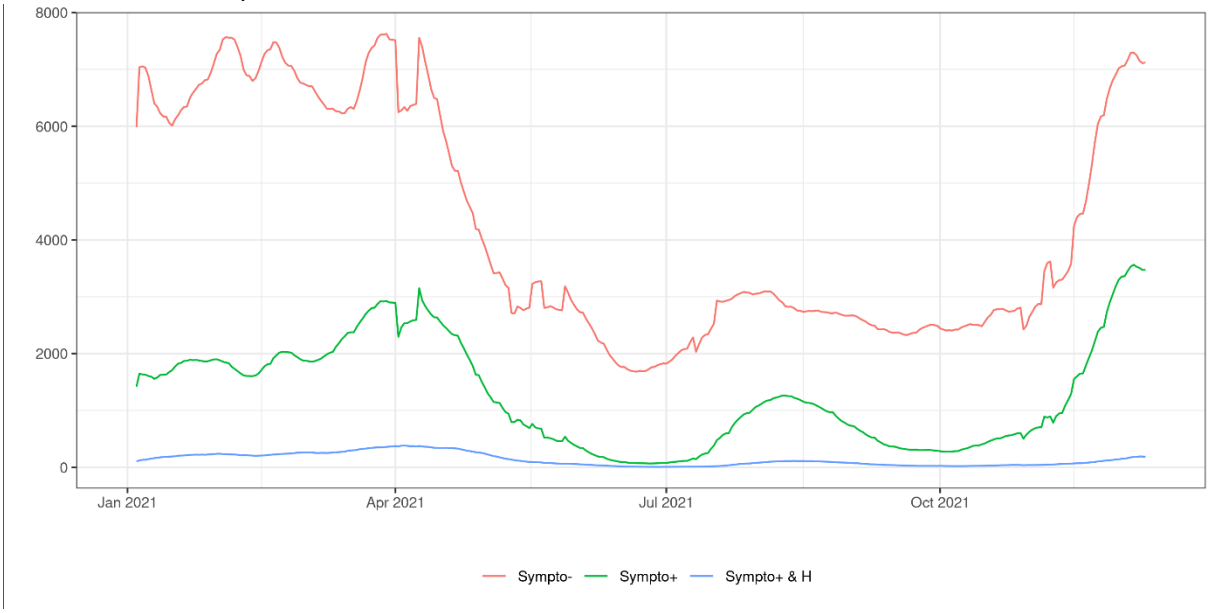
15/06/2021	Opening of vaccination to 12-17 years old
21/07/2021	Extension of the use of the health pass to public gatherings off more than 50 people
09/08/2021	Extension of the use of the health pass to all places of sociability without size criteria, to interregional public transport, etc.
01/09/2021	Opening of booster dose to persons aged 65 or over, elderly home residents, persons with comorbidities six months after the initial complete vaccination
15/09/2021	Mandatory vaccination for health workers and certain professions dealing with people
15/10/2021	End of reimbursement of tests by the French health Insurance, except on prescription and for vaccinated persons and minors
27/11/2021	Opening of booster dose to all eligible adults and eligibility for the booster vaccination is lowered to five months after the initial complete vaccination
28/12/2021	Eligibility for the booster vaccination is lowered to three months after the initial complete vaccination

Appendix 2 • Description of the study population

Table 1. • Descriptive characteristics of the sample, data collected from January 1st to December 12, 2021.

	Symptomatic negatives	Symptomatic positives	Hospitalized
Number of persons	**N=1,475,037**	**N=437,693**	**N=45,802**
Characteristic			
Sex — no. (%)			
Female	848,818 (57.5)	226,306 (51.7)	18,592 (40.6)
Male	626,208 (42.5)	211,387 (48.3)	27,210 (59.4)
Missing data	11 (<0.1)	1 (<0.1)	0
Age — no. (%)			
50-64 yr	815,682 (55.3)	276,597 (63.2)	14,323 (31.3)
65-74 yr	348,718 (23.6)	95,273 (21.8)	11,733 (25.6)
75-84 yr	174,709 (11.8)	39,127 (8.9)	9,690 (21.2)
≥ 85 yr	135,928 (9.2)	26,697 (6.1)	10,056 (22.0)
Comorbidity — no. (%)			
No	289,793 (19.6)	162,870 (37.2)	12,051 (26.3)
Yes	1,185,244 (80.4)	274,824 (62.8)	33,751 (73.7)
One dose — no. (%)			
No	812,653 (55.1)	291,036 (66.5)	36,345 (79.4)
Yes	662,384 (44.9)	146,658 (33.5)	9457 (20.6)
One dose type — no. (%)			
Comirnaty (Pfizer/BioNTech)	471,622 (71.2)	100,159 (68.3)	6,597 (69.8)
Spikevax (Moderna)	55,554 (8.4)	8,314 (5.7)	605 (6.4)
Vaxzevria (AstraZeneca)	121,270 (18.3)	32,864 (22.4)	1,865 (19.7)
Janssen	13,938 (2.1)	5,321 (3.6)	390 (4.1)
Two doses — no. (%)			
No	970,735 (65.8)	330,638 (75.5)	41,262 (90.1)
Yes	504,302 (34.2)	107,056 (24.5)	4,540 (9.9)
Two doses type — no. (%)			
Comirnaty (Pfizer/BioNTech)	390,933 (77.5)	78,262 (73.1)	3,373 (74.3)
Spikevax (Moderna)	47,118 (9.3)	6,116 (5.7)	278 (6.1)
Vaxzevria (AstraZeneca)	66,251 (13.1)	22,678 (21.2)	889 (19.6)

Figure 6 • Daily counts of controls, symptomatic and hospitalized cases (averaged over the last 7 days), data collected from January 1st to December 12, 2021



Abbreviations: Sympto+ (cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection (cases); Sympto+ & H (hospitalized cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection and hospital admission for Covid-19. Sympto- (controls): individuals with symptoms non-related to SARS-CoV-2 infection.

Appendix 3 •

Table 2. • Covid-19 vaccine effectiveness (in %) against symptomatic infections and hospitalizations among persons aged 50 years or over, according to the time elapsed since the injection of each vaccine dose, data collected from January 1st to December 12, 2021.

Age	**50 years or over**		**50 years or over with comorbity**	
Vaccination status	VE(S+)	VE(H+)	VE(S+)	VE(H+)
D1: 0-14	-20.8 (-23.3--18.3)	15.0 (11.1-18.8)	-5.5 (-8.5--2.4)	28.0 (24.2-31.7)
D1: 15-21	26.2 (23.9-28.4)	59.9 (56.8-62.9)	28.5 (25.5-31.6)	61.6 (58.4-64.9)
D1: 22-28	44.5 (42.5-46.6)	76.0 (73.7-78.3)	44.6 (41.9-47.3)	76.3 (73.8-78.9)
D2: 0-7	50.4 (47.4-53.4)	76.7 (73.0-80.4)	57.6 (54.0-61.2)	80.0 (76.5-83.5)
D2: 8-14	70.0 (68.1-71.8)	84.5 (82.1-87.0)	71.0 (68.6-73.5)	85.6 (83.0-88.2)
D2: 15-30	82.4 (81.5-83.2)	90.9 (89.6-92.2)	82.9 (81.7-84.1)	91.0 (89.5-92.4)
D2: 1M-2M	76.7 (76.0-77.4)	94.1 (93.4-94.8)	78.4 (77.4-79.3)	94.5 (93.9-95.2)
D2: 2M-3M	70.5 (69.7-71.4)	93.5 (92.8-94.2)	69.9 (68.5-71.2)	93.2 (92.4-94.0)
D2: 3M-4M	65.7 (64.8-66.7)	92.7 (92.0-93.4)	66.0 (64.6-67.4)	92.5 (91.6-93.3)
D2: 4M-5M	56.2 (55.2-57.3)	91.7 (91.0-92.4)	56.2 (54.5-57.9)	91.4 (90.6-92.2)
D2: 5M-6M	53.7 (52.6-54.8)	92.2 (91.6-92.8)	49.6 (47.8-51.5)	91.2 (90.4-91.9)
D2: > 6M	53.1 (51.9-54.3)	89.8 (89.1-90.6)	47.0 (44.9-49.0)	88.1 (87.0-89.1)
DR: 1-7	56.6 (54.3-59.0)	91.3 (89.7-93.0)	51.7 (47.9-55.5)	90.2 (88.1-92.2)
DR > 7	91.9 (91.6-92.3)	98.7 (98.5-99.0)	90.5 (89.9-91.1)	98.4 (98.2-98.7)

Table 3. • Covid-19 vaccine effectiveness (in %) by age group against symptomatic infections and hospitalizations among persons aged 50 years or over, according to the time elapsed since the injection of each vaccine dose, data collected from January 1st to December 12, 2021.

Age	50-64 yr		65-74 yr		75-85 yr		≥ 85 yr	
Vaccination status	VE(S+)	VE(H+)	VE(S+)	VE(H+)	VE(S+)	VE(H+)	VE(S+)	VE(H+)
D1: 0-14	-17.2 (-20.4--14.0)	13.3 (5.8-20.8)	-23.7 (-29.2--18.2)	6.5 (-2.1-15.2)	-29.9 (-37.7--22)	-4.9 (-15.5-5.6)	-20.5 (-28.8--12.2)	2.0 (-8.4-12.4)
D1: 15-21	33.0 (30.1-35.9)	72.2 (67.2-77.3)	25.2 (20.4-30.0)	56.7 (50.1-63.2)	15.9 (9.0-22.9)	46.0 (37.8-54.2)	15.9 (7.5-24.3)	39.1 (29.3-49.0)
D1: 22-28	47.0 (44.3-49.8)	83.0 (78.8-87.1)	45.8 (41.6-50.0)	80.6 (76.3-84.9)	42.9 (37.4-48.5)	68.6 (62.6-74.6)	23.4 (14.6-32.2)	52.3 (43.2-61.5)
D2: 0-7	51.0 (46.9-55.2)	82.5 (75.4-89.5)	56.6 (50.7-62.6)	86.6 (81.1-92.2)	49.3 (41.5-57.1)	73.0 (64.8-81.2)	55.6 (47.1-64.2)	60.7 (49.0-72.5)
D2: 8-14	71.4 (69.0-73.8)	80.2 (74.1-86.2)	73.5 (69.8-77.3)	82.7 (76.9-88.5)	67.4 (62.2-72.5)	82.3 (76.6-88.0)	68.4 (62.8-74.0)	85.0 (80.0-90.1)
D2: 15-30	81.1 (79.9-82.2)	91.8 (89.4-94.2)	83.8 (81.9-85.6)	89.1 (85.9-92.3)	86.4 (84.4-88.5)	92.6 (90.2-94.9)	84.7 (82.2-87.2)	89.8 (86.7-92.8)
D2: 1M-2M	75.9 (75.0-76.8)	95.4 (94.4-96.5)	75.6 (74.0-77.2)	94.0 (92.6-95.4)	82.5 (80.8-84.3)	93.8 (92.3-95.3)	82.3 (80.2-84.4)	92.0 (90.2-93.8)
D2: 2M-3M	71.4 (70.4-72.4)	95.5 (94.5-96.5)	70.1 (68.3-71.9)	92.6 (91.2-94.1)	71.7 (68.7-74.6)	90.1 (87.8-92.5)	75.9 (72.7-79.1)	90.7 (88.4-93.1)
D2: 3M-4M	68.4 (67.4-69.5)	94.6 (93.6-95.7)	62.8 (60.7-64.9)	92.4 (91.0-93.8)	63.4 (59.9-66.8)	88.4 (86.1-90.8)	60.9 (56.0-65.8)	82.7 (78.9-86.6)
D2: 4M-5M	60.3 (59.1-61.6)	94.7 (93.7-95.7)	57.1 (54.9-59.3)	91.0 (89.5-92.5)	52.3 (48.2-56.3)	87.0 (84.6-89.4)	38.2 (31.0-45.4)	72.1 (66.6-77.5)
D2: 5M-6M	59.3 (58.1-60.6)	95.5 (94.7-96.3)	52.5 (50.2-54.9)	92.4 (91.2-93.5)	44.1 (39.7-48.5)	82.6 (79.9-85.4)	30.4 (23.0-37.8)	73.2 (68.3-78.1)
D2: > 6M	58.6 (57.2-60.0)	94.0 (92.9-95.2)	52.8 (50.2-55.4)	90.0 (88.3-91.6)	36.9 (32.0-41.8)	82.2 (79.5-85.0)	27.4 (20.0-34.8)	69.8 (64.8-74.8)
DR: 1-7	64.8 (62.0-67.6)	95.7 (93.1-98.3)	53.4 (49.0-57.9)	93.1 (90.4-95.8)	38.3 (28.9-47.6)	85.8 (80.7-91.0)	37.3 (21.5-53.0)	62.8 (47.9-77.8)
DR > 7	93.0 (92.3-93.6)	98.8 (98.0-99.6)	92.5 (91.8-93.1)	99.0 (98.7-99.4)	89.9 (88.8-90.9)	98.2 (97.7-98.7)	89.0 (87.5-90.5)	97.3 (96.5-98.1)

Table 4. • Covid-19 vaccine effectiveness (in %) by variant of concern against symptomatic infections and hospitalizations among persons aged 50 years or over, according to the time elapsed since the injection of each vaccine dose, data collected from January 1st to December 12, 2021.

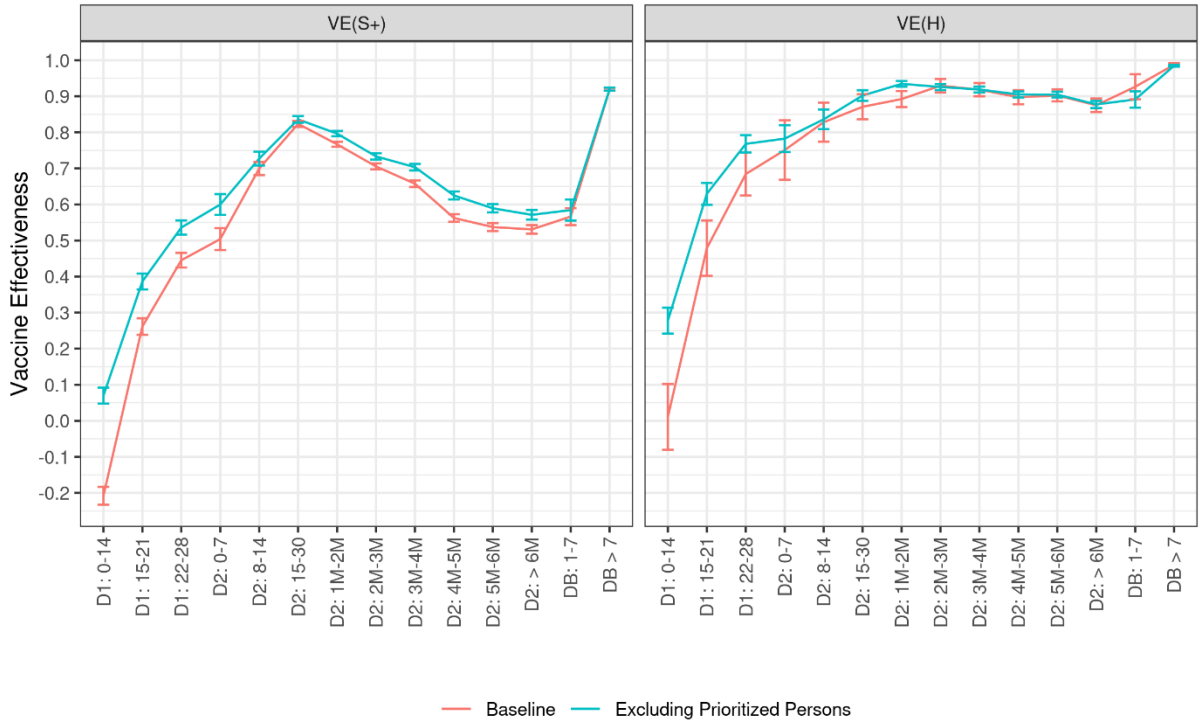
Variant	Original strain		Alpha		Beta/Gamma		Delta	
Vaccination status	VE(S+)	VE(H+)	VE(S+)	VE(H+)	VE(S+)	VE(H+)	VE(S+)	VE(H+)
D1: 0-14	-32.6 (-43.5--21.7)	1.7 (-16.7-20.1)	-23.9 (-27.6--20.2)	4.8 (-1.3-10.8)	-20.1 (-33.7--6.4)	2.2 (-20.4-24.7)	4.5 (-0.2-9.2)	16.7 (6.0-27.4)
D1: 15-21	24.0 (14.3-33.6)	61.3 (48.2-74.4)	26.5 (23.2-29.8)	56.6 (51.9-61.3)	4.6 (-11.2-20.4)	40.8 (19.3-62.4)	38.9 (34.6-43.2)	63.3 (55.4-71.3)
D1: 22-28	49.4 (41.7-57.1)	69.6 (57.4-81.8)	43.8 (40.8-46.8)	75.7 (72.3-79.2)	30.6 (17.3-43.8)	55.8 (36.8-74.7)	51.3 (47.4-55.2)	79.9 (73.9-85.8)
D2: 0-7	64.6 (51.6-77.6)	80.8 (62.5-99.2)	58.4 (53.9-62.9)	79.4 (74.2-84.7)	28.3 (3.7-52.9)	50.7 (17.3-84.1)	48.4 (43.7-53.2)	79.3 (72.7-85.9)
D2: 8-14	82.3 (75.5-89.2)	93.6 (86.8-100.4)	75.6 (72.7-78.6)	87.9 (84.3-91.4)	57.7 (42.0-73.4)	79.2 (59.1-99.3)	69.4 (66.9-72.0)	80.6 (75.8-85.3)
D2: 15-30	91.9 (88.3-95.5)	95.8 (91.6-100)	91.3 (90.1-92.5)	93.7 (91.8-95.6)	84.2 (78.2-90.3)	98.2 (95.7-100.8)	78.6 (77.4-79.9)	89.3 (87.2-91.4)
D2: 1M-2M	84.5 (78.5-90.6)	97.2 (93.1-101.3)	87.0 (85.8-88.3)	95.2 (94.0-96.4)	68.0 (59.1-76.9)	90.6 (83.3-97.8)	74.0 (73.1-74.8)	94.1 (93.3-95.0)
D2: 2M-3M	88.7 (78.9-98.5)	93.3 (78.7-107.9)	84.0 (81.8-86.2)	96.9 (95.4-98.3)	61.2 (45.7-76.8)	96.7 (90.1-103.3)	68.6 (67.6-69.5)	92.7 (91.9-93.6)
D2: 3M-4M							64.6 (63.6-65.5)	92.2 (91.4-93.0)
D2: 4M-5M							56.3 (55.2-57.4)	91.5 (90.7-92.2)
D2: 5M-6M							53.8 (52.7-54.9)	92.0 (91.4-92.6)
D2: > 6M							52.4 (51.1-53.7)	89.5 (88.7-90.3)
DR: 1-7							55.9 (53.5-58.3)	90.9 (89.1-92.7)
DR > 7							91.9 (91.5-92.3)	98.7 (98.5-99.0)

Delta variant cases are approximated by cases from July 7 to December 12, 2021.

Appendix 4 • Sensitivity analyses

Presence of comorbidities is derived either from prior knowledge from the health insurance on the person status or because a physician recommended to prioritize a non-eligible (at-the-time) individual during the vaccination campaign. Thus, the latter is rare for unvaccinated persons. An alternative specification excludes from the sample persons who are classified as comorbid on a physician recommendation in order to benefit from the vaccine in priority. In this alternative specification, the odd ratio in the early period post first injection indicates a decreased risk [OR: 0.93 (CI 95% 91-95)] instead of the increase risk observed in the baseline specification. The comparison of our estimates to this alternative may inform on the extent of the downward bias due to targeting individuals on unobserved factors. The downward bias in the vaccine effectiveness against symptomatic diseases is very limited in the first month following the second injection, but could reach six percentage points after four months. In contrast, vaccine effectiveness against hospitalization are very similar in both alternatives.

Figure 7 • Covid-19 vaccine effectiveness against symptomatic infections and hospitalizations among persons aged 50 years or over, according to the time elapsed since the injection of each vaccine dose, data collected from January 1st to December 12, 2021, when excluding persons prioritized by a physician for vaccine administration.



Appendix 5 • Matching characteristics

Among persons aged 50 years or over hospitalized for Covid-19 (data source: SI-VIC), 72 % have a matched positive RT-PCR test, collected from fifteen days before admission to the end of their stay (source: SI-DEP) over our analysis period. Among persons aged 50 years or over hospitalized for Covid-19 (data source: SI-VIC), 73 % have a match in the VAC-SI register, which covers nearly all French residents and allows to recover the vaccination status. Among persons aged 50 years reporting symptoms in the last seven days before a RT-PCR test (data source: SI-DEP), 84 % have a match in the VAC-SI register, thus a known vaccination status.

Vaccine-induced and naturally acquired protection against Omicron symptomatic Covid-19 and severe outcomes: Evidence from the Covid-19 surveillance national databases in France

1. Introduction

First designated by WHO as a variant of concern on the 26th of November, the SARS-Cov-2 Omicron (B.1.1.529) variant rapidly became dominant in multiple countries worldwide. In the following days, several Omicron cases were reported in France. By the 13th of December, this variant represented about 10% of positive cases while the Delta variant was still largely circulating in the country.
By that time, a large portion of the population had already been infected or vaccinated. Before the Omicron upsurge, observational studies indicated that naturally acquired immunity offered equal or greater protection against SARS-CoV-2 infections compared to individuals receiving two doses of an mRNA vaccine, a protection lasting for over one year with mild to no decline over time. Hybrid immunity (vaccination and previous infection) conferred the greatest protection against infections (Pilz et al. 2022). Nonetheless, early evidence pointed towards a reduced immunity against Omicron infections following both vaccination (Andrews et al. 2021 ; Nyberg et al. 2022) and infection (Altarawneh et al., 2022). The effectiveness of previous infection in preventing symptomatic reinfection was 92% (95% CI, 88 – 95) against the Delta variant but 56 % (95% CI, 51 – 61) against the Omicron variant (Altarawneh et al., 2022). However, vaccine-induced immunity against severe forms of the diseases was equivalent against both variants (Auvigne et al., 2022). Yet, there is still limited evidence on the protection against Omicron symptomatic infections and severe forms of Covid-19 , with little knowledge on the relative role of past infection and of the multiple vaccination doses, at the different stages of disease progression. A comparison of vaccine-induced and naturally acquired protection against the Omicron variant can guide epidemic public health responses.
We investigated the impact of vaccination against Covid-19 (primary vaccination scheme and booster dose), and of previous SARS-CoV-2 infection, at the individual level, on the risk of Covid-19 symptomatic infections, inpatient admissions, ICU admissions and deaths attributable to the Omicron variant.

2. Material and methods

2.1 Data

Data sources on vaccination against Covid-19 (VAC-SI), SARS-Cov-2 testing (SI-DEP), and on the hospitalization of people infected with SARS CoV-2 (SI-VIC), as well as the data linkage methods have been described previously (Suarez Castillo et al. 2022, Auvigne et al. 2022): further description is reported in Appendix B. The data used were extracted on the 4th of February 2022, for observations from December 13, 2021 to January 31, 2022.
In France, following the national surveillance strategy, part of positive RT-PCR samples are submitted to mutation screening in order to characterize the likely variant. A set of predefined mutations are targeted to identify the circulating variants with good confidence, and results are centralized into the SI-DEP databases. Over our study period, the following characteristics could be reported by laboratories for each analysed sample: detection of Spike mutation E484K, encoded as “A”, detection of Spike mutation L452R encoded as “C”, detection of at least one of Spike deletion 69-70; mutations K417N; N501Y ; S371L-S373P; Q493R encoded as “D”, according to the following codes (0: not detected; 1: detected; 8: searched but inconclusive; 9: not searched). Code D was added to the operating system by on the 20th of December, but it took a few weeks before this modification was fully implemented. During the transition period, the absence of E484K and L452R (A0C0) was considered as a high suspicion for Omicron since none of these mutations is present on this strain. In this study, we consider individuals infected with SARS-CoV2 variant with A0C0 or D1 mutation profiles, as Omicron infections. Interpretable screened samples which did not meet criteria for Omicron were categorized as Delta cases.

2.2 Study design

We used a two-step analysis to estimate vaccine effectiveness against severe forms of Covid-19, defined as leading to hospitalizations, intensive care units (ICU) admissions, or inpatient deaths as described previously (Suarez Castillo et al. 2022). First, we used a test-negative case–control design to estimate naturally acquired, vaccine-induced or hybrid immunity against symptomatic Covid-19 infections. Then, we performed a survival analysis among individuals with symptomatic forms of Covid-19, to evaluate a possible additional risk reduction provided by the immune status against severe forms of the disease.

2.3 Statistical analysis

Symptomatic positive individuals were randomly matched to controls (symptomatic negative individuals) on age (ten-year age brackets), sex, area of residence (NUTS-3 level), week of testing and presence or absence of a comorbidity qualifying for prioritization in the vaccination campaign. The odds ratios (OR) were estimated using a conditional logistic regression according to their immune status. We then estimated the risk of severe outcome (hospitalization, ICU admission, or death) among individuals with RT-PCR-confirmed SARS-CoV-2 symptomatic infection, according to their immune status. We fitted a Cox survival model on the time interval between the date of the test and the date of the inpatient admission, ICU-admission or death, if applicable, or the end of the follow-up period. The latter was censored at 15 days post-test or at the end of the study period (January 31, 2022). A hazard ratio of hospitalization (respectively ICU admission or death) was then estimated according to the immune status, controlling for the same variables as those used in the case-control study.

2.4 Study population

We included tests performed on individuals: *(i)* aged 18 years or over; *(ii)* tested by RT-PCR, to focus on recent infections for which the causative variant could be identified; *(iii)* reporting symptoms in the seven days prior to the time of screening. We included only individuals present in the VAC-SI register and with non-missing information about the presence or absence of comorbidities considered for prioritizing vaccine injection in the 2021 French vaccination campaign. To study severe forms of Covid-19, we included the inpatients aged 18 years or over that were present in all three databases (SI-VIC, SI-DEP and VAC-SI). In addition, *(i)* persons hospitalized and infected by SARS-CoV-2 but whose admission was not attributable to Covid-19 (persons hospitalized for other conditions may have been systematically screened) were not considered as Covid-19 inpatient admissions; and *(ii)* we excluded inpatients with no symptomatic positive RT-PCR test recorded within 15 days before hospital admission, or within two days after. In case of symptomatic positive RT-PCR test within two days after admission, inpatients are reclassified as tested on the day of admission to avoid negative durations in the survival analysis, and kept in the analysis.
We defined a previous infection as individuals with a confirmed SARS-CoV-2 infection at least 60 days prior to the time of screening (in coherence with the European Surveillance System definition of suspected cases of SARS-CoV-2 reinfection). A confirmed SARS-CoV-2 infection was defined based on a previous positive RT-PCR, antigenic or serological test. Without evidence of prior infection, the immune status was defined according to the time elapsed since each vaccine dose (first, second and booster dose). With evidence of prior infection, four distinct subcategories were used to define the immune status: unvaccinated, vaccinated with only one injection, full primary vaccination cycle with (at least)[1] two doses but without booster dose, and full primary vaccination cycle with booster dose.

3. Results

3.1. Description of the study population

[1] In France, immunocompromised persons needed more than two injections to complete their primary cycle, and vaccination with only one injection and evidence of prior infection was sufficient to complete the primary cycle.

Over the period from December 13, 2021, to January 31, 2022, 4 472 927 individuals were tested by RT-PCR and reported symptoms at the time of screening. 3 332 529 (75%) of them were aged 18 years or over and 2 884 996 (87%) of the latter were successfully linked to vaccination data with non-missing data on comorbidities. We excluded 183 004 individuals with unusual vaccination schemes. We found at least one SI-DEP test sampled before the study period for 39 % of the remaining individuals,[2] 18 % of whom had a confirmed past infection history. Overall, 7% of the remaining individuals, 193 789 had a known past infection prior to the time of screening. Appendix A provides more details on testing history in the analytic sample. 1 541 995 (57 %) were tested positive for SARS-CoV-2. Finally, 761 744 (50 %) were classified as Omicron cases and 166 009 (11 %) were classified as Delta cases.

The study population for the test-negative design analysis consisted of 926 376 positive cases (1 377 cases were excluded because of the lack of similar controls) and 1 852 752 controls (two matched controls for each case). Almost none of them was vaccinated at the beginning of the year 2021, 50% had received one dose by June, the 18th of 2021, and two doses by July, the 24th of 2021 (Appendix A). By the end of 2021, 84% of them had completed their primary vaccination cycle and 33 % of them had received a booster dose.

The study population for the survival analyses consisted of the 927 753 persons with confirmed SARS-CoV-2 symptomatic infection associated with either the Omicron or the Delta variant. Among the 761 744 Omicron cases, there were 2 994 hospitalizations, 387 ICU admissions and 407 inpatient deaths recorded in SI-VIC. Among the 166 009 Delta cases, there were 3 367 hospitalizations, 1 006 ICU admissions and 524 inpatient deaths recorded in SI-VIC. We did not consider the 8 692 hospitalizations that did not meet the criteria listed in the study population section.

3.2. Vaccine effectiveness against Omicron and Delta symptomatic infections

Among vaccinated persons aged 18 years and over, the protection against Omicron symptomatic infections reached 43 % in the first month following the second dose (Table 1, OR: 0.57 (0.55-0.59), equivalent to a vaccine effectiveness of 100*(1-OR) = 43%) and 64 % two weeks after the booster dose (OR: 0.36 (0.36-0.37)). These levels were largely below those reached against Delta symptomatic infections for similar immune statuses (respectively 78 % and 91 %). Additionally, the waning of protection after vaccine injections was much faster against Omicron than Delta infections (Figure 1, top panel). Vaccine effectiveness against Omicron symptomatic infections decreased by 14 p.p. from one week after the booster to three months after. Whereas, vaccine effectiveness against Delta symptomatic infections was stable above 90 % up to three months following the booster dose (Table 1). The age-specific analyzes underlie that most of the waning of the protection against Omicron after the booster dose happens among persons aged 65 years and over (Appendix C).

3.3. Natural and Hybrid immunity against Omicron and Delta symptomatic infections

The protection conferred by a prior infection among unvaccinated persons was of 51 % against symptomatic infections with the Omicron variant (Table 1), while it was 89 % with the Delta variant. Hybrid immunity (prior infection and at least one injection) reached 67 % protection and 81 % with a booster dose against Omicron, and even higher levels (>90%) against Delta.

3.4. Protection against severe outcomes following Omicron or Delta symptomatic infections

Following a symptomatic infection with either the Omicron or the Delta variant, most immune statuses (naturally acquired, vaccine-induced or hybrid) conferred similar protection levels against diseases progression leading to inpatient admission (Figure 1). Only the protection against Omicron-induced severe outcomes was significantly lower than against the Delta variant, from three months after the second injection to the week following the booster dose. These conclusions are similar for protection

[2] As a benchmark, by August 2021, about 60 % of the 25-64 year-olds and 40 % of the 65 and above year-olds had already realized a Covid-19 virological test (Insee France Portrait Social 2021).

against ICU-admissions or in-hospital deaths (Table 2, Figure 2).

4. Discussion

We used three large and exhaustive datasets on Covid-19 screening, vaccination and hospitalizations in France to assess the protection conferred by naturally acquired, vaccine-induced and hybrid immunity during the concomitant Omicron and Delta epidemic waves in France. We found a lower vaccine effectiveness against symptomatic diseases induced by Omicron, but similar levels of protection of vaccines against disease progression to severe forms of the disease, in particular for individuals with a full primary vaccination scheme with a booster dose. Vaccine effectiveness against Omicron-induced symptomatic forms decreased over time at a faster pace than that against Delta-induced symptomatic forms after the completion of the primary vaccination cycle. While we found no evidence of waning immunity against Delta symptomatic infections up to three months following the booster dose, vaccine effectiveness against Omicron symptomatic infections decreased over time by 14 percentage points. However, protection against severe forms declined much slower and vaccine effectiveness remained high up to three months following the booster dose, above 90 % for both variants. The protection against reinfection conferred by a previous SARS-Cov-2 infection was almost 40 p.p. higher against Delta than against Omicron. The highest protection against Omicron symptomatic infections was conferred by hybrid-immunity, acquired after both SARS-CoV-2 infection and a full vaccination cycle with a booster dose., Prior infection did not conferred additional protection against severe forms of the diseases to those already fully vaccinated with a booster dose.
Our findings show that the drop in vaccine protection against the Omicron variant seems mainly due to a greater capacity of this variant (compared to the Delta variant) to escape vaccine protection at all stages of the vaccination cycle, combined with a faster decline in vaccine protection. The exhaustiveness of the databases and the possibility to match them together to get information at an individual scale are the great strengths of this study. However, the observational nature of the data itself also brings about some limitations. We used a test-negative design in order to reduce selection biases that are difficult to measure such as health-seeking behavior, access to testing and case ascertainment. This method allowed limiting the effect of the evolution of screening policies on the propensity of getting tested. Yet, test-negative designs rely on strong assumptions, the applicability of which is difficult to assess and may have varied over the study period (Jackson and Nelson, 2013; Dean et al, 2021). The control variables that are used to limit the selection bias in immune statuses may not be sufficient, as a given vaccination status or the existence of a prior infection at a given time may reflect unobserved factors related to the risk of infection or the likelihood to develop a severe form of Covid-19. In addition, being vaccinated or aware of its immune status could affect: *(i)* the perception of the need to be screened in case of symptoms and *(ii)* the probability of exposure to the virus, if being vaccinated leads to an increase in social interactions or to a lesser application of barrier gestures. The definition of immune statuses was error prone as many infections remain undetected, given (i) the frequency of asymptomatic infections, and (ii) the imperfection in data linkage that may impair the tracing of past infections. In this sense, naturally acquired and hybrid immunity might be underestimated. The screening methods used to identify variants are imperfect: to maximize external validity and population coverage, we used a rather liberal definition of the Delta and Omicron variants. Using an alternative more conservative definition as in Auvigne et al. (2022) does not change qualitatively our results (Appendix C). The matching between the three databases was not perfect, which led to sample restrictions that could affect the representativeness of the results obtained. However, the corrections made to improve the matching between databases have not resulted in significant revisions of the results. Our findings only relate to vaccine effectiveness against symptomatic infections, but these symptoms were self-reported, without medical advice. We did not attempt to distinguish results by type of vaccine, although the durability of vaccine protection and the ability to protect against different variants may differ (EPI-PHARE, 2021; Andrews et al., 2021).

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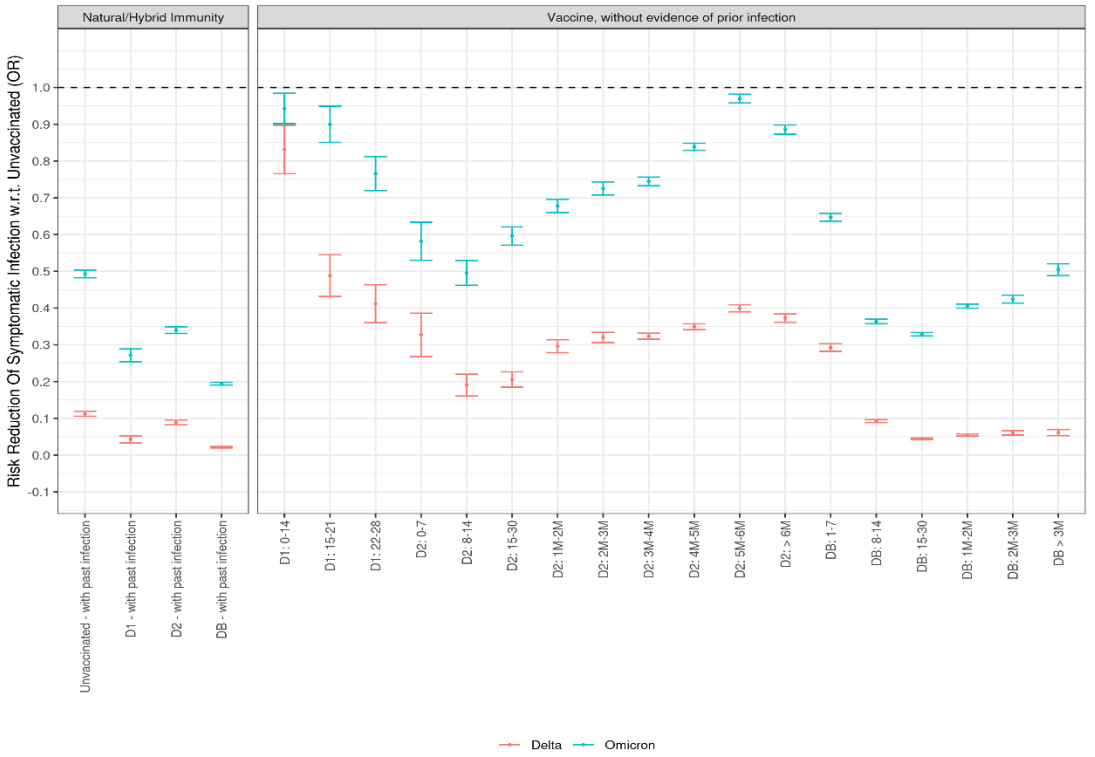
Figure 1 • Variant-specific odd ratios of symptomatic infections and hazard ratios of hospitalizations after symptomatic infections among persons aged 18 years or over, according to the time elapsed since the injection of each vaccine dose and evidence of prior infection. Data collected from December 13th, 2021 to January 31th, 2022



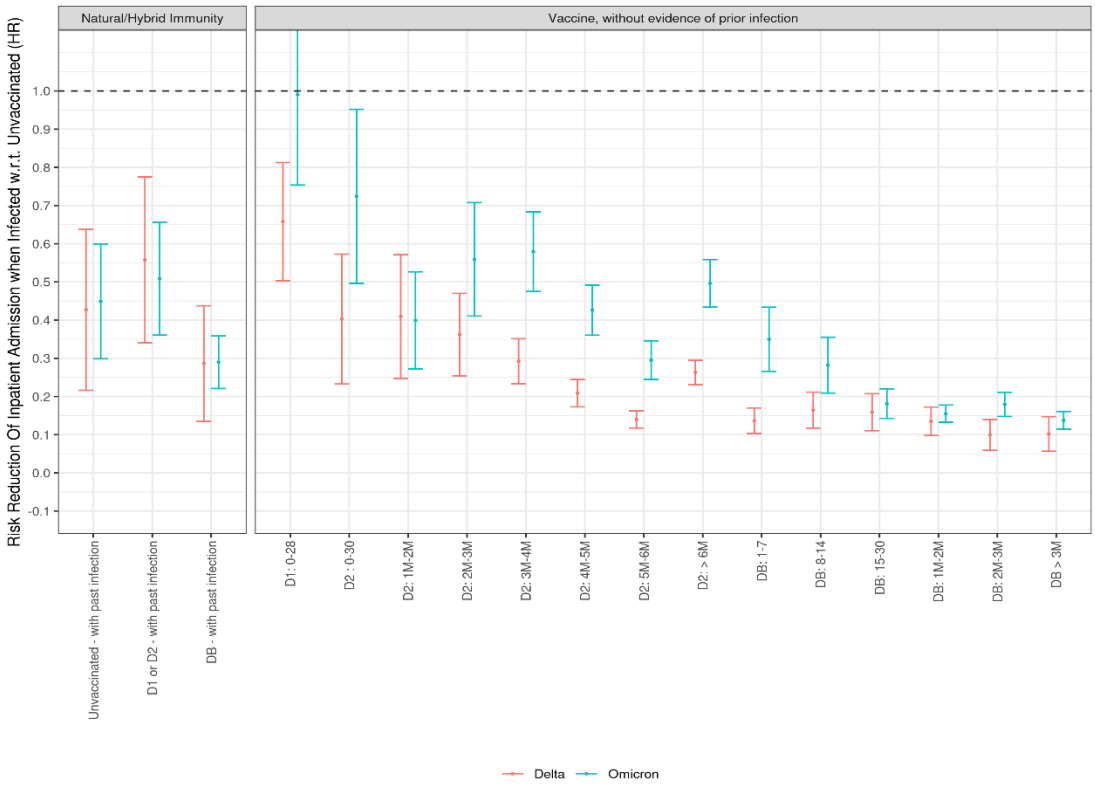


Table 1. Protection against Omicron or Delta symptomatic and inpatient admissions for Covid-19. Odd ratios of symptomatic infections and hazard ratios of hospitalizations after symptomatic infections among persons aged 18 years or over, according to the time elapsed since the injection of each vaccine dose and evidence of prior infection. Data collected from December 13th, 2021 to January 31th, 2022

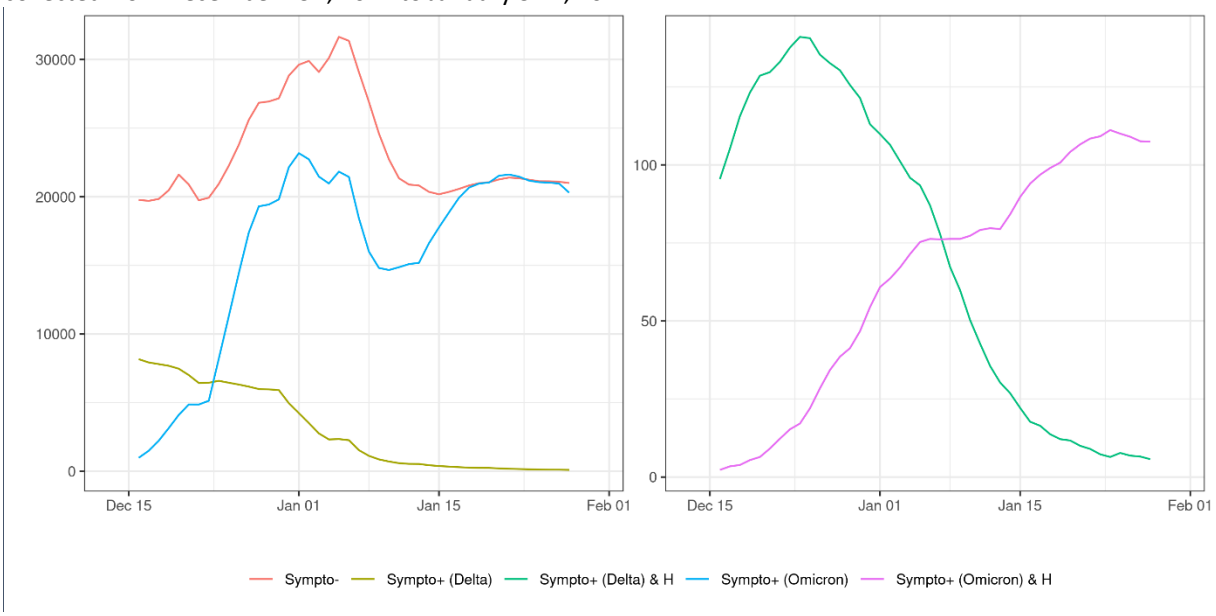
	Omicron			Delta		
	Risk Reduction against		Protection	Risk Reduction against		Protection
Immune Status	Symptomatic Infection (OR)	Inpatient Admission among Symptomatic Cases (HR)	1 – OR x HR	Symptomatic Infection (OR)	Inpatient Admission among Symptomatic Cases (HR)	1 – OR x HR
Vaccinated (réf.: Unvaccinated without prior infection evidence)						
D1: 0-28	0.88[0.86-0.91]	0.99[0.75-1.23]	0.12[-0.09-0.34]	0.62[0.59-0.66]	0.66[0.50-0.81]	0.59[0.49-0.69]
D2: 0-30	0.57[0.55-0.59]	0.72[0.50-0.95]	0.59[0.46-0.72]	0.22[0.20-0.23]	0.40[0.23-0.57]	0.91[0.87-0.95]
D2: 1M-2M	0.68[0.66-0.70]	0.40[0.27-0.53]	0.73[0.64-0.82]	0.30[0.28-0.31]	0.41[0.25-0.57]	0.88[0.83-0.93]
D2: 2M-3M	0.73[0.71-0.74]	0.56[0.41-0.71]	0.59[0.49-0.70]	0.32[0.31-0.33]	0.36[0.25-0.47]	0.88[0.85-0.92]
D2: 3M-4M	0.74[0.73-0.76]	0.58[0.48-0.68]	0.57[0.49-0.65]	0.32[0.32-0.33]	0.29[0.23-0.35]	0.91[0.89-0.92]
D2: 4M-5M	0.84[0.83-0.85]	0.43[0.36-0.49]	0.64[0.59-0.70]	0.35[0.34-0.36]	0.21[0.17-0.24]	0.93[0.91-0.94]
D2: 5M-6M	0.97[0.96-0.98]	0.30[0.24-0.35]	0.71[0.66-0.76]	0.40[0.39-0.41]	0.14[0.12-0.16]	0.94[0.94-0.95]
D2: > 6M	0.89[0.87-0.90]	0.50[0.43-0.56]	0.56[0.51-0.62]	0.37[0.36-0.38]	0.26[0.23-0.29]	0.90[0.89-0.91]
DB: 1-7	0.65[0.64-0.66]	0.35[0.27-0.43]	0.77[0.72-0.83]	0.29[0.28-0.30]	0.14[0.10-0.17]	0.96[0.95-0.97]
DB: 8-14	0.36[0.36-0.37]	0.28[0.21-0.36]	0.90[0.87-0.92]	0.09[0.09-0.10]	0.16[0.12-0.21]	0.98[0.98-0.99]
DB: 15-30	0.33[0.32-0.33]	0.18[0.14-0.22]	0.94[0.93-0.95]	0.04[0.04-0.05]	0.16[0.11-0.21]	0.99[0.99-1.00]
DB: 1M-2M	0.41[0.40-0.41]	0.16[0.13-0.18]	0.94[0.93-0.95]	0.05[0.05-0.06]	0.14[0.10-0.17]	0.99[0.99-0.99]
DB: 2M-3M	0.42[0.41-0.43]	0.18[0.15-0.21]	0.92[0.91-0.94]	0.06[0.05-0.07]	0.10[0.06-0.14]	0.99[0.99-1.00]
DB > 3M	0.50[0.49-0.52]	0.14[0.11-0.16]	0.93[0.92-0.94]	0.06[0.05-0.07]	0.10[0.06-0.15]	0.99[0.99-1.00]
Naturally acquired Immunity (réf.: Unvaccinated without prior infection evidence)						
Unvaccinated	0.49[0.48-0.50]	0.45[0.30-0.60]	0.78[0.70-0.85]	0.11[0.11-0.12]	0.43[0.22-0.64]	0.95[0.93-0.98]
D1 or D2	0.33[0.32-0.34]	0.51[0.36-0.66]	0.83[0.78-0.88]	0.08[0.08-0.09]	0.56[0.34-0.77]	0.95[0.94-0.97]
DB	0.19[0.19-0.20]	0.29[0.22-0.36]	0.94[0.93-0.96]	0.02[0.02-0.02]	0.29[0.13-0.44]	0.99[0.99-1.00]

Table 2. Risk Reduction (Hazard Ratio) against Inpatient Admission, ICU Admission, Inpatient Death among Symptomatic Cases aged 18 years and older, according to the time elapsed since the injection of each vaccine dose and evidence of prior infection. Data collected from December 13th, 2021 to January 31th, 2022

	Omicron			Delta		
Immune Status	Inpatient Admission	ICU Admission	Death	Inpatient Admission	ICU Admission	Death
Vaccinated (réf.: Unvaccinated without prior infection evidence)						
D1: 0-28	0.99[0.75-1.23]	1.09[0.49-1.69]	1.09[0.53-1.65]	0.66[0.50-0.81]	0.43[0.21-0.65]	0.93[0.48-1.37]
D2: 0-30	0.72[0.50-0.95]	0.54[0.06-1.02]	0.71[0.14-1.29]	0.40[0.23-0.57]	0.32[0.04-0.60]	0.44[0.01-0.87]
D2: 1M-2M	0.40[0.27-0.53]	0.32[0.06-0.59]	0.38[0.10-0.67]	0.41[0.25-0.57]	0.52[0.21-0.84]	0.14[-0.13-0.42]
D2: 2M-3M	0.56[0.41-0.71]	0.22[0.00-0.43]	0.12[-0.05-0.29]	0.36[0.25-0.47]	0.35[0.16-0.54]	0.11[-0.04-0.26]
D2: 3M-4M	0.58[0.48-0.68]	0.25[0.09-0.42]	0.43[0.22-0.65]	0.29[0.23-0.35]	0.18[0.10-0.26]	0.31[0.12-0.49]
D2: 4M-5M	0.43[0.36-0.49]	0.15[0.07-0.24]	0.30[0.14-0.45]	0.21[0.17-0.24]	0.17[0.12-0.23]	0.37[0.20-0.53]
D2: 5M-6M	0.30[0.24-0.35]	0.19[0.11-0.28]	0.32[0.15-0.48]	0.14[0.12-0.16]	0.10[0.07-0.13]	0.20[0.11-0.28]
D2: > 6M	0.50[0.43-0.56]	0.32[0.21-0.42]	0.51[0.36-0.65]	0.26[0.23-0.29]	0.14[0.11-0.18]	0.35[0.25-0.44]
DB: 1-7	0.35[0.27-0.43]	0.12[0.02-0.22]	0.29[0.07-0.50]	0.14[0.10-0.17]	0.06[0.03-0.10]	0.29[0.15-0.43]
DB: 8-14	0.28[0.21-0.36]	0.12[0.02-0.21]	0.14[0.00-0.28]	0.16[0.12-0.21]	0.07[0.02-0.12]	0.24[0.09-0.39]
DB: 15-30	0.18[0.14-0.22]	0.13[0.07-0.20]	0.18[0.08-0.28]	0.16[0.11-0.21]	0.15[0.07-0.23]	0.15[0.02-0.29]
DB: 1M-2M	0.16[0.13-0.18]	0.06[0.03-0.08]	0.15[0.10-0.21]	0.14[0.10-0.17]	0.13[0.07-0.19]	0.16[0.06-0.25]
DB: 2M-3M	0.18[0.15-0.21]	0.08[0.04-0.13]	0.14[0.08-0.20]	0.10[0.06-0.14]	0.08[0.00-0.15]	0.09[0.01-0.16]
DB > 3M	0.14[0.11-0.16]	0.05[0.01-0.09]	0.13[0.08-0.17]	0.10[0.06-0.15]	0.03[-0.03-0.09]	0.10[0.01-0.19]
Naturally acquired Immunity (réf.: Unvaccinated without prior infection evidence)						
Unvaccinated	0.45[0.30-0.60]	0.14[-0.05-0.33]	0.24[-0.09-0.58]	0.43[0.22-0.64]	0.54[0.10-0.97]	1.06[0.02-2.10]
D1 or D2	0.51[0.36-0.66]	0.42[0.12-0.72]	0.34[0.07-0.61]	0.56[0.34-0.77]	0.39[0.08-0.71]	0.90[0.17-1.62]
DB	0.29[0.22-0.36]	0.16[0.05-0.28]	0.19[0.06-0.32]	0.29[0.13-0.44]	0.13[-0.05-0.30]	0.11[-0.11-0.33]

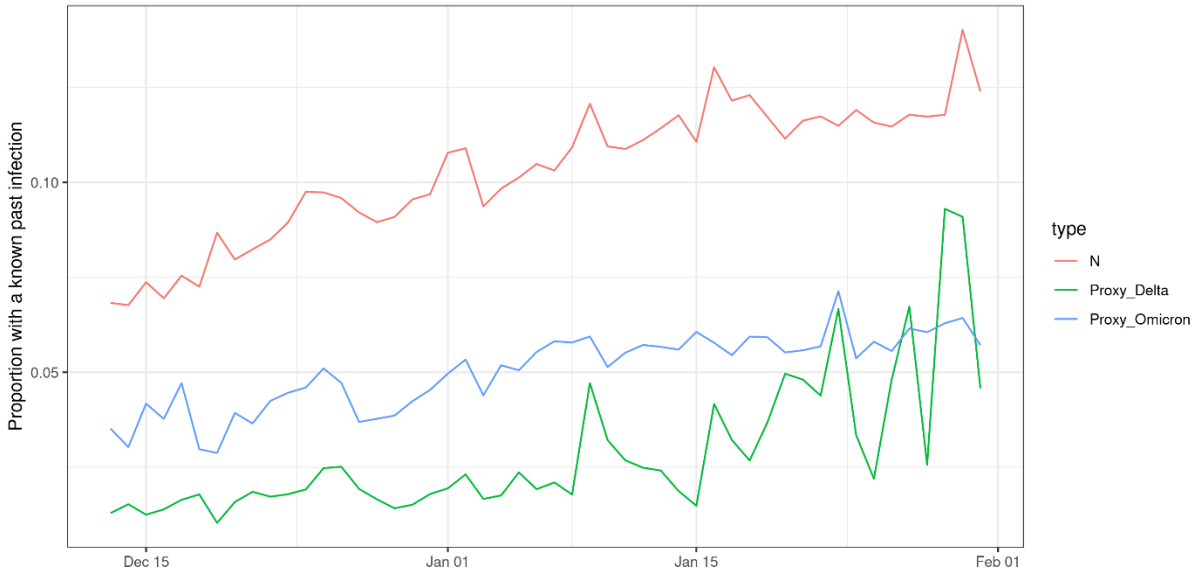
Appendix. Supplementary materials
Appendix A. Study Population

Figure A.1 • Daily counts of controls, symptomatic and hospitalized cases (averaged over the last 7 days), data collected from December 13th, 2021 to January 31 th, 2022



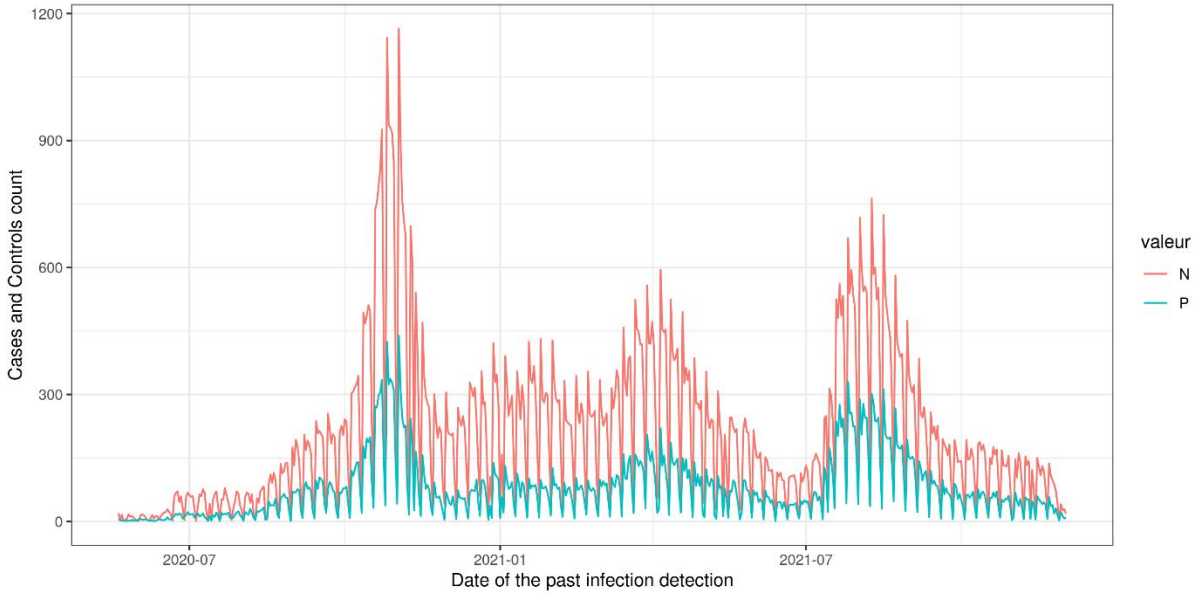
Abbreviations: Sympto+ (cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection (cases); Sympto+ & H (hospitalized cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection and hospital admission for Covid-19. Sympto- (controls): individuals with symptoms non-related to SARS-CoV-2 infection.

Figure A.2 • Proportion of controls and cases with evidence of prior SARS-Cov-2 infection, data collected from December 13th, 2021 to January 31 th, 2022



Abbreviations: Proxy_Delta (Delta cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection with screened mutations indicative of the Delta variant; Proxy_Omicron (Omicron cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection with screened mutations indicative of the Omicron variant;. N (controls): individuals with symptoms non-related to SARS-CoV-2 infection.

Figure A.3 • Counts of cases and controls with prior evidence of infection by date of past infection detection, data collected from December 13th, 2021 to January 31 th, 2022



Abbreviations: P (cases): symptomatic individuals with a laboratory confirmed SARS-CoV-2 infection (cases) with screened mutations indicative of the Delta or Omicron variant; N (controls): individuals with symptoms non-related to SARS-CoV-2 infection.

Appendix B. Data description and Data linkage characteristics

Three National databases created to monitor the epidemic and the vaccination campaign were matched together.

SI-VIC, the information system for monitoring victims of attacks and exceptional health situations, provides, for people infected with SARS-CoV-2, the daily number of hospitalizations in general wards and ICU, and the number of inpatient deaths. The diagnosis of infection relies on RT-PCR testing or thoracic CT scanning. This reporting system, maintained by the ANS (*Agence du Numérique en Santé*), is exhaustive and covers all healthcare structures (public and private) over the French territory.

SI-DEP, the screening information system, provides the daily number of tests performed (RT-PCR, serology and antigenic tests) for SARS-CoV-2 and the results of these tests. This database, maintained by the AP-HP (*Assistance Publique - Hôpitaux de Paris*), is exhaustive for all tests performed on the French territory (but self-tests). Since mid-2020, PCR testing was available to the population without prescription and covered by national health insurance (Appendix 1). As of January 2021, a molecular screening was performed on all RT-PCR positive samples: first to identify known variant strains (wild-type, alpha, beta, gamma); then, from June 2021, to identify some key mutations (E484K, E484Q, L452R). The presence or absence of symptoms in tested individuals should be systematically reported, but this information is missing for 20% of the RT-PCR tests performed in 2021.

VAC-SI, the Covid-19 vaccine information system, maintained by the CNAM, the French national Health Insurance (*Caisse Nationale d'Assurance Maladie*), provides the number of administrated vaccines and vaccinated persons on the French territory. This dataset covers nearly the entire French population (all those affiliated to the French Health Care System [Social security]), whether vaccinated or not, and all individuals vaccinated in France. This database contains information on vaccination (dates of injection, vaccine brand name), and information on vaccine priority populations (presence of comorbidities, healthcare professionals or social workers, retirement homes residents).

To match these databases, a pseudonym (non-meaningful character string identifying each person) was generated from the concatenation and encryption of identifying information (surname, first name, sex and date of birth). The pseudonym (but not the identifying information) is present in all the databases transmitted to the Statistics office of the French Ministry for Solidarity and Health (DREES) for statistical use, which allows the matching of data on screening, hospitalization and vaccination at the individual level. However, matching imperfections may remain (DREES, 2021; Appendix 5).

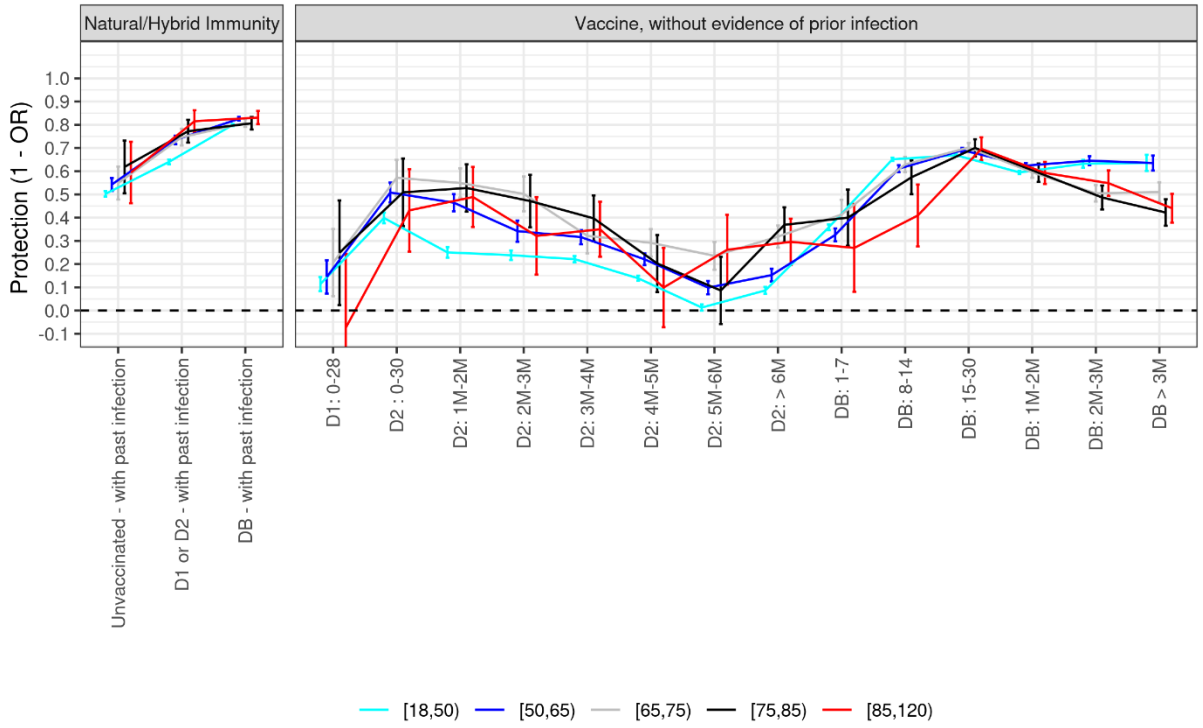
The deployment of these three databases was authorized by the French Data Protection Authority (*Commission Nationale Informatique et Libertés*). No consent of the patients is required, and the patients must be informed of their right to access, modify, rectify and delete any data concerning them. The French Ministry for Health is accountable to implement legal, technical and organizational measures to guarantee data protection.

Among persons aged 18 years or over hospitalized for Covid-19 (data source: SI-VIC), 75 % have a matched positive RT-PCR test, collected from fifteen days before admission to the end of their stay (source: SI-DEP) over our analysis period. Among persons aged 18 years or over hospitalized for Covid-19 (data source: SI-VIC), 66 % have a match in the VAC-SI register, which covers nearly all French residents and allows to recover the vaccination status. Among persons aged 18 years reporting symptoms in the last seven days before a RT-PCR test (data source: SI-DEP), 81 % have a match in the VAC-SI register, thus a known vaccination status.

Appendix C. Supplementary results

Figure C.1 • Covid-19 vaccine effectiveness against Omicron (a) and Delta (b) symptomatic infections by age, according to the time elapsed since the injection of each vaccine dose, data collected December 13th, 2021 to January 31th, 2022

(a) Omicron



(b) Delta

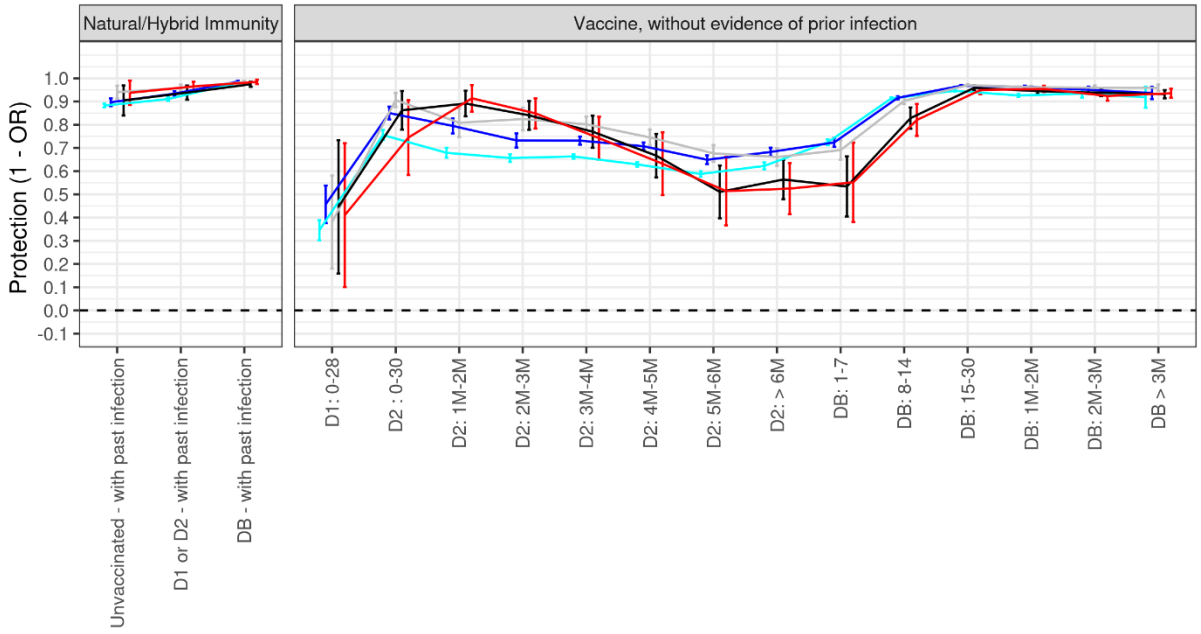
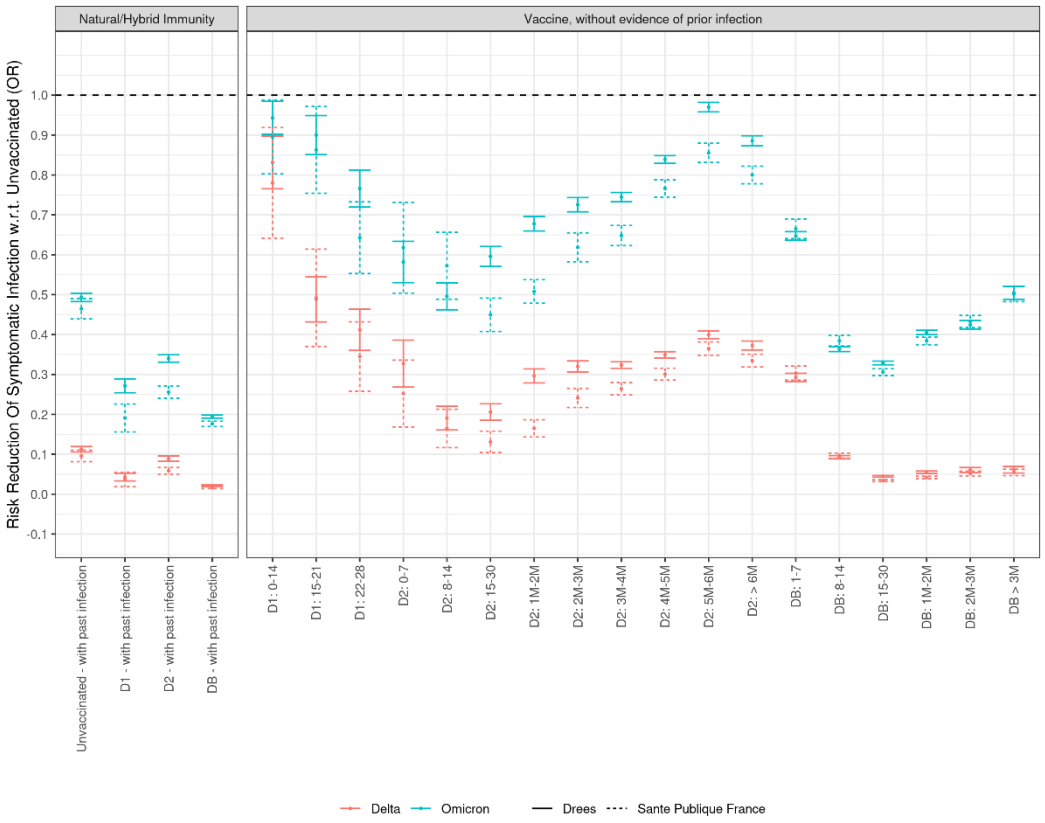
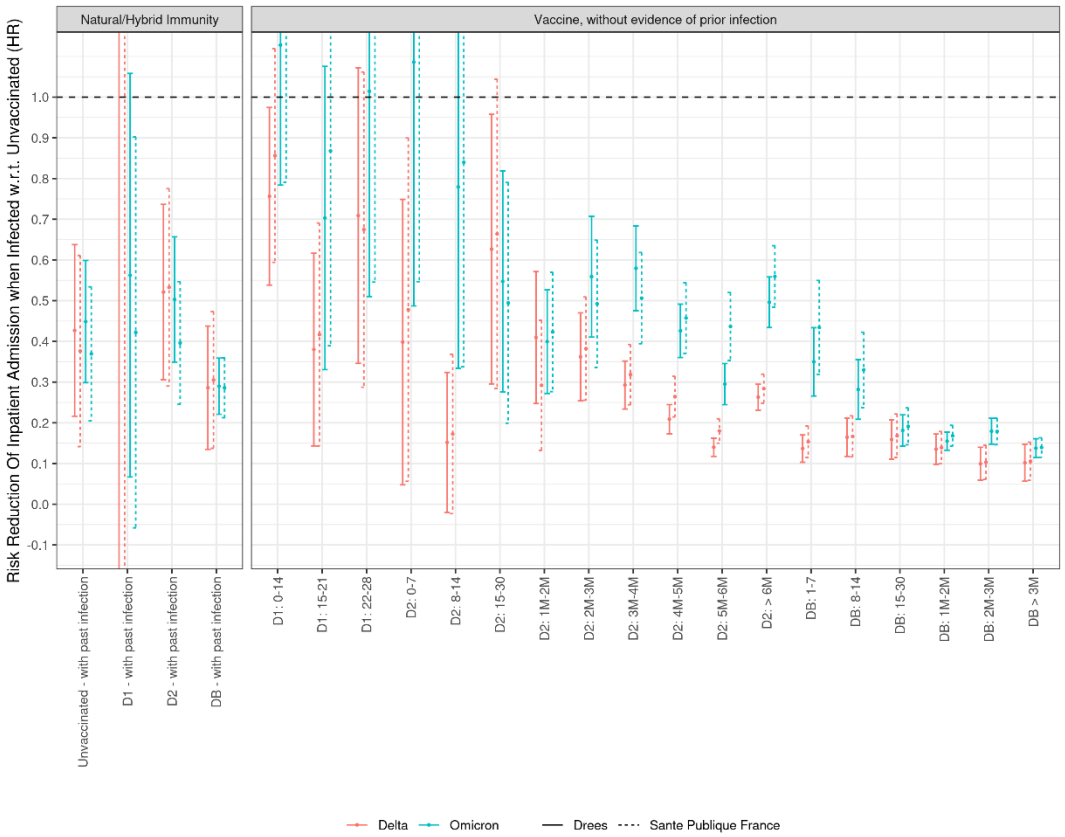


Figure C.2 • Variant-specific odd ratios of symptomatic infections and hazard ratios of hospitalizations after symptomatic infections among persons aged 18 years or over, according to Drees or Santé Publique France definition of Omicron and Delta cases. Data collected from December 13th, 2021 to January 31th, 2022


Natural/Hybrid Immunity
Vaccine, without evidence of prior infection
Risk Reduction Of Symptomatic Infection w.r.t. Unvaccinated (OR)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Unvaccinated - with past infection
D1 - with past infection
D2 - with past infection
DB - with past infection
D1: 0-14
D1: 15-21
D1: 22-28
D2: 0-7
D2: 8-14
D2: 15-30
D2: 1M-2M
D2: 2M-3M
D2: 3M-4M
D2: 4M-5M
D2: 5M-6M
D2: > 6M
DB: 1-7
DB: 8-14
DB: 15-30
DB: 1M-2M
DB: 2M-3M
DB > 3M
Delta
Omicron
Drees
Sante Publique France


Natural/Hybrid Immunity
Vaccine, without evidence of prior infection
Risk Reduction Of Inpatient Admission when Infected w.r.t. Unvaccinated (HR)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Unvaccinated - with past infection
D1 - with past infection
D2 - with past infection
DB - with past infection
D1: 0-14
D1: 15-21
D1: 22-28
D2: 0-7
D2: 8-14
D2: 15-30
D2: 1M-2M
D2: 2M-3M
D2: 3M-4M
D2: 4M-5M
D2: 5M-6M
D2: > 6M
DB: 1-7
DB: 8-14
DB: 15-30
DB: 1M-2M
DB: 2M-3M
DB > 3M
Delta
Omicron
Drees
Sante Publique France