Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France

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The Lancet Regional Health - Europe 2022;13: 100278
Published online 26 November 2021
https://doi.org/10.1016/j.lanepe.2021.100278

Summary

Background We aimed to assess the settings and activities associated with SARS-CoV-2 infection in the context of B.1.617.2 (Delta) variant circulation in France, as well as the protection against symptomatic Delta infection.

Methods In this nationwide case-control study, cases were SARS-CoV-2 infected adults recruited between 23 May and 13 August 2021. Controls were non-infected adults from a national representative panel matched to cases by age, sex, region, population density and calendar week. Participants completed an online questionnaire and multivariable logistic regression analysis was used to determine the association between acute SARS-CoV-2 infection and recent activity-related exposures, past history of SARS-CoV-2 infection, and COVID-19 vaccination.

Findings We did not find any differences in the settings and activities associated with Delta versus non-Delta infections and grouped them for subsequent analyses. In multivariable analysis involving 12634 cases (8644 Delta and 3990 non-Delta) and 5560 controls, we found individuals under 40 years and attending bars (aOR:1.9; 95%CI:1.6-2.2) or parties (aOR:3.4; 95%CI:2.8-4.2) to be at increased risk of infection. In those aged 40 years and older, having children attend daycare (aOR:1.9; 95%CI:1.1-3.3), kindergarten (aOR:1.6; 95%CI:1.2-2.1), primary school (aOR:1.4; 95%CI:1.2-1.6) or middle school (aOR:1.3; 95%CI:1.2-1.6) were associated with increased risk of infection. We found strong protection against symptomatic Delta infection for those with prior infection whether it was recent (2-6 months) (95%; 95%CI:90-97) or associated with one dose (85%; 95%CI:78-90) or two doses of mRNA vaccine (96%; 95%CI:87-99). For those without past infection, protection was lower with two doses of mRNA vaccine (67%; 95%CI:63-71).

Interpretation In line with other observational studies, we find reduced vaccine effectiveness against symptomatic Delta infections. The settings and activities at increased risk of infection indicate where efforts to reinforce individual and public health measures need to be concentrated.

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# These two authors had equivalent contribution to the study

Introduction

The B.1.617.2 (Delta) SARS-CoV-2 variant has emerged with an increase in transmissibility,[1] likely driven by higher viral loads, shorter time to peak viral load and shorter incubation period,[2,3] and abrogated neutralization capacity, compared to non-Delta SARS-CoV-2.[4] Nonetheless, early estimates of vaccine effectiveness

Research in context

Evidence before this study

The B.1.617.2 (Delta) variant of SARS-CoV-2, the virus that causes COVID-19, was first identified in India, and subsequent surges in transmission of the variant in a number of countries, including the United Kingdom, led the World Health Organization to designate Delta as a Variant of Concern (VOC) on 11 May 2021. The observed increased transmissibility of Delta is driven by a clear fitness advantage, derived in part from higher viral loads and shorter generation time, that appears to allow it to replace other variants in circulation. However, it is unclear whether the increased transmissibility leads to changes in the settings which facilitate SARS-CoV-2 transmission. Further, Delta may have properties of immune escape, so it is important to quantify the effectiveness of current COVID-19 vaccines against symptomatic Delta infection. We conducted a systematic search of PubMed and pre-print servers for observational studies of 1. places associated with transmission of Delta, and 2. the effectiveness of COVID-19 vaccines against Delta using the terms 'COVID-19 vaccine effect', and 'Delta variant'. We did not find any study that could determine the frequency or relative risk of Delta infection by setting. For vaccine effectiveness, we identified 19 studies assessing the effectiveness of current COVID-19 vaccines, predominantly mRNA vaccines, against Delta, with outcomes ranging from asymptomatic infection to hospitalization and severe disease.

Added value of this study

We analysed data from an ongoing nationwide case-control study to assess the places of transmission, and effectiveness of current vaccines against COVID-19 with the Delta variant, adjusting for a large series of potential confounders. We did not find any differences in the settings and activities associated with Delta versus non-Delta infections, and therefore have grouped all cases for the subsequent analysis. Attending bars or parties (night-clubs and private) was associated with increased risk of infection for individuals less than 40 years of age, whereas for those over the age of 40 years, having children attend daycare centre, kindergarten, primary school, or middle school were all associated with increased risk of infection. We found strong protection against symptomatic Delta for those with prior infection whether it was recent (2-6 months) or associated with one or two doses of mRNA vaccine. For those without prior infection, protection was lower with two doses of mRNA vaccine (67%; 95%CI:63-71). Finally, we found that the mean incubation period was shorter for Delta compared to non-Delta infections (4.3 and 5.0 days, respectively).

Implications of all available evidence

We continue to identify settings and activities at increased risk of infection and are able to highlight where efforts to reinforce individual infection prevention and control and/or public health and social measures need to be concentrated, even for those who have been vaccinated. This is all the more important given the shorter incubation period, which likely helps to explain the rapid spread of the Delta variant in France. There appears to be a noticeable reduction in vaccine protection against symptomatic infection with Delta, particularly for those who have not had prior infection, however other studies indicate that protection against severe disease is maintained which will be critical to the impact of current vaccination campaigns on health care systems.

(VE) suggested that high levels of protection against COVID-19 were maintained with two doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines against the Delta variant.[5]

The emergence of the Delta variant in France took place in June 2021, at a time of overall decreasing SARS-CoV-2 incidence and reopening of public places like bars, restaurants, and cultural places. Incidence accelerated in July and understanding how and where infections occurred is key to informing the public health response to COVID-19. We used an on-going nationwide case-control study to identify settings and activities which have driven the spread of Delta in France from June 2021 onwards, and to estimate the protection associated with past infection and current COVID-19 vaccines against this new variant, as has been previously done for other SARS-CoV-2 variants of concern (VOC).[6,7] In a separate analysis, we used data from symptomatic cases from January 2021 who reported a single contact with the person who infected them to estimate the incubation period (time from contact to onset of first symptoms) and compare the incubation periods of the various VOC, including Delta.

Methods

Study population

The methodology of the ongoing case-control study (ComCor project) has been previously described.[6,7] Briefly, the nationwide case control study uses SARS-CoV-2 infection diagnoses obtained through the Caisse Nationale d'Assurance Maladie (CNAM) database, which receives notification of all diagnoses in France, and non-infected controls selected from a panel representative of the French population from Ipsos, a market research and public opinion specialist company, using frequency-matching on age (three age categories), sex, region, population density, and calendar week. Since 27 October 2020, cases and selected controls are invited by email and receive information online about the study before completing a questionnaire that covered sociodemographic characteristics, exposure information, SARS-CoV-2 testing information and vaccination

details. Prior to administration, the questionnaire was pilot-tested among 40 hospitalized patients.

Identification of B.1.617.2 (Delta) SARS-CoV-2 infections

In France since early 2021, a second round of screening RT-PCR is used to identify SARS-CoV-2 VOC and applied nationwide to the majority of positive RT-PCR test results. During the study period, the L452R, E484K and E484Q mutations were used to identify VOC, with cases with the L452R mutation considered as infected with the Delta variant. Further, whole genome sequencing data submitted to the GISAID database from France indicates that during the study period, of all sequences with L452R mutation, 92% in week 23 were confirmed as Delta variant and this increased to 95% or above after week 33.[8]

Statistical analyses

The methodology for the statistical analyses for the case-control study and estimation of the VE has been previously described.[7] The period for data analysis for this analysis covered the emergence of the Delta variant in France at the time of reopening of outdoor terraces of bars and restaurants, and cultural places (19 May), then indoor facilities of bars, restaurants, sports centres (9 June), and night clubs (9 July) for those with a 'Health pass' (evidence of recent (<72 hours) negative RT-PCR test, proof of COVID-19 vaccination or recovery from recent (<6 months) COVID-19). The study period ended upon the nationwide extension of the 'Health pass' to all public settings on 9 August. Since the mean incubation period was estimated at 4 days for infections with the Delta variant, a 4-day interval was added to these dates for inclusion of cases, so that the study population consisted of cases and controls recruited during the period 23 May to 13 August. For the purpose of these analyses, we included only participants with complete SARS-CoV-2 RT-PCR screening (identifying Delta and non-Delta infections) and vaccination (type of vaccine, dates of vaccination) details.

The first analysis aimed to identify through multivariable logistic regression the factors associated with SARS-CoV-2 infections, first separating Delta and non-Delta infection as the outcome, and then grouping them since there were no marked differences in risk factors associated with Delta infections (Table S1). Figure 1 details the selection process for the observations for this analysis. Variables introduced into the models were the matching variables (age in ten-year categories, sex, region, population density, and calendar week), socio-demographic characteristics (level of educational attainment, type of profession, type of housing), co-morbidities (overweight and obesity, diabetes, high blood pressure, chronic respiratory diseases, and immunosuppression), smoking status, activities (full or partial remote working, private and professional meetings, car-pooling, regular means of transportation, recent travel, delivery of food or items, sports activities), places recently visited (cultural, religious, shops, medical facilities, bars, restaurants and night clubs), past history of SARS-CoV-2 infection and vaccination status (participants were considered as non-vaccinated until thirteen days after the first dose, as vaccinated with one dose of vaccine until six days after the second dose, and as vaccinated with two doses of vaccines from seven days after the second dose). Interaction terms were used to explore whether the magnitude of the associations with SARS-CoV-2 infection for several exposures varied according to age categories (with the median age of the study population being 38 years, <40 and ≥40 years were chosen as cut-offs for exploring the interaction with age), sex, or population density. Strata-specific ORs are shown when interaction terms were statistically significant (P <0.05). We also performed a separate analysis taking into account the dates of opening of bars, restaurants, and night clubs, to explore the dynamics of transmission in these places as they opened during the study period. There was no correction of P values related to multiple testing. There were no missing data at the analysis stage since only questionnaires that were fully completed were available in the database for analysis.

The second analysis aimed to estimate the effectiveness of current COVID-19 vaccines against symptomatic Delta infections. As before,[7] VE was calculated as one minus the adjusted odds-ratio (OR).[9–10] Figure 1 details the selection process for the analysis, retaining only cases with symptomatic Delta infections. To examine whether the vaccination coverage among controls reflected that of the French population, we compared the age-stratified vaccination rates of the control group to those of the French population during the study period and calculated a standardized vaccination ratio and its 95% confidence interval using an equation used for standardized mortality ratios.[11]

A third and separate analysis was performed to estimate the incubation period for VOC and non-VOC symptomatic infections. This analysis used the same database for the symptomatic Delta variant cases, to which other VOC and non-VOC symptomatic SARS-CoV-2 infections were added going back to the introduction of screening RT-PCR for VOCs in January 2021. Symptomatic cases with variant information from RT-PCR screening who knew who infected them and who had had a single contact with that person were included in this analysis. The incubation period was defined as the number of days between the single contact and the onset of symptoms. Cases who reported past SARS-CoV-2 infection or COVID-19 vaccination were excluded since these events may alter the duration of the incubation period and were more common for cases infected with the Delta variant compared to others. Incubation periods longer than 15 days were excluded since these

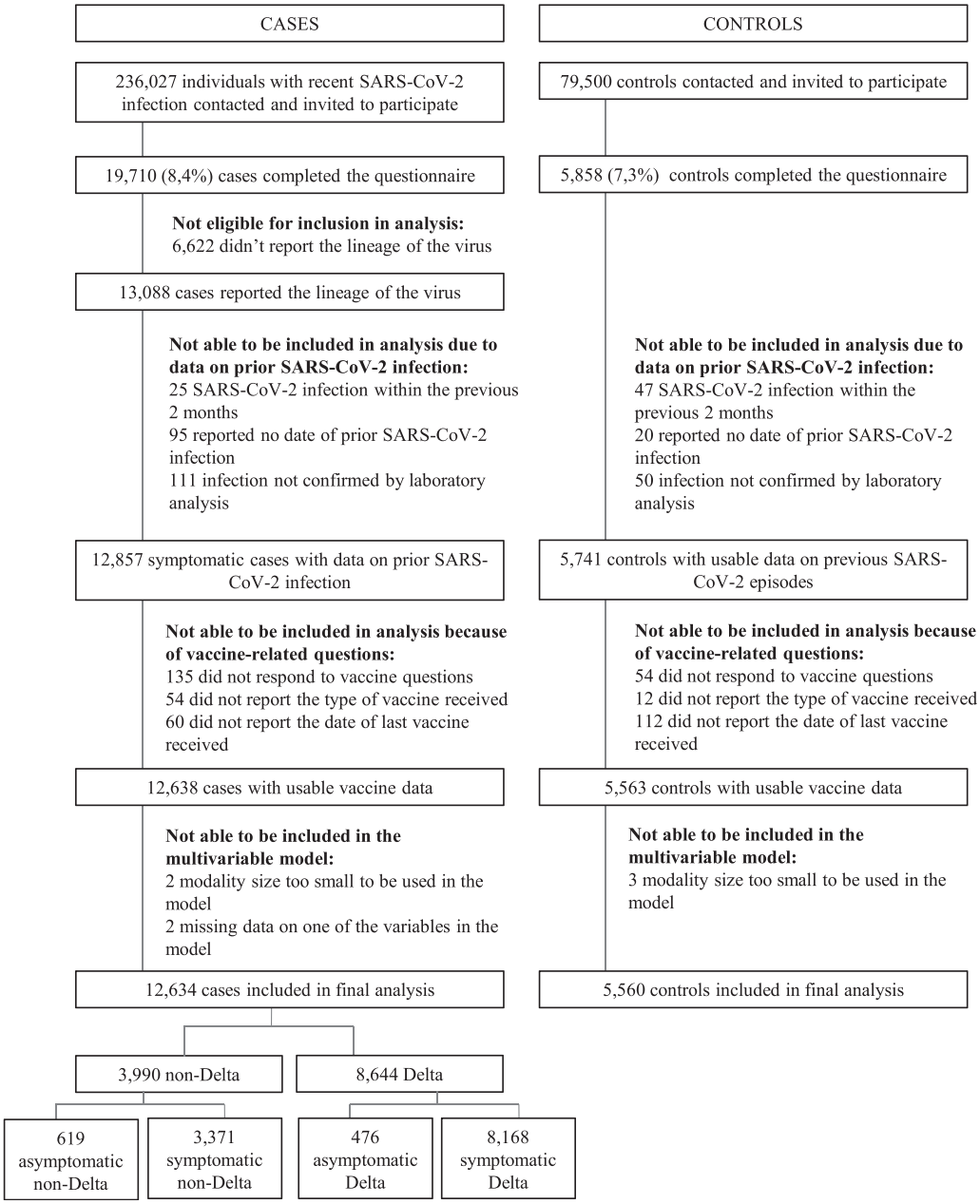

Figure 1. Selection of cases and controls for analysis on characteristics associated with SARS-CoV-2 infection, and for estimation of protection / vaccine effectiveness against symptomatic Delta variant infection, 23 May-13 August 2021, France.

may have been related to reporting errors. Mean incubation periods were compared between cases infected with the Delta variant and other VOCs using a Student's *t* test.

Since this is an on-going study for which analyses were triggered by new events (e.g., emergence of a new variant; vaccine deployment), a sample size based on these expected outcomes was not calculated prior to the start of the study. The final sample size was the number of cases and controls who matched the criteria chosen for the analysis. A description of the recruitment process and numbers available is shown on the Figure 1. All statistical analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA).

Ethical considerations

This study received ethical approval by the Comité de Protection des Personnes Sud Ouest et Outre Mer 1 on 21 September 2020. The data protection authority

Commission Nationale de l'Informatique et des Libertés (CNIL) authorized the processing of data on 21 October 2020. Informed consent was obtained online from all participants. The study is registered with ClinicalTrials.gov under the identifier NCT04607941.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between 23 May (week 20) and 13 August 2021 (week 32), 19710 individuals with recent diagnosis of SARS-CoV-2 infection and 5858 non-infected controls were recruited in the study, of which 12634 cases and 5560 controls were kept for the analysis based on the data available (Figure 1). Of the 12634 cases included in our study, secondary RT-PCR screening identified 8644 Delta infections, and 3990 non-Delta infections. The Delta variant became rapidly predominant, increasing from 3% of all cases in week 23 to over 80% from week 28 onwards. Compared to non-Delta infections, the Delta variant infections were more frequent in younger populations, in urban areas of South and South-West of France which are popular places during the summer holiday season (Table 1).

We did not find any differences in the settings and activities associated with Delta versus non-Delta infections – described in the Supplementary Material (Table S1) – consistent with those presented in Table 2. In multivariable analysis, in participants less than 40 years of age, attending bars (aOR:1.9; 95%CI:1.6-2.2) and parties (night clubs and private gatherings) (aOR:3.4; 95%CI:2.8-4.2) were associated with increased risk of infection. In those 40 years and older, individuals attending parties were also at increased risk of infection (aOR:1.5; 95%CI:1.1-1.9), but with a lower magnitude in the increase in risk compared to younger adults, and with only a small fraction of those over 40 years old attending such events (3.1% of controls). In those 40 years and older, having children attend daycare centre (aOR:1.9; 95%CI:1.1-3.3), kindergarten (aOR:1.6; 95%CI:1.2-2.1), primary school (aOR:1.4; 95%CI:1.2-1.6) or middle school (aOR:1.3; 95%CI:1.2-1.6) was associated with increased risk of infection. Across all age groups, independent risk factors for infection were living in shelters or social housing (aOR:2.3; 95%CI:1.2-4.3); having children attended by a childminder (aOR:1.6; 95%CI:1.3-2.0); carpooling with family and friends (aOR:1.3; 95%CI:1.2-1.4); travelling by taxi (aOR:1.5; 95%CI:1.2-1.8), subway (aOR:1.2; 95%CI:1.0-1.4), national train (aOR:1.3; 95%CI: 1.1-1.6), or aeroplane (aOR:1.7; 95%CI:1.3-2.2); recent travel overseas (aOR:1.3; 95%CI:1.1-1.6); and attending a private ceremony (aOR:1.7; 95%CI:1.4-2.2). Of note, 291 (33.9%) of the 859 cases who recently travelled overseas had travelled to Spain. Importantly, public transportation (except subway), car-sharing platforms, visits to cultural places, shopping areas (except convenience stores (aOR:1.3; 95%CI:1.2-1.4)), hairdressers, beauty salons, sporting activities, or restaurants, were not found to constitute an increased risk of infection.

In more detailed analysis of specific activities associated with SARS-CoV-2 infection by time period and by sex (Table 3), we found that for those under 40 years, attending bars or private parties particularly during the period 13 June – 12 July to be associated with an increased risk of infection. The risk was more pronounced for males (bars aOR:5.1; 95%CI:2.4-10.9; private parties aOR:15.3; 95%CI:3.0-77.2) than females (bars aOR:2.5; 95%CI:1.7-3.7; private parties aOR:3.2; 95%CI:1.6-6.1). The risk decreased dramatically in these settings after the opening of night clubs (9 July) which themselves became places at high risk of transmission: aOR: 7.9; 95%CI:4.3-14.5 for less than 40 years, and 2.7; 95%CI:1.2-6.1 for more than 40 years.

In an updated analysis of protection/VE (95% CI) against symptomatic Delta variant infection, prior infection, either recent (2-6 months), or combined with one or two doses of mRNA vaccines, was associated with high protection/VE: 95% (90-97), 85% (78-90) and 96% (87-99), respectively (Figure 2 and Table S2). The protection associated with past infection seemed to decrease after six months in the absence of vaccination (74%; 58-84). Among those without past infection, VE was lower, both for those who received two doses of mRNA vaccine (67% (63-71)) or heterologous vaccination (ChAdOx1 nCoV-19 followed by mRNA vaccine) (61% (45-72)). One dose of mRNA vaccine had low VE (22% (10-32)) against symptomatic COVID-19. Age-stratified vaccination rates among controls during the study period were slightly higher compared to those of the French population (Table S3), giving a standardized vaccination ratio of 1.09 (95%CI: 1.04-1.15).

Finally, for the third analysis estimating the incubation period, we used all case data from the ongoing case-control study since variant screening was introduced in France in January 2021 retaining all those who knew who infected them and had a single contact with that person, including the Delta infections in the analysis above (n=11071). After excluding cases with history of vaccination (n=1722), past infection (n=213), and estimated incubation period of more than 15 days (n=43), we ended up with 1540 cases reporting non-VOC infections, and 7553 with VOC infections. Among the latter, 6374 were Alpha, 528 Beta/Gamma, and 651 Delta. Using this combined case data, we calculated the incubation period to be shorter for Delta (mean (SD) = 4.3 (2.4) days; median (IQR)= 4 (3-5)), compared to non-Delta infections (mean (SD) = 5.0 (2.4) days; median (IQR)= 5 (3-7)) ($P < 0.001$). Among non-Delta

	Non-infected controls (%) n=5560	All SARS-CoV-2 infected cases (%) n=12634	SARS-CoV-2 infected cases according to variant of infection		
			Non-Delta (%) n=3990	Delta (%) n=8644	P value*
Age (years)					*<0.001*
<30	1310 (23.6)	3372 (26.7)	1006 (25.2)	2366 (27.4)	
30-39	972 (17.5)	3503 (27.7)	1038 (26.0)	2465 (28.5)	
40-49	1630 (29.3)	2900 (23.0)	1030 (25.8)	1870 (21.6)	
50-59	1030 (18.5)	1776 (14.1)	616 (15.4)	1160 (13.4)	
60-69	328 (5.9)	778 (6.2)	224 (5.6)	554 (6.4)	
≥70	290 (5.2)	305 (2.4)	76 (1.9)	229 (2.6)	
Sex					0.361
Male	1793 (32.2)	3904 (30.9)	1255 (31.5)	2649 (30.6)	
Female	3767 (67.8)	8730 (69.1)	2735 (68.5)	5995 (69.4)	
Region of residence:					*<0.001*
Île-de-France	1289 (23.2)	1936 (15.3)	693 (17.4)	1243 (14.4)	
Centre — Val de Loire	162 (2.9)	233 (1.8)	113 (2.8)	120 (1.4)	
Bourgogne — Franche-Comté	157 (2.8)	305 (2.4)	136 (3.4)	169 (2.0)	
Normandie	282 (5.1)	435 (3.4)	180 (4.5)	255 (3.0)	
Hauts-de-France	374 (6.7)	738 (5.8)	311 (7.8)	427 (4.9)	
Grand Est	374 (6.7)	803 (6.4)	296 (7.4)	507 (5.9)	
Pays de la Loire	305 (5.5)	654 (5.2)	267 (6.7)	387 (4.5)	
Bretagne	284 (5.1)	508 (4.0)	181 (4.5)	327 (3.8)	
Nouvelle-Aquitaine	546 (9.8)	1372 (10.9)	391 (9.8)	981 (11.3)	
Occitanie	684 (12.3)	1990 (15.8)	542 (13.6)	1448 (16.8)	
Auvergne-Rhône-Alpes	636 (11.4)	1898 (15.0)	547 (13.7)	1351 (15.6)	
Provence-Alpes-Côtes d'Azur and Corse	467 (8.4)	1762 (13.9)	333 (8.3)	1429 (16.5)	
Population density of place of residence (inhabitants)					*<0.001*
Rural or < 5,000	1278 (23.0)	2844 (22.5)	986 (24.7)	1858 (21.5)	
5,000 - 19,999	518 (9.3)	1194 (9.5)	395 (9.9)	799 (9.2)	
20,000 - 99,999	621 (11.2)	1500 (11.9)	461 (11.6)	1039 (12.0)	
100,000 +	2021 (36.3)	5335 (42.2)	1527 (38.3)	3808 (44.1)	
Paris agglomeration	1122 (20.2)	1761 (13.9)	621 (15.6)	1140 (13.2)	
Calendar week					*<0.001*
21	318 (5.7)	880 (7.0)	878 (22.0)	2 (0.0)	
22	292 (5.3)	816 (6.5)	809 (20.3)	7 (0.1)	
23	347 (6.2)	411 (3.3)	398 (10.0)	13 (0.2)	
24	363 (6.5)	207 (1.6)	168 (4.2)	39 (0.5)	
25	289 (5.2)	153 (1.2)	106 (2.7)	47 (0.5)	
26	377 (6.8)	237 (1.9)	100 (2.5)	137 (1.6)	
27	501 (9.0)	439 (3.5)	127 (3.2)	312 (3.6)	
28	629 (11.3)	880 (7.0)	156 (3.9)	724 (8.4)	
29	985 (17.7)	1899 (15.0)	308 (7.7)	1591 (18.4)	
30	531 (9.6)	2105 (16.7)	314 (7.9)	1791 (20.7)	
31	391 (7.0)	2165 (17.1)	267 (6.7)	1898 (22.0)	
32	503 (9.0)	2171 (17.2)	319 (8.0)	1852 (21.4)	
33	34 (0.6)	271 (2.1)	40 (1.0)	231 (2.7)	

***Table 1*: Characteristics of SARS-CoV-2 infected cases and non-infected controls, according to variant of infection, 23 May-13 August 2021, France**

* Compares Delta and non-Delta cases.

	Cases (%) N=12634	Controls (%) N=5560	Odds ratio* (95%CI)**	Adjusted odds ratio*** (95%CI)
Professional category:				
Employee	2790 (22.1)	1455 (26.2)	1 (ref)	1 (ref)
Senior executive	2675 (21.2)	1158 (20.8)	1.9 (1.7-2.1)	**1.9 (1.7-2.2)**
Intermediate profession	3597 (28.5)	1134 (20.4)	1.2 (1.1-1.4)	**1.3 (1.2-1.5)**
Worker, farmer, etc.	1319 (10.4)	493 (8.9)	1.4 (1.2-1.6)	**1.2 (1.1-1.4)**
Retired	797 (6.3)	566 (10.2)	0.6 (0.5-0.8)	**0.5 (0.4-0.7)**
Unemployed or inactive people	498 (3.9)	389 (7.0)	0.6 (0.5-0.7)	**0.5 (0.4-0.6)**
Student	958 (7.6)	365 (6.6)	1.4 (1.2-1.6)	**1.6 (1.3-1.9)**
BMI (in kg/m^2) category:				
Underweight (<18.5)	546 (4.3)	296 (5.3)	0.6 (0.5-0.8)	**0.6 (0.5-0.7)**
Healthy weight (≥18.5 & <25)	7373 (58.4)	2866 (51.6)	1 (ref)	1 (ref)
Overweight (≥ 25 & <30)	3228 (25.6)	1521 (27.4)	0.9 (0.8-1.0)	1.0 (0.9-1.1)
Obesity (≥ 30)	1487 (11.8)	877 (15.8)	0.7 (0.6-0.8)	**0.8 (0.7-0.9)**
Diabetes	234 (1.9)	204 (3.7)	0.6 (0.5-0.8)	0.8 (0.6-1.0)
High blood pressure	733 (5.8)	494 (8.9)	0.8 (0.7-0.9)	0.9 (0.8-1.1)
Chronic respiratory diseases	999 (7.9)	368 (6.6)	1.3 (1.1-1.4)	**1.4 (0.2-1.7)**
Immunosuppression				
Yes	277 (2.2)	151 (2.7)	0.9 (0.7-1.1)	1.1 (0.8-1.4)
Does not want to answer	80 (0.6)	20 (0.4)	2.0 (1.2 -3.4)	**1.9 (1.1-3.5)**
Housing type:				
House	6823 (54.0)	3181 (57.2)	1 (ref)	1 (ref)
Apartment	5741 (45.4)	2364 (42.5)	1.1 (1.0-1.2)	1.1 (1.0-1.2)
Shelters	70 (0.6)	15 (0.3)	2.1 (1.2-3.8)	**2.3 (1.2-4.3)**
Child in household:				
Attending daycare center				
under 40 years old	375 (5.5)	132 (5.8)	0.8 (0.7-1.1)	1.0 (0.8-1.3)
40 years old and above	88 (1.5)	22 (0.7)	2.3 (1.4-3.8)	**1.9 (1.1-3.3)**
Looked after by a childminder	512 (4.1)	129 (2.3)	1.3 (1.0-1.6)	**1.6 (1.3-2.0)**
Attending kindergarten				
under 40 years old	934 (13.6)	331 (14.5)	0.8 (0.7-0.9)	1.1 (0.9-1.3)
40 years old and above	380 (6.6)	132 (4.0)	1.8 (1.5-2.3)	**1.6 (1.2-2.1)**
Attending primary school				
under 40 years old	1105 (16.1)	415 (18.2)	0.6 (0.6-0.7)	0.9 (0.8-1.1)
40 years old and above	1023 (17.8)	460 (14.0)	1.5 (1.3-1.7)	**1.4 (1.2-1.6)**
Attending middle school				
under 40 years old	547 (8.0)	237 (10.4)	0.6 (0.5-0.8)	**0.8 (0.6-1.0)**
40 years old and above	1337 (23.2)	641 (19.6)	1.3 (1.2-1.5)	**1.3 (1.2-1.6)**
Attending high school				
under 40 years old	305 (4.4)	149 (6.5)	0.7 (0.6-0.9)	0.9 (0.7-1.1)
40 years old and above	1230 (21.4)	651 (19.9)	1.1 (1.0-1.2)	1.2 (1.0-1.4)
Attending college or university	1038 (8.2)	588 (10.6)	0.9 (0.8-1.0)	1.0 (0.8-1.1)
Location of work-related activity				
Office work with no remote working	2369 (18.8)	960 (17.3)	1 (ref)	1 (ref)
Not working	2588 (20.5)	1281 (23.0)	0.9 (0.8-1.0)	**1.3 (1.1-1.6)**
Working but no office work	4631 (36.7)	1939 (34.9)	1.0 (0.9-1.1)	1.0 (0.9-1.1)
Split office/ remote working	1769 (14.0)	968 (17.4)	0.8 (0.7-0.9)	**0.7 (0.6-0.8)**
Complete remote working	1277 (10.1)	412 (7.4)	1.4 (1.2-1.6)	1.1 (0.9-1.3)
In-person work-related meeting	2717 (21.5)	1378 (24.8)	0.9 (0.9-1.0)	1.0 (0.9-1.1)
Carpooling:				
With family and friends	3446 (27.3)	1340 (24.1)	1.1 (1.1-1.2)	**1.3 (1.2-1.4)**
Via car sharing platform	178 (1.4)	127 (2.3)	0.5 (0.4-0.7)	**0.5 (0.3-0.6)**
Taxi	849 (6.7)	255 (4.6)	1.7 (1.5-2.0)	**1.5 (1.2-1.8)**

(*continued*)

Table 2 (Continued)

	Cases (%) N=12634	Controls (%) N=5560	Odds ratio* (95%CI)**	Adjusted odds ratio*** (95%CI)
Regular means of transport				
Bus	1510 (12.0)	1026 (18.5)	0.6 (0.5-0.7)	**0.7 (0.6-0.7)**
Tram	823 (6.5)	545 (9.8)	0.6 (0.5-0.7)	**0.7 (0.6-0.8)**
Subway	1565 (12.4)	827 (14.9)	1.0 (0.9-1.1)	**1.2 (1.0-1.4)**
Train	971 (7.7)	626 (11.3)	0.7 (0.6-0.8)	**0.6 (0.6-0.8)**
Recent travel:				
Outside region of residence	3850 (30.5)	1647 (29.6)	1.0 (0.9-1.0)	**0.9 (0.8-1.0)**
Overseas	859 (6.8)	224 (4.0)	1.8 (1.5-2.1)	**1.3 (1.1-1.6)**
Means of transport for recent national or international travel				
Aeroplane	650 (5.1)	144 (2.6)	1.9 (1.6-2.3)	**1.7 (1.3-2.2)**
Train	815 (6.5)	347 (6.2)	1.1 (1.0-1.3)	**1.3 (1.1-1.6)**
Bus	206 (1.6)	118 (2.1)	0.8 (0.6-1.0)	0.8 (0.6-1.1)
Car	220 (1.7)	79 (1.4)	1.1 (0.8-1.5)	1.3 (0.9-1.9)
Boat	101 (0.8)	27 (0.5)	1.4 (0.9-2.2)	1.2 (0.7-2.0)
Private gathering:				
Ceremony (marriage, funeral etc.)	489 (3.9)	144 (2.6)	1.4 (1.1-1.7)	**1.7 (1.4-2.2)**
Meal	3676 (29.1)	1848 (33.2)	0.8 (0.7-0.8)	**0.8 (0.7-0.9)**
Coffee	2070 (16.4)	914 (16.4)	1.0 (0.9-1.1)	0.9 (0.8-1.0)
Birthday	1479 (11.7)	761 (13.7)	0.8 (0.7-0.9)	1.0 (0.8-1.1)
Party	1284 (10.2)	720 (12.9)	0.8 (0.7-0.8)	**0.7 (0.7-0.9)**
Religious gathering	406 (3.2)	242 (4.4)	0.8 (0.6-0.9)	0.8 (0.7-1.0)
Continuing education courses	269 (2.1)	326 (5.9)	0.4 (0.4-0.5)	**0.5 (0.4-0.6)**
Cultural events:				
Theatre	97 (0.8)	83 (1.5)	0.6 (0.4-0.8)	0.7 (0.5-1.0)
Cinema	766 (6.1)	550 (9.9)	0.5 (0.5-0.6)	**0.7 (0.6-0.8)**
Museum	257 (2.0)	182 (3.3)	0.6 (0.5-0.7)	**0.7 (0.5-0.9)**
Concert	183 (1.4)	86 (1.5)	1.1 (0.8-1.4)	1.0 (0.7-1.4)
Shops:				
Supermarket	6033 (47.8)	3633 (65.3)	0.5 (0.5-0.5)	**0.6 (0.5-0.6)**
Shopping mall	2410 (19.1)	1496 (26.9)	0.6 (0.6-0.7)	**0.7 (0.7-0.8)**
Convenience store	4462 (35.3)	2098 (37.7)	0.9 (0.9-1.0)	**1.3 (1.2-1.4)**
Market	1722 (13.6)	956 (17.2)	0.7 (0.7-0.8)	0.9 (0.8-1.0)
Other	358 (2.8)	271 (4.9)	0.6 (0.5-0.8)	0.7 (0.5-0.8)
Hairdressing salon	1078 (8.5)	944 (17.0)	0.5 (0.4-0.5)	**0.5 (0.5-0.6)**
Beauty salon	874 (6.9)	439 (7.9)	0.8 (0.7-0.9)	0.9 (0.8-1.1)
Takeaway food	4970 (39.3)	2164 (38.9)	0.9 (0.9-1.0)	1.1 (1.0-1.1)
Delivery of food or items	2880 (22.8)	1202 (21.6)	1.1 (1.0-1.2)	1.1 (1.0-1.2)
Sports:				
Outdoor	3380 (26.8)	1782 (32.1)	0.8 (0.7-0.8)	**0.8 (0.7-0.9)**
Indoor	721 (5.7)	302 (5.4)	1.0 (0.9-1.2)	1.2 (1.0-1.4)
Gymnasium	115 (0.9)	121 (2.2)	0.5 (0.4-0.7)	**0.7 (0.5-0.9)**
Martial arts	26 (0.2)	53 (1.0)	0.2 (0.1-0.4)	**0.3 (0.1-0.5)**
Swimming pool	640 (5.1)	378 (6.8)	0.6 (0.6-0.7)	**0.8 (0.7-1.0)**
Health care worker	1442 (11.4)	494 (8.9)	1.2 (1.1-1.3)	**1.4 (1.3-1.7)**
Visit to health care facilities:				
Medical practice	1352 (10.7)	1008 (18.1)	0.6 (0.5-0.6)	**0.7 (0.6-0.8)**
Dental practice	285 (2.3)	285 (5.1)	0.5 (0.4-0.6)	**0.6 (0.5-0.8)**
Medical analysis laboratory	752 (6.0)	356 (6.4)	1.0 (0.8-1.1)	**1.4 (1.2-1.7)**
Hospital consultation	684 (5.4)	401 (7.2)	0.8 (0.7-0.9)	1.0 (0.8-1.1)
Hospital stay	85 (0.7)	70 (1.3)	0.5 (0.4-0.7)	**0.5 (0.2-0.8)**
Paramedical practice	527 (4.2)	372 (6.7)	0.6 (0.5-0.7)	**0.8 (0.7-1.0)**
Psychology practice	110 (0.9)	106 (1.9)	0.5 (0.4-0.7)	0.8 (0.5-1.1)

(*continued*)

Table 2 (Continued)

	Cases (%) N=12634	Controls (%) N=5560	Odds ratio* (95%CI)**	Adjusted odds ratio*** (95%CI)
Medical imaging centre	250 (2.0)	261 (4.7)	0.5 (0.4-0.6)	**0.6 (0.5-0.8)**
Pharmacy	2030 (16.1)	1255 (22.6)	0.7 (0.6-0.7)	**0.9 (0.8-1.0)**
Long-term care facility	73 (0.6)	49 (0.9)	0.7 (0.5-1.0)	0.9 (0.6-1.4)
Bars:				
under 40 years old	2447 (35.6)	597 (26.2)	2.1 (1.8-2.3)	**1.9 (1.6-2.2)**
40 years old and above	874 (15.2)	556 (17.0)	0.8 (0.7-0.9)	1.1 (0.9-1.2)
Restaurants	5263 (41.7)	2369 (42.6)	0.9 (0.8-1.0)	1.0 (0.9-1.1)
Parties (night clubs and private):				
under 40 years old	1503 (21.9)	184 (8.1)	3.2 (2.8-3.9)	**3.4 (2.8-4.2)**
40 years old and above	304 (5.3)	102 (3.1)	1.2 (0.9-1.5)	**1.5 (1.1-1.9)**

***Table 2*: Characteristics, settings and activities associated with SARS-CoV-2 infection, 23 May-13 August 2021, France.**

* Univariable model adjusted for matching factors: age, sex, region, population density and calendar week.

** P<0.05 in the multivariable analysis are in bold.

*** Multivariable model adjusted for matching factors, all variables shown in the model, plus history of past infection, vaccine, body mass index, smoking, co-morbidities, educational attainment, and number of people living in the household.

infections, the mean (SD) incubation time was 5.0 (2.3) days for Alpha, median (IQR)= 5 (3-7); 5.1 (2.7) for Beta/Gamma median (IQR)= 5 (3-7); and 5.1 (2.5) for non-VOC median (IQR)= 5 (3-7).

Discussion

In this ongoing nationwide case-control study in France, we found that during the period 23 May to 13 August 2021, corresponding to the emergence of the Delta variant in France, individuals under 40 years attending bars or parties were at increased risk of infection. In those 40 years and older, having children attend daycare centre, kindergarten, primary school or middle school was associated with increased risk of infection. We found strong protection against symptomatic Delta infection for those with prior infection, whether it was recent (2-6 months) (95%; 95%CI:90-97) or associated with one dose (85%; 95%CI:78-90) or two doses of mRNA vaccine (96%; 95%CI:87-99). For those without prior infection, we found reduced effectiveness of two doses of mRNA vaccine (67%; 95%CI:63-71) against symptomatic Delta infection.

Importantly, we did not find any differences in the settings and activities associated with Delta versus non-Delta infections. Nonetheless, our analyses allow us to make inferences as to the settings that facilitated the rapid spread of the Delta variant in France. We did not observe any increase in the risk of transmission following the reopening of outdoor terraces of both bars (aOR:1.2; 95%CI:0.8-1.7 for those less than 40 years old; aOR:0.7; 95%CI:0.4-1.0 for those more than 40 years old) or restaurants (aOR:1.0; 95%CI:0.7-1.2), likely due in part to reduced capacity and adequate ventilation both reducing the risk of transmission. This was followed by a substantial increase in the risk of transmission associated with attending bars and private parties, particularly among men (bars aOR:5.1; 95%CI:2.4-10.9; private parties aOR:15.3; 95%CI:3.0-77.2) coinciding with: 1. the reopening of indoor facilities of these settings on 9 June, 2. the UEFA European Football Championships from 11 June – 11 July and 3. the predominance of the Delta variant in France. The risk associated with these settings decreased following the opening of night clubs (9 July) which themselves became places at high risk of transmission during the period (aOR: 7.9; 95%CI:4.3-14.5 for those less than 40 years old, and 2.7; 95%CI:1.2-6.1 for those more than 40 years old) despite entry being limited to those with a 'Health Pass'.

For those over 40 years, having children in the household was a likely source of infection. This is a particularly pressing concern as schools return for the beginning of the academic year in France in early September 2021. Encouragingly, we found that public transportation (except subway), car-sharing platforms, visits to cultural places, shopping areas (except convenience stores), hairdressers, beauty salons, sporting activities, or restaurants, were not found to constitute an increased risk of infection. This likely reflects adherence to infection prevention and control measures (mask wearing, hand hygiene, improved ventilation) in places where physical distance may be easier to comply with.

For the second analysis estimating the incubation period using all case data since January 2021, we found that the mean incubation period was shorter for Delta, compared non-Delta. The shorter incubation period is consistent with findings in two outbreaks of Delta in Guangdong, China,[3,12] and would be a key factor in explaining the rapid spread of Delta, particularly if combined with an increase in the transmission during the pre-symptomatic period and higher viral load.[12]

Despite preliminary estimates of VE suggesting that high levels of protection against symptomatic Delta

	23 May-12 June			13 June-12 July						13 July-12 August		
				Men			Women					
	Cases (%) n=2175	Controls (%) n=1036	aOR (95%CI)	Cases (%) n=433	Controls (%) n=576	aOR (95%CI)	Cases (%) n=879	Controls (%) n=1089	aOR (95%CI)	Cases (%) n=8876	Controls (%) n=2825	aOR (95%CI)
Bars												
<40 years old	198 (18.7)	88 (20.4)	1.2 (0.8-1.7)	130 (59.4)	46 (26.4)	**5.1 (2.4-10.9)**	280 (48.9)	130 (27.3)	**2.5 (1.7-3.7)**	1813 (37.0)	329 (27.7)	1.3 (1.0-1.7)
≥40 years old	75 (6.7)	68 (11.3)	0.7 (0.4-1.0)	35 (16.4)	81 (20.1)	0.7 (0.4-1.4)	44 (14.4)	95 (15.5)	1.2 (0.7-1.9)	697 (17.5)	306 (18.7)	1.0 (0.8-1.3)
Restaurants	368 (16.9)	229 (22.1)	1.0 (0.7-1.2)	207 (47.8)	238 (41.3)	1.0 (0.6-1.5)	441 (50.2)	515 (47.3)	0.8 (0.6-1.1)	4147 (46.7)	1368 (48.4)	1.1 (0.9-1.3)
Night club												
<40 years old	NA	NA	NA	NA	NA	NA	NA	NA	NA	704 (16.5)	16 (3.5)	**7.9 (4.3-14.5)**
≥40 ans	NA	NA	NA	NA	NA	NA	NA	NA	NA	82 (2.3)	10 (1.3)	**2.7 (1.2-6.1)**
Private parties												
<40 years old	43 (4.1)	18 (4.2)	1.5 (0.7-3.2)	49 (22.4)	7 (4.0)	**15.3 (3.0-77.2)**	96 (16.8)	24 (5.0)	**3.2 (1.6-6.1)**	696 (16.3)	83 (18.2)	0.8 (0.6-1.1)
≥40 years old	6 (0.5)	2 (0.3)	5.7 (0.4-74.1)	5 (2.3)	4 (1.0)	5.9 (0.6-56.4)	4 (1.3)	2 (0.3)	2.4 (0.3-17.9)	198 (5.4)	80 (10.6)	**0.6 (0.4-0.8)**

Table 3: **Specific activities associated with SARS-CoV-2 infection by time period and by sex, 23 May-12 August 2021, France.**
Important dates: Reopening of outdoor terraces at bars and restaurants – 19 May 2021; Reopening of indoor dining and drinking at bars and restaurants – 9 June 2021; Reopening of nightclubs for those with a 'Health Pass' (evidence of recent (<72 hours) negative RT-PCR test, proof of COVID-19 vaccination or recovery from recent (<6 months) COVID-19) – 9 July 2021; Nationwide introduction of 'Health Pass' – 9 August 2021.

infection are maintained with two doses of BNT162b2 or ChAdOx1 nCoV-19 vaccines,[5] subsequent observational studies with longer post-vaccination follow-up, indicate reduced protection against symptomatic infection.[13–16] In line with these latter studies, we also observed reduced VE against symptomatic Delta infection. It is not clear whether this reflects reduced effectiveness of current vaccines against the Delta variant and/or waning immunity. Importantly however, it appears that the high levels of protection against severe disease are maintained,[15–17] which will be critical in terms of the overall impact of vaccination campaigns. Any decision as to the need for additional vaccine doses will depend on if and how fast immunity wanes, and whether protection against severe disease is shown to be reduced.

France is one of the few countries in which vaccination is considered complete after one dose for those who have documented prior natural infection (the vaccine dose is administered at least six months after the infection).[18] We assessed VE with and without prior infection and found strong protection for those with recent (2-6 months) prior infection (95%; 95%CI:90-97), and associated with one dose (85%; 95%CI:78-90) or two doses of mRNA vaccine (96%; 95%CI:87-99), supporting the original policy decision on dosing schedule for those with prior infection. This finding is in line with previous reports highlighting the strong protection associated with combined natural and vaccine-induced immunity.[19] Of note, one dose of mRNA in the absence of prior infection was associated with limited protection against symptomatic infection with the Delta variant, as already shown by others.[5]

This study has several limitations, which have been previously described.[6,7] Briefly, we cannot exclude the possibility of asymptomatic infection in the controls. This would underestimate the strength of some associations reported. It is also important to interpret the findings in the context of the public health and social measures that were implemented in France during the study period, which likely influenced the exposures of certain activities and settings. During the time period of the study, France was progressively reopening public places (outdoor dining on 19 May, indoor dining on 9 June, night clubs on 9 July for those with a 'Health pass'). Another issue is the extent to which the source population for cases and controls was the same, a concern that may be exacerbated by the low response rate (8% for cases, and 7% for controls). Cases were recruited nationwide, and controls were selected from a panel from a market and public opinion research company, which can be considered to be representative of the French population. However, previous analysis of the study population has revealed that respondents, both cases and controls, tended to be younger, more female, and wealthier, compared to the source population.[6] Selection bias, and confounding, may have been attenuated through multivariable analysis, and our

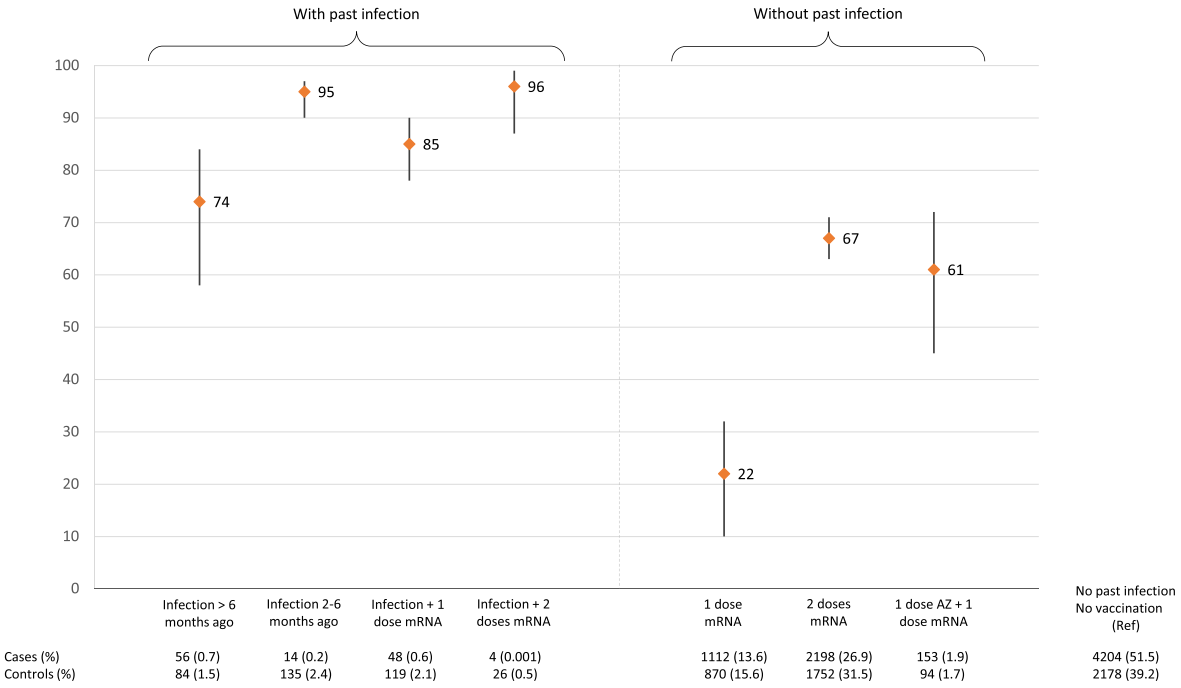

Figure 2. Protection/Vaccine effectiveness (VE) (%, and vertical bars indicating 95% CI) against symptomatic Delta variant infection, according to dose, vaccine type and prior SARS-CoV-2 infection, 23 May-13 August 2021, France*

*The analysis of vaccine effectiveness and protection associated with past infection was adjusted for age, sex, region, population density of place of residence, calendar week, body mass index, smoking status, co-morbidities (overweight and obesity, diabetes, high blood pressure, chronic respiratory diseases, and immunosuppression), educational attainment, number of people living in the household, and all variables (characteristics, setting and activities) shown in Table 2.

findings were overall consistent with those in the published literature. We did not focus on the social factors associated with infection, but rather controlled for them through matching (population density) and adjustment in the multivariable analysis (professional categories, level of educational attainment, type of housing, and number of people living in the household). In accordance with the French data protection authority (CNIL), we were not able to collect data on ethnicity. As shown in the Results section, the vaccine coverage among controls was slightly higher than that of the French population, in line with what would be expected from a wealthier population, which would lead to an overestimate of the VE unless the same selection bias also applied to cases. The online questionnaire may also have prevented those with limited internet access and/or command of the French language from participating in the study. Our results may therefore not be generalisable to the entire French adult population despite nationwide sampling. Some important changes in OR between uni- and multivariable analysis for some places at increased risk of infection, like aeroplanes and medical laboratories, suggest that these results should be interpreted with caution. It is not clear whether an increase in risk associated with travel by aeroplanes reflects transmission in aeroplanes themselves, or the risk associated with the travel destination (33.9% of cases who said they travelled overseas had gone to Spain, where the Delta variant was actively circulating during the study period). Similarly, the increase in risk associated with medical laboratories could reflect differences in health seeking behaviours. Finally, the use of case-control studies for determining vaccine effectiveness requires careful selection of cases and controls, and adjustment for potential confounders.[20] Our ability to control for a very large number of potential confounders, and the overall consistency of our vaccine effectiveness estimates against symptomatic Alpha and Beta variant in the previous study,[7] and Delta variant in this study, with other published studies using other methodologies increase our confidence in the results.

In summary, the ongoing nationwide case-control study continues to identify settings and activities at increased risk of infection and highlight where efforts to reinforce individual infection prevention and control and/or public health and social measures need to be concentrated. This is all the more important given the shorter incubation period, which may partly help to explain the rapid spread of the Delta variant in France. The risk posed by children attending school is concerning ahead of the start of the academic year, with children remaining a largely unvaccinated proportion of the population. Finally, our study suggests reduced vaccine effectiveness and/or waning immunity, particularly in those with no prior

SARS-CoV-2 infection. The need for an additional dose of vaccine warrants further investigation.

Author contributions

AF, SG, TC, LS, FO, CD, FC, SC, AM, and DLB designed the investigation.

SG, TC, LS, AF, AS, AM, and DLB developed the study questionnaire.

FO, CD, CB, AR managed the data collection online.

OC, CVP and TC oversaw the adherence of the study to the regulatory requirements.

TC and LS oversaw the collection of the data and maintained the database.

TC, LS, JP, YM, and AF performed the statistical analyses.

RG, TC and AF drafted the first versions of the manuscript.

All authors critically reviewed and approved the final version of the manuscript.

Declaration of interests

All authors have nothing to declare.

Data availability statement

The data that support the findings of this study are available from the Caisse Nationale d'Assurance Maladie, a national health insurance agency in France and from Ipsos, a French market research and public opinion specialist company. Restrictions apply to the availability of these data, which were used under authorized agreement for this study by the data protection authority Commission Nationale de l'Informatique et des Libertés (CNIL). Access to these data would therefore require prior authorization by the CNIL.

Funding statement

The study was funded by Institut Pasteur and Research, Action Emerging Infectious Diseases (REACTing), and the French Agency ANRS- Maladies Infectieuses Emergentes (ComCor project). AF's laboratory receives support from the Labex IBEID (ANR-10-LABX-62-IBEID) and the INCEPTION project (PIA/ANR-16-CONV-0005) for studies on emerging viruses. TC is funded by the Fondation de France (Alliance "Tous unis contre le virus").

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2021.100278.

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