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1 Delay between COVID-19 complete vaccination and SARS-CoV-2 infection among healthcare
2 workers.

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24 Abstract

25 Objectives: Healthcare workers (HCWs), at increased risk of coronavirus disease 2019
26 (COVID-19) were among the primary targets for vaccination, which became mandatory for
27 them on September 15th, 2021 in France. In November they were confronted to the fifth
28 COVID-19 wave despite excellent vaccine coverage. We aimed to estimate the incidence of
29 SARS-CoV-2 infection after complete vaccination among HCWs with different vaccination
30 schemes, and its determinants.

31 Methods: We enrolled all HCWs in the university hospital of Rennes, France who had received
32 complete vaccination (two doses of COVID-19 vaccine). The delay from last vaccination dose
33 to SARS-CoV-2 infection was computed. Fitted mixed Cox survival model with a random
34 effect applied to exposure risk periods to account for epidemic variation was used to estimate
35 the determinants of SARS-CoV-2 infection after complete vaccination.

36 Results: Of the 6674 (82%) HCWs who received complete vaccination (36% BNT162b2, 29%
37 mRNA-1273, and 34% mixed with ChAdOx1 nCoV-19) and were prospectively followed-up
38 for a median of 7.0 [6.3-8.0] months, 160 (2.4%) tested positive for SARS-CoV-2 by RT-PCR.
39 Incidence density of SARS-CoV-2 infection after complete vaccination was 3.39 [2.89-3.96]
40 infections per 1000 person-month. Median time from vaccine completion to SARS-CoV-2
41 infection was 5.5 [3.2-6.6] months. Using fitted mixed Cox regression with the delay as a time-
42 dependent variable and random effect applied to exposure risk periods, age ($P < 0.001$) was
43 independently associated with the incidence of SARS-CoV-2 infection. Vaccine schemes were

44 not associated with SARS-CoV-2 infection ($P=0.068$). A period effect was significantly
45 associated with the incidence of SARS-CoV-2 infection ($P<0.001$).

46 Conclusions: In this real-world study, incidence of SARS-CoV-2 infection increases with time
47 in fully vaccinated HCWs with no differences according to the vaccination scheme. The short
48 delay between complete vaccination and incident SARS-CoV-2 infection highlights the need
49 for sustained barrier measures even in fully vaccinated HCWs.

50

51 Keywords: COVID-19; Vaccine; SARS-CoV-2 infection; complete vaccination; healthcare
52 workers

Highlights

- COVID-19 complete vaccination is mandatory for healthcare workers (HCWs)
- Incidence density of infections increases with time from full vaccination in HCWs
- Median time from vaccine completion to SARS-CoV-2 infection was 5.5 months
- Using Fitted mixed Cox model, vaccines were not associated with SARS-CoV-2 infection

53 Introduction

54 Healthcare workers (HCWs) are at increased risk for exposure to severe acute respiratory
55 syndrome coronavirus 2 (SARS-CoV-2) due to their interactions with patients in addition to
56 their household and community (1). In France, COVID-19 vaccines have been available since
57 January 2021, with priority initially given to individuals at high risk of severe coronavirus
58 disease 2019 (COVID-19), and HCWs. At that time, the alpha variant was predominant and
59 responsible for the third wave. From June, the Delta variant progressively replaced the alpha
60 variant to become predominant in July 2020, responsible for the fourth wave followed by the
61 fifth wave (Data extracted from Santé Publique France;
62 [https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-
63 et-evolution-de-la-covid-19-en-france-et-dans-le-monde](https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde)). Since September 15th, 2021,
64 complete vaccination was set compulsory for all HCWs to protect them, their patients, and
65 their relatives against COVID-19. In our institution, 82% (6674 out of 8165) HCWs received
66 complete vaccination, an increase in the number of positive HCWs for SARS-CoV-2 has been
67 observed concomitant to fifth wave. We performed a prospective monocentric cohort study to
68 evaluate the risk of SARS-CoV-2 infection and assess its determinants among fully
69 vaccinated HCWs.

70

71 Methods

72 Study design

73 We performed a monocentric prospective cohort study in the university hospital of Rennes, a
74 1,800-bed tertiary care hospital in Western France, to evaluate the incidence of SARS-CoV-2
75 infection over time after complete vaccination with different vaccine schemes, in a real-world
76 setting among HCWs. All HCWs who received two doses of COVID-19 vaccines, whether

77 BNT162b2, mRNA-1273 and ChAdOx1 nCoV-19, were defined as completely vaccinated and
78 included in our study. For the purpose of contact tracing, all HCWs are requested to inform the
79 occupational department when they are diagnosed with SARS-CoV-2 infection, and this data
80 was prospectively monitored throughout the study period. Tests for SARS-CoV-2 infection
81 were available in our institution, and in a large number of facilities, with no charge in
82 vaccinated people. Patients who received three doses of vaccines were excluded (n= 395; 6%).

83

84 Definitions

85 Complete vaccination was defined as the administration of 2 doses of COVID-19 vaccines.

86 Vaccine schemes were defined as follows: ‘BNT162b2’ for administration of two doses of
87 BNT162b2 vaccine, ‘mRNA-1273’ for two doses of mRNA-1273 vaccine, ‘mixed mRNA’ for
88 one dose of BNT162b2 and one dose of mRNA-1273 vaccines and ‘schemes including
89 ChAdOx1 nCoV-19’ for one dose of ChAdOx1 nCoV-19 vaccine and the other with
90 BNT162b2 or mRNA-1273 or ChAdOx1 nCoV-19 vaccines.

91 Cases were defined as HCWs who tested positive for SARS-CoV-2 by reverse-transcription
92 polymerase-chain-reaction (RT-PCR) from a nasopharyngeal sample, independently of the
93 presence of symptoms. HCWs with SARS-CoV-2 infection prior to complete vaccination and
94 infections within 14 days of complete vaccination were not considered as cases. HCWs were
95 tested in case of any symptom suggestive of COVID-19, or for the purpose of contact tracing
96 when they were identified as contact of someone with SARS-CoV-2 infection.

97

98 Data collection

99 Data were prospectively collected from January 21st, 2021 (first HCW fully vaccinated) until
100 the December 14th, 2021, to restrict the study period to the circulation of the Alpha and Delta
101 variants, as the first Omicron variant was identified in our hospital on December 14th, 2021.
102 The 31/05/2021 and 31/10/2021 were retained to define the 3rd, 4th and 5th waves respectively.

103 Two prospective databases systematically recorded in our institution were merged:

104 (a) HCWs who received complete COVID-19 vaccination as previously described (2).
105 Collected data included baseline demographic data (age), type of vaccine (BNT162b2 vaccine,
106 mRNA-1273 or ChAdOx1 nCoV-19 vaccines), date of last dose, number of doses received.

107 (b) HCWs positive for SARS-CoV-2. SARS-CoV-2 RT-PCR results were retrieved from
108 laboratory data and from patient's phone interview. All HCWs with positive RT-PCR were
109 contacted within 48 hours of diagnosis using a standardized questionnaire. Date of positive
110 RT-PCR, and symptoms by the time RT-PCR was positive were retrieved. Delay between
111 complete vaccination and SARS-CoV-2 infection was systematically computed.

112 Data were anonymized before analysis, and HCWs were informed of the study and its results
113 through our institution website according to the French law on clinical research. This study
114 was conducted in accordance with the principles of the Declaration of Helsinki.

115

116 Statistical analyses

117 Data are reported as numbers with percentage for qualitative variables or median with
118 interquartile interval for quantitative variables.

119 The delay from complete vaccination to SARS-CoV-2 infection was represented according to

120 vaccine schemes over time using box plot and modelled as a time-dependent variable using
121 Kaplan-Meier survival curves. Influence of time from last vaccination to SARS-CoV-2
122 infection according to the vaccine scheme was assessed using log-rank analysis. Complete
123 vaccination with BNT162b2 vaccine was defined as the reference.

124 To account for variations in the infection rate and variant circulation throughout the study
125 period, a time-dependent fitted mixed Cox model was performed using i) random effect applied
126 to the different exposure risk periods to account for the following risk throughout the COVID-
127 19 waves, and ii) delay from complete vaccination to SARS-CoV-2 infection as a time-
128 dependent variable, to assess risk factors associated with positivity for SARS-CoV-2 after
129 complete vaccination. Exposure risk periods were defined according to the month last vaccine
130 dose was received. HCWs who received their last dose in November and December were
131 considered as exposed to the same risk (fifth wave). Variables were selected if significant
132 ($P < 0.2$) in the univariate analysis (**Table 1**). Conditional stepwise regression with, 0.2 as the
133 critical P value for entry, and, 0.1, as the P value for removal, was used. Type of vaccine was
134 planned *a priori* to be forced into the final model, if not previously selected. Results are
135 presented as hazard risks (adjusted Hazard Ratio, HR) with 95%CI.

136 Statistical significance was considered using two-sided tests with a critical alpha risk of 0.05.
137 Statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical
138 Computing).

139

140 Results

141 We included the 6674 (82%, out of 8165 HCWs in our institution) HCWs whom received
142 complete vaccination (**Figure 1**). Progression of complete vaccination among HCWs is shown
143 in **Figure 2a**, and SARS-CoV-2 infection in HCWs over the different COVID-19 waves in

144 **Figure 2b.** With a median follow-up of 7.0 [6.3-8.0] months, 160 cases (2.4%) tested positive
145 for SARS-CoV-2, with a median time from last vaccination dose of 5.5 [3.2-6.6] months
146 (**Figure 2c**). Median overall incidence density of SARS-CoV-2 infection during the study
147 period was 3.39 [2.89-3.96] per 1000 person-month (0.19 [0.08-0.36] during the third wave,
148 1.04 [0.77-1.37] during the fourth wave, and 2.17 [1.77-2.64] during the fifth wave). The
149 incidence at 3 and 6 months of complete vaccination was 7 [5-10] and 12 [9-15] per 1000
150 person-month respectively.

151 HCWs had a median age of 34 [26-47] years when they were diagnosed with SARS-CoV-2
152 infection, and they were mostly vaccinated with 2 doses of BNT162b2 (44%) or a combination
153 of 2 different vaccines (BNT162b2 or mRNA-1273 with ChAdOx1 nCoV-19; 29%). Among
154 positive HCWs, 145 (91%) were symptomatic with predominant complains being rhinorrhea
155 (72%) followed by headaches (61%) and cough (59%) (**Table 1**).

156

157 In univariate analysis, HCWs with SARS-CoV-2 infection were younger (median age, 34 [26-
158 47] versus 39 [29-49] years, $P=0.015$). We found no association between patterns of
159 vaccination and the incidence of SARS-CoV-2 infection ($P=0.244$; **Table 1**), or the delay
160 between complete vaccination and SARS-CoV-2 infection ($P=0.245$; **Figure 2**).

161

162 Taking into account the delay between the last dose and SARS-CoV-2 infection as a time-
163 dependent variable, Kaplan-Meier survival curves showed no difference in the incidence of
164 SARS-CoV-2 infection according to the type of received vaccination ($P = 0.42$; **Figure 3**).

165 Using fitted mixed Cox regression with random effect applied to exposure risk periods and the
166 delay from complete vaccination to SARS-CoV-2 infection as a time-dependent variable,
167 adjusted on age and vaccine scheme, age (HR 0.96 [0.94-0.98]; $P<0.001$) remained
168 independently associated with the incidence of SARS-CoV-2 infection. No difference among

169 vaccines schemes was observed with the incidence of SARS-CoV-2 infection throughout time
170 from complete vaccination ($P=0.108$) (**Table 2**). Conversely, the different exposure risk
171 periods effect was significantly associated with the incidence of SARS-CoV-2 infection
172 ($P<0.001$).

173

174 Discussion and conclusion

175 Among fully vaccinated HCWs, we observed an incidence density of SARS-CoV-2 infection
176 after complete vaccination of 3.4 infections per 1000 person-month after a median delay of 5.5
177 months for all vaccine schemes, which increased over time from complete vaccination. In the
178 multivariate analysis, when accounting for variations in the infections rate throughout the study
179 period, vaccine schemes were not associated with the incidence of SARS-CoV-2.

180

181 Effectiveness of vaccines against symptomatic COVID-19 in HCWs was previously assessed
182 in the literature for mRNA vaccines and revealed 88.8% (95% CI, 84.6 to 91.8) and 96.3%
183 (95% CI, 91.3 to 98.4) effectiveness after complete vaccination with BNT162b2 vaccine and
184 mRNA-1273 vaccine respectively according to a 2-week interval follow-up (3). After a follow-
185 up of 2 months, mRNA-1273 showed 94.1% efficacy after 2 doses of vaccine (4) and ChAdOx1
186 nCoV-19 62.1% (5). In addition, complete vaccination with BNT162b2 reduced the risk of
187 COVID-19 and absenteeism among HCWs (6).

188 During the circulation of the Alpha variant, while only 15% HCWs had received full
189 vaccination, 9 cases of SARS-CoV-2 infections were detected. In mid-June, while 83% of
190 HCWs had received full vaccination, 151 were diagnosed with SARS-CoV-2 infection while
191 the Delta variant was circulating. Since November 2021, an increase in the number of SARS-
192 CoV-2 infections was reported, concomitant to the fifth wave. With a longer follow-up of 7
193 months, incidence density of SARS-CoV-2 infection with time increased with the delay from

194 full vaccination suggesting reduced vaccines efficiency over time, with a median delay of 5.5
195 [3.2-6.6] months since last injection, consistent with other reports in the general population
196 (7,8). Our observations are in agreement with other studies reporting reduced effectiveness
197 from 82% to 53% after 6 months of two-dose mRNA vaccine in HCWs during Delta variant
198 circulation (9). Waning immunity might play a crucial role in COVID-19 breakthrough. Other
199 hypotheses have been raised to explain the recent COVID-19 breakthrough including the entry
200 into the winter period, relaxation of barrier measures due to vaccination or reduced efficacy of
201 vaccines against the Delta variant. Of importance, this recent increase cannot be ascribed to the
202 emergence of Omicron variant, as our study was interrupted on December 14th, 2021 just before
203 the first Omicron case was diagnosed in our institution.

204 In addition, the different exposure risk periods were independently associated with SARS-
205 CoV-2 infection suggesting differences in SARS-CoV-2 infections throughout the different
206 COVID-19 waves. The infection risk increased with time from last vaccination but also along
207 the different variants. Yamamoto and colleagues reported COVID-19 breakthrough infection
208 among fully vaccinated HCWs during the fifth wave, dominated by the delta variant with
209 reduced neutralizing antibodies against COVID-19 variants (10).

210 Interestingly, age was independently associated with the incidence of SARS-CoV-2 infection
211 with younger HCWs at increased risk of infection in our study. This observation might be
212 explained by the fact that younger HCWs are more exposed and may take more risk with
213 reduced barrier measures.

214

215 Our study has limitations. First, as a monocentric study, its findings may not be generalizable
216 to other settings, given the variability of the epidemiology of SARS-CoV-2 variants. In
217 addition, our results might not extrapolate to the Omicron variant. However, our study includes
218 homogeneous data with appropriate follow-up and data were adjusted on the different waves

219 taking into account the circulation of the different strains. Second, we may have slightly
220 underestimated the incidence of SARS-CoV-2 infections, as few HCWs did not communicate
221 their results to the occupational health department when tested outside the institution. However,
222 this underestimate is considered independent from the vaccine strategies, and to only have a
223 slight effect on statistical power without bias. SARS-CoV-2 infections prior to and within 14
224 days of complete vaccination were not considered as cases but at risk of reinfection and were
225 not excluded from the analysis. Excluding these patients in a sensitivity analysis did not change
226 our results. At last, three COVID-19 vaccines were used in our hospital during the study period,
227 according to authorizations of the French drug agency and to their availability. Following
228 reports of severe thrombotic events related to the ChAdOx1 nCoV-19 vaccine, its
229 administration was interrupted on March 15th in France, and restarted on the 20th March,
230 thereafter restricted to people aged 55 years and older which resulted in imbalance between the
231 vaccine groups. Few HCWs received schemes with mixed mRNA. Consequently, our study
232 was underpowered to identify an association with this vaccine scheme.

233

234 To our knowledge, this is the first study estimating the elapsed time since complete vaccination
235 with different vaccine schemes and the incidence of SARS-CoV-2 infection among HCWs in
236 France. Other strengths of this work include the follow-up of 7 months as compared to short
237 follow-up periods in other studies.

238 In conclusion, our work suggests that independent of COVID-19 vaccination scheme, vaccine
239 efficiency after two doses of either BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19
240 decreases over time, especially after 3 months, in HCWs. Additional large-scale studies are
241 requested to assess the effect of the third dose regarding the incidence of SARS-CoV-2
242 infection which might be helpful regarding the current Omicron variant diffusion.

243 **Conflict of interest statement**

244 We declare no conflict of interest related to this work.

245

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248 commercial, or not-for-profit sectors.

249

250 **References**

251 1. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine
252 coverage in health-care workers in England and effectiveness of BNT162b2 mRNA
253 vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet Lond*
254 *Engl.* 2021 May 8;397(10286):1725–35.

255 2. Paris C, Perrin S, Hamonic S, Bourget B, Roué C, Brassard O, et al. Effectiveness of
256 mRNA-BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 vaccines against COVID-19 in
257 healthcare workers: an observational study using surveillance data. *Clin Microbiol Infect*
258 *Off Publ Eur Soc Clin Microbiol Infect Dis.* 2021 Nov;27(11):1699.e5-1699.e8.

259 3. Pilishvili T, Gierke R, Fleming-Dutra KE, Farrar JL, Mohr NM, Talan DA, et al.
260 Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel. *N Engl J*
261 *Med.* 2021 Sep 22;

262 4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety
263 of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021 Feb 4;384(5):403–16.

264 5. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety

- 265 and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an
266 interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK.
267 *Lancet Lond Engl.* 2021 Jan 9;397(10269):99–111.
- 268 6. Maltezou HC, Panagopoulos P, Sourri F, Giannouchos TV, Raftopoulos V, Gamaletsou
269 MN, et al. COVID-19 vaccination significantly reduces morbidity and absenteeism among
270 healthcare personnel: A prospective multicenter study. *Vaccine.* 2021 Nov
271 26;39(48):7021–7.
- 272 7. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning
273 Immunity after the BNT162b2 Vaccine in Israel. *N Engl J Med.* 2021 Dec 9;385(24):e85.
- 274 8. Israel A, Merzon E, Schäffer AA, Shenhar Y, Green I, Golan-Cohen A, et al. Elapsed time
275 since BNT162b2 vaccine and risk of SARS-CoV-2 infection: test negative design study.
276 *BMJ.* 2021 Nov 24;375:e067873.
- 277 9. Poukka E, Baum U, Palmu AA, Lehtonen TO, Salo H, Nohynek H, et al. Cohort study of
278 Covid-19 vaccine effectiveness among healthcare workers in Finland, December 2020 -
279 October 2021. *Vaccine.* 2021 Dec 18;S0264-410X(21)01640-6.
- 280 10. Yamamoto S, Maeda K, Matsuda K, Tanaka A, Horii K, Okudera K, et al. COVID-19
281 breakthrough infection and post-vaccination neutralizing antibody among healthcare
282 workers in a referral hospital in Tokyo: a case-control matching study. *Clin Infect Dis Off*
283 *Publ Infect Dis Soc Am.* 2021 Dec 24;ciab1048.

1 Tables

2 Table 1. Characteristics of the healthcare workers.

	Overall	No SARS-CoV-2 infection	SARS-CoV-2 infection	<i>P</i>
n	6674	6506	160	
Age (years)	39 [29-49]	39 [29-49]	34 [26-47]	0.015
Follow-up (months)	7.0 [6.3-8.0]	7.0 [6.4-8.0]	5.5 [3.2-6.6]	<0.001
Vaccination strategy				
Type of vaccine*				0.244
BNT162b2	2426 (36)	2353 (36)	70 (44)	
mRNA-1273	1931 (29)	1886 (29)	42 (27)	
Mixed mRNA	44 (1)	42 (1)	1 (1)	
ChAdOx1 nCoV-19	50 (0.7)	40 (0.8)	0 (0)	
Mixed schemes including ChAdOx1 nCoV-19	2219 (33)	2173 (33)	45 (29)	
Delay from complete vaccination to SARS-CoV-2 infection (months)				
	-	-	5.5 [3.2 - 6.6]	
COVID-19 waves				
Third wave	-	-	9 (6)	
Fourth wave	-	-	49 (31)	
Fifth wave			102 (64)	
Symptoms				
	-	-	145 (91)	
Headache	-	-	97 (61)	
Cough	-	-	94 (59)	
Thrill	-	-	55 (35)	
Fever	-	-	52 (33)	
Aches	-	-	62 (39)	

Sore Throat	-	-	76 (48)
Nasal discharge	-	-	76 (45)
Rhinorrhoe	-	-	114 (72)
Anosmia/agueusia	-	-	59 (37)

3 Data are reported as numbers with percentage for qualitative variables or median with interquartile interval for
4 quantitative variables.

5 *Vaccine schemes were defined as follows: 'BNT162b2' for administration of two doses of BNT162b2 vaccine,
6 'mRNA-1273' for two doses of mRNA-1273 vaccine, 'mixed mRNA' for one dose of BNT162b2 and one dose
7 of mRNA-1273 vaccines, 'ChAdOx1 nCoV-19' for two doses of ChAdOx1 nCoV-19 vaccines and 'schemes
8 including ChAdOx1 nCoV-19' for one dose of ChAdOx1 nCoV-19 vaccine and the other with BNT162b2 or
9 mRNA-1273 or ChAdOx1 nCoV-19 vaccines.

10

11 **Table 2. Risk factors associated with time to SARS-CoV-2 infection after complete**
12 **vaccination**

Variables	Fitted mixed cox regression	
	HR CI95%	P value
Type of vaccine*	-	0.068
BNT162b2	1.00	-
mRNA-1273	1.20 [0.47-3.10]	0.70
Mixed mRNA	1.41 [0.19-10.75]	0.740
Schemes including ChAdOx1 nCoV-19	0.53 [0.26-1.10]	0.087
Age (per one year)	0.96 [0.94-0.98]	<0.001
Risk exposure periods	-	<0.001

13 Data are reported as numbers with percentage for qualitative variables or median with interquartile interval for
14 quantitative variables.

15 *Vaccine schemes were defined as follows: 'BNT162b2' for administration of two doses of BNT162b2 vaccine,
16 'mRNA-1273' for two doses of mRNA-1273 vaccine, 'mixed mRNA' for one dose of BNT162b2 and one dose
17 of mRNA-1273 vaccines and 'schemes including ChAdOx1 nCoV-19' for one dose of ChAdOx1 nCoV-19
18 vaccine and the other with BNT162b2 or mRNA-1273 or ChAdOx1 nCoV-19 vaccines.

1 **Figure legend**

2 **Figure 1. Flow-chart of the study.**

3 **Figure 2. SARS-CoV-2 infection after complete vaccination with time.** A) Kernel density
4 of fully vaccinated HCWs throughout the study period from January 21 to November 30, 2021.
5 B) Kernel density of SARS-CoV-2 infection in fully vaccinated HCWs throughout the study
6 period from March 4 to December 14, 2021. C) Incidence of SARS-CoV-2 infections
7 according to the delay from complete vaccination for the different vaccine schemes.

8 **Figure 3. Kaplan-Meier survival curve representing the incidence of SARS-CoV-2**
9 **infection with the delay from complete vaccination as a time-dependent variable.** A)
10 Kaplan-Meier survival curve representing overall incidence of SARS-CoV-2 infection with
11 time. B) Kaplan-Meier survival curve representing overall incidence of SARS-CoV-2 infection
12 according to vaccine schemes with time. The red curve corresponds to scheme with
13 BNT162b2, the blue to scheme with mRNA-1273, green schemes including ChAdOx1 nCoV-
14 19 and purple mixed mRNA schemes. No difference was found between the different vaccine
15 schemes ($P=0.42$) in the incidence of SARS-CoV-2 infection taking the delay as the time-
16 dependent variable, compared using a Log-Rank test. Time is given in days.

8165 HCWs

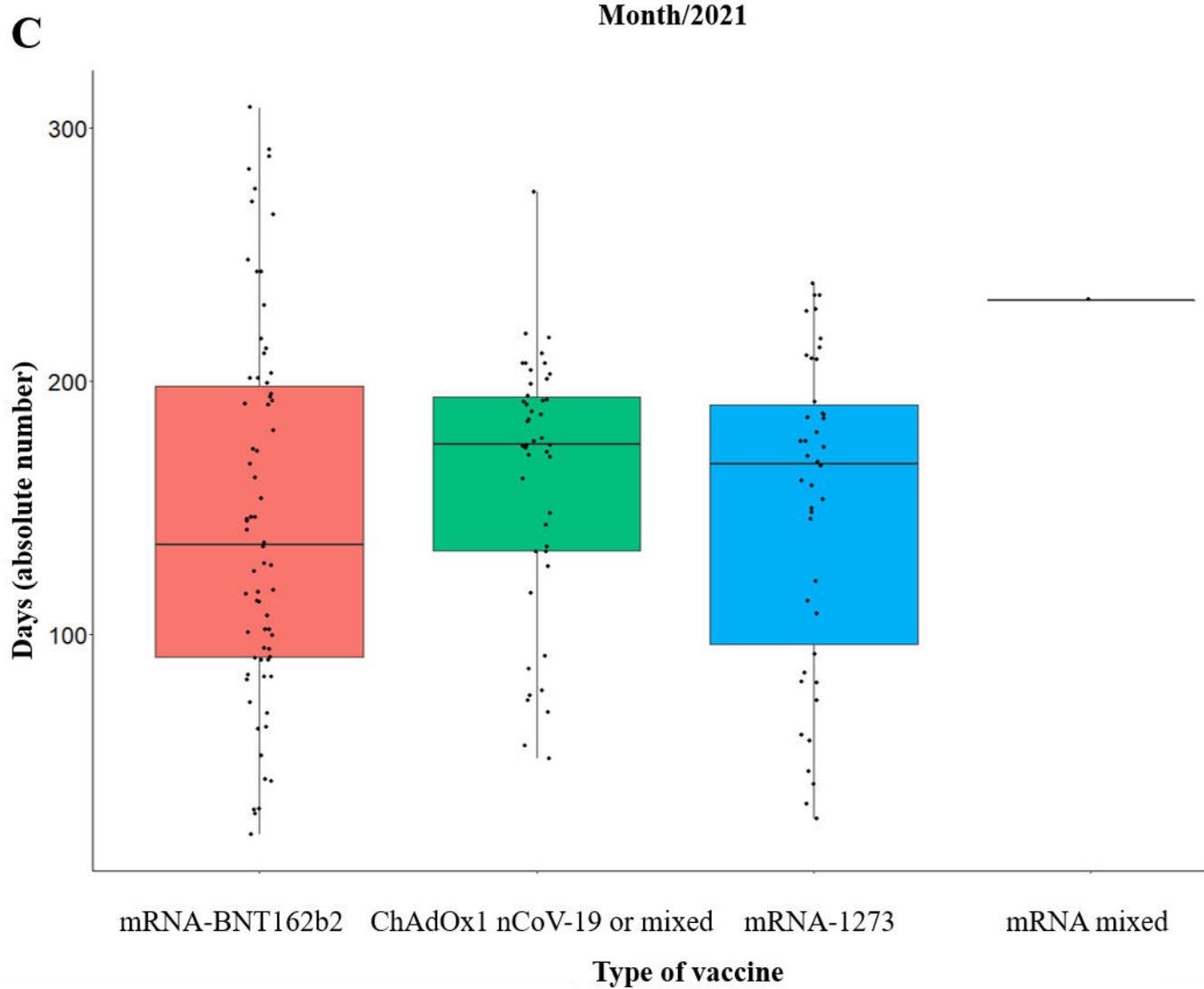
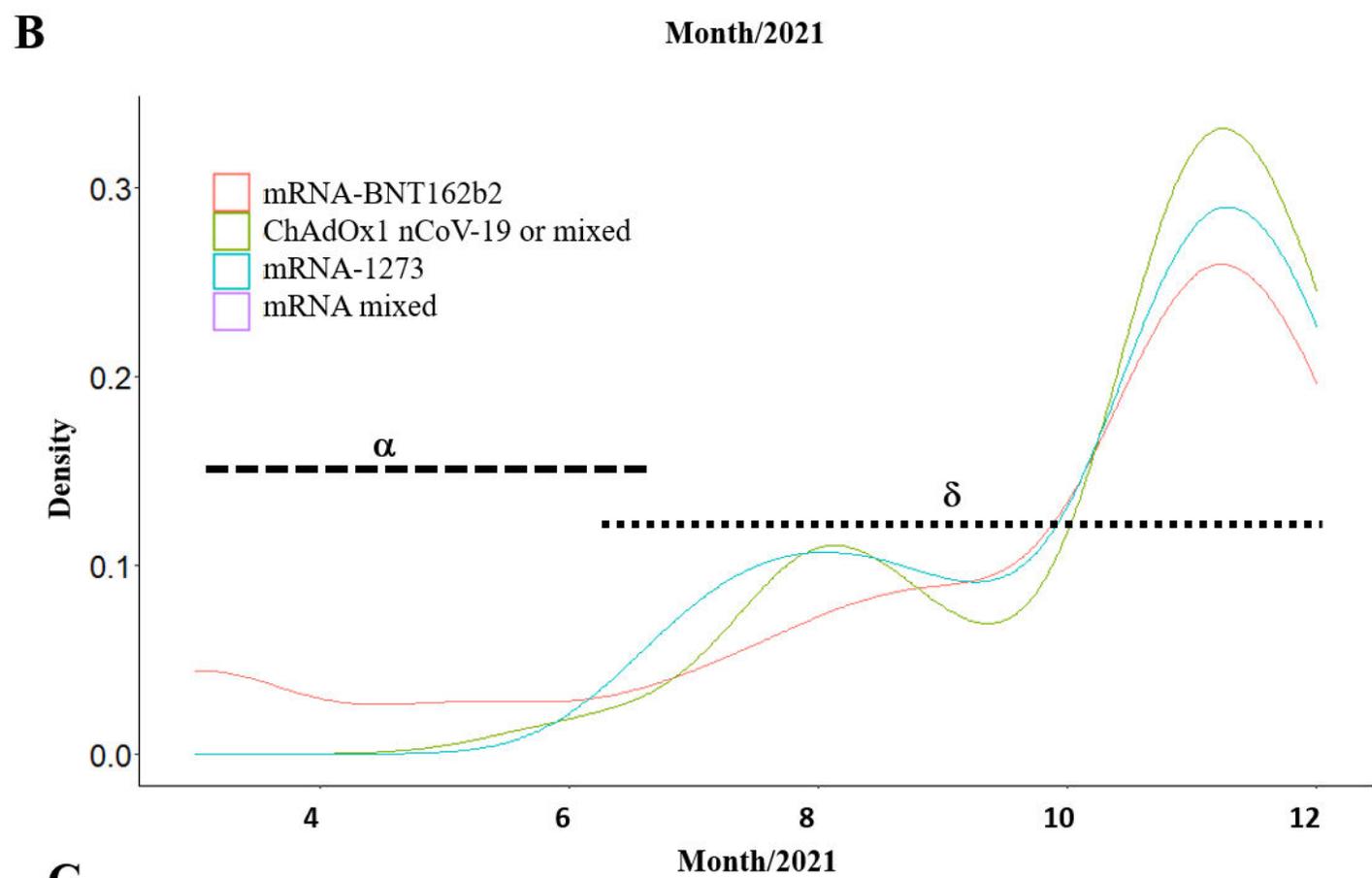
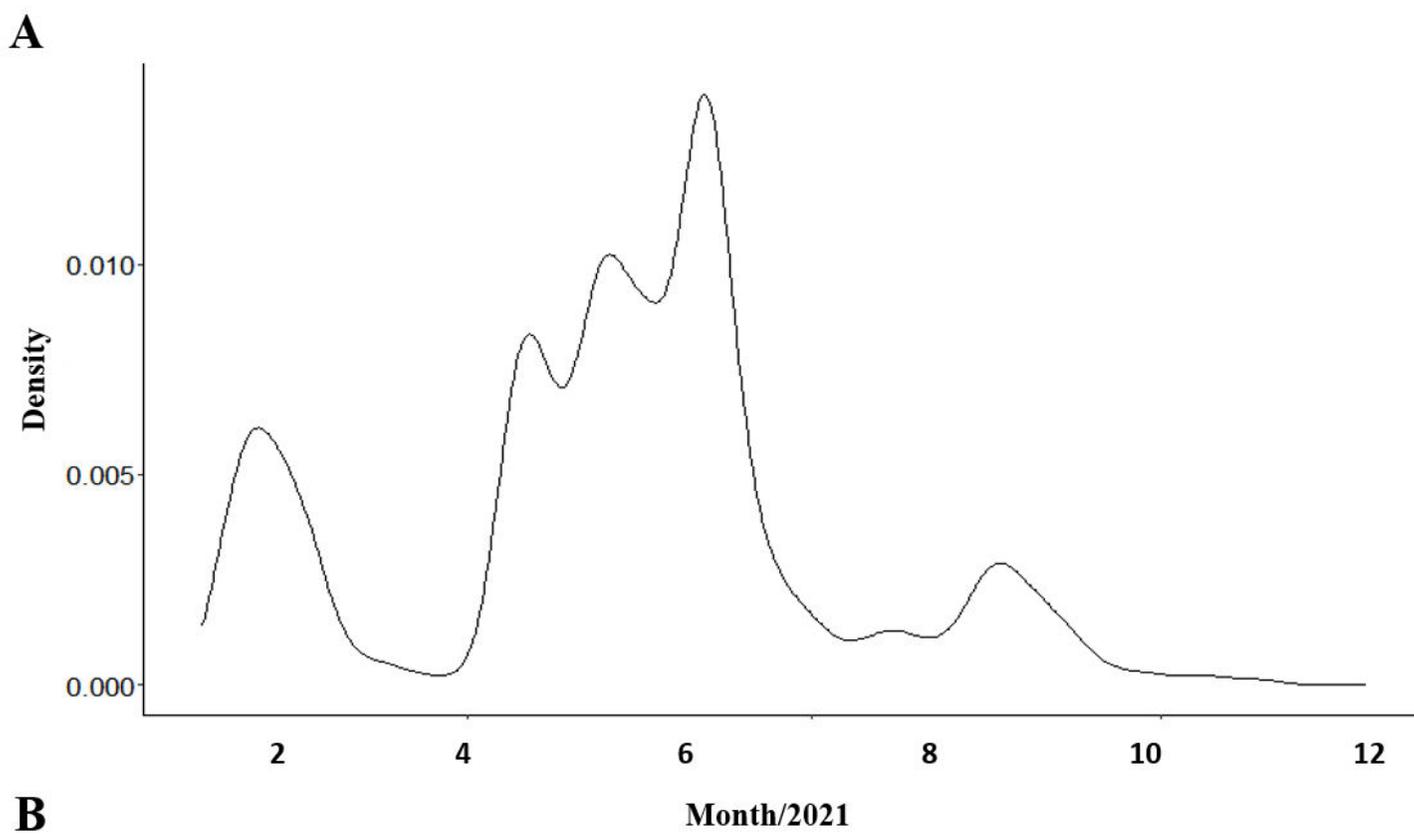
**7069 HCWs with
complete vaccination**

**395 (6%) HCWs
with 3 doses were
excluded**

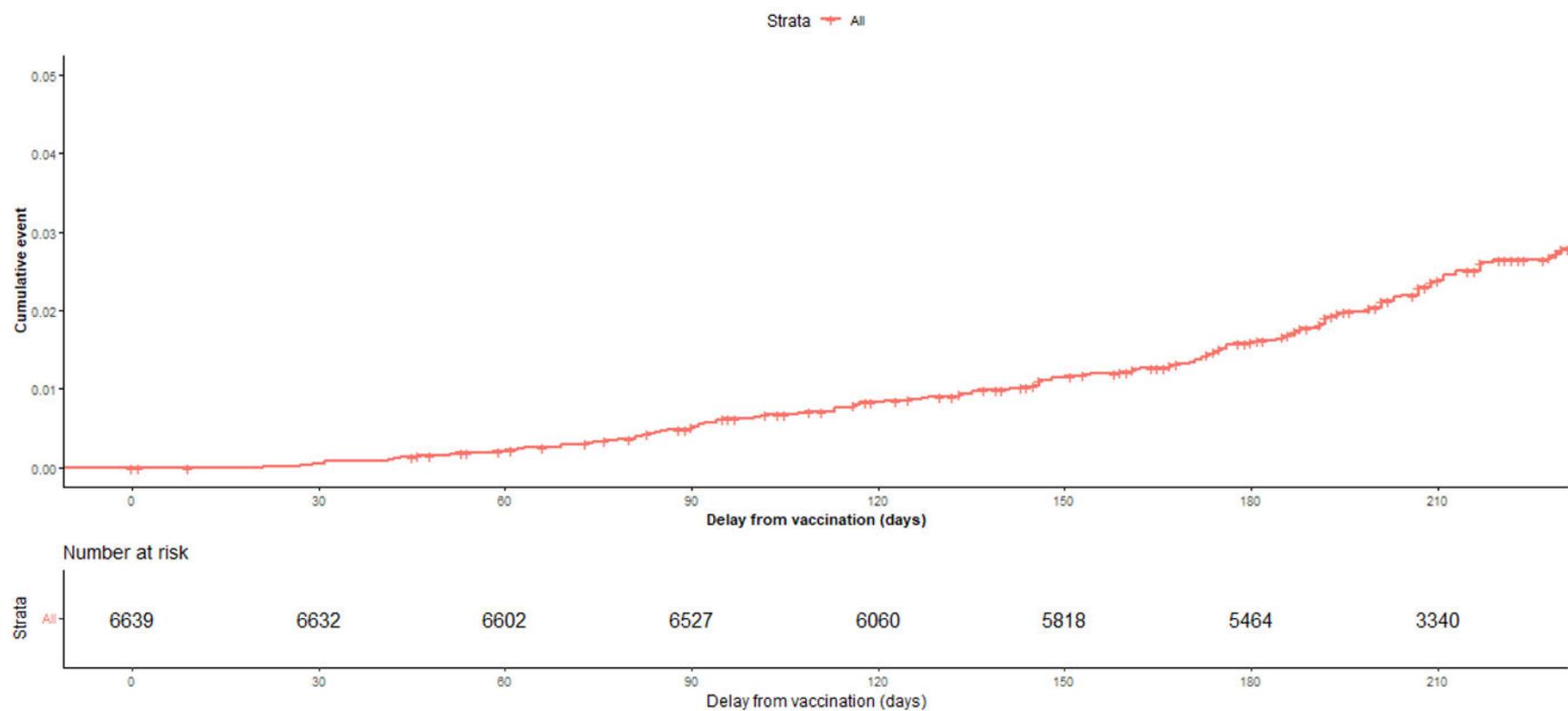
**6674 HCWs
with 2 doses**

**160 (2.4%) HCWs
tested positive**

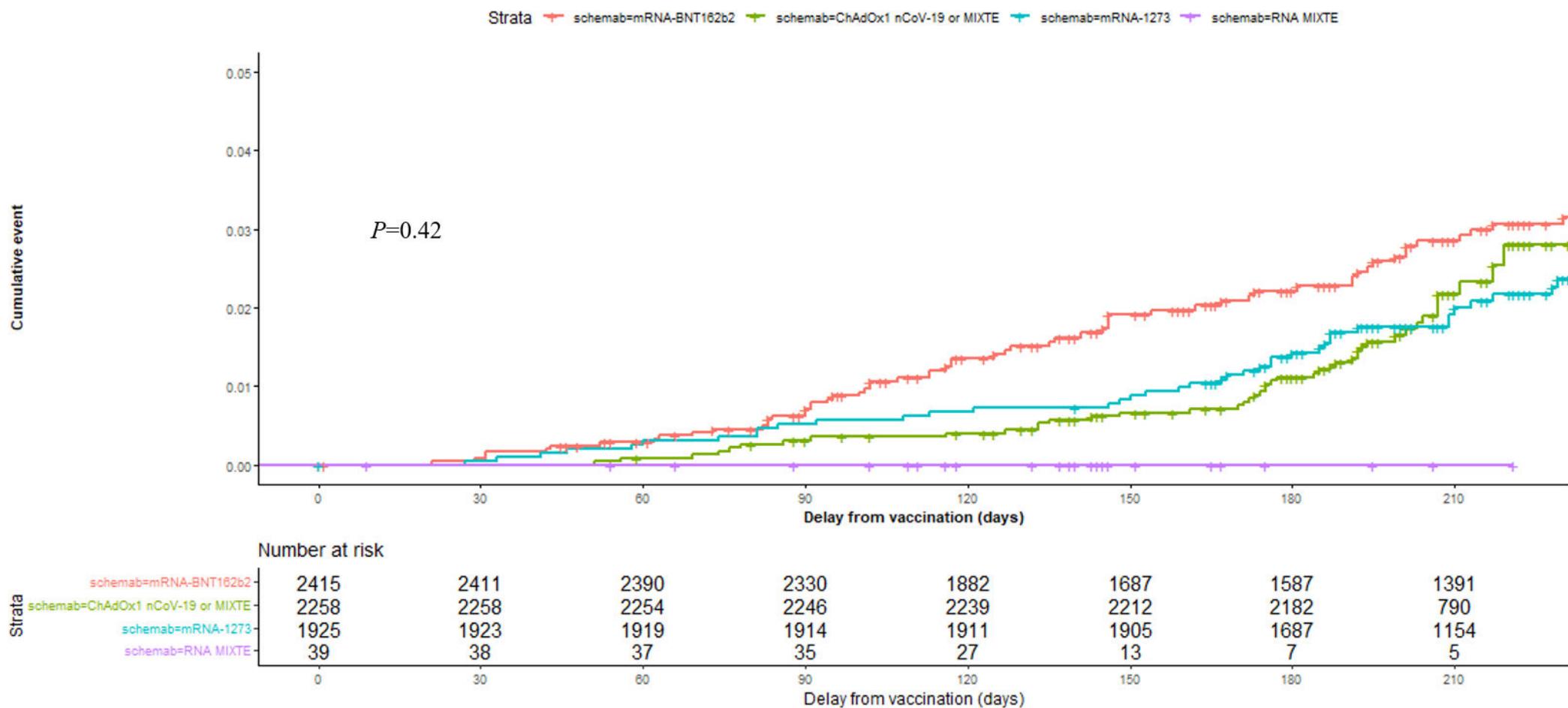
**145 (91%) HCWs
were symptomatic**



A

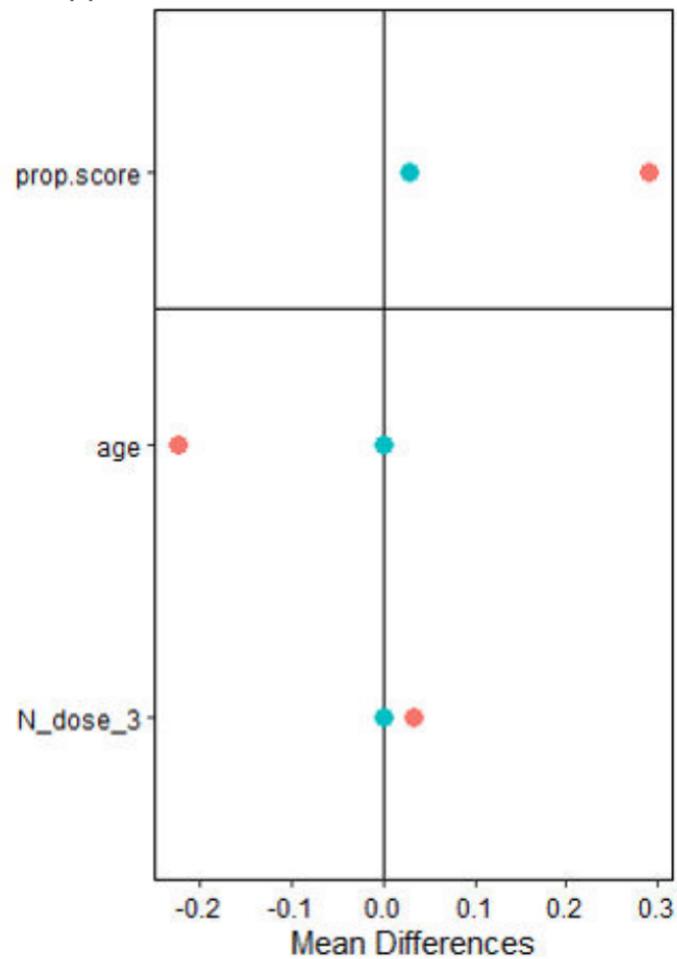


B

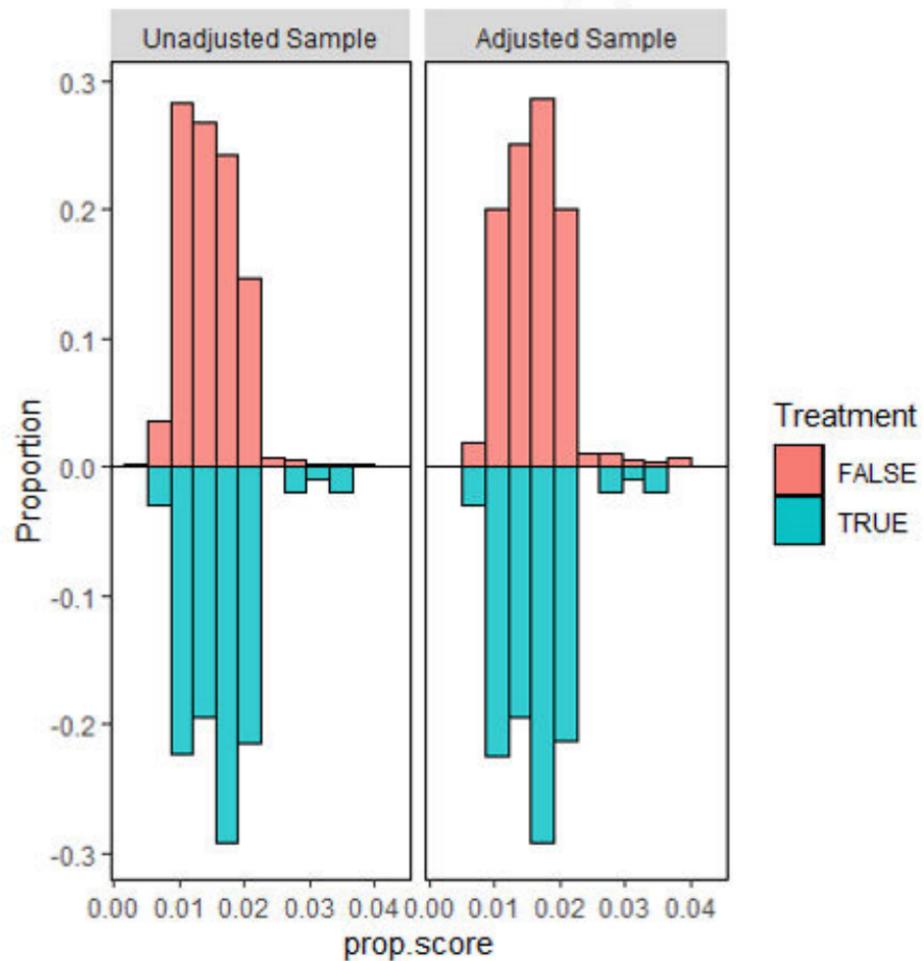


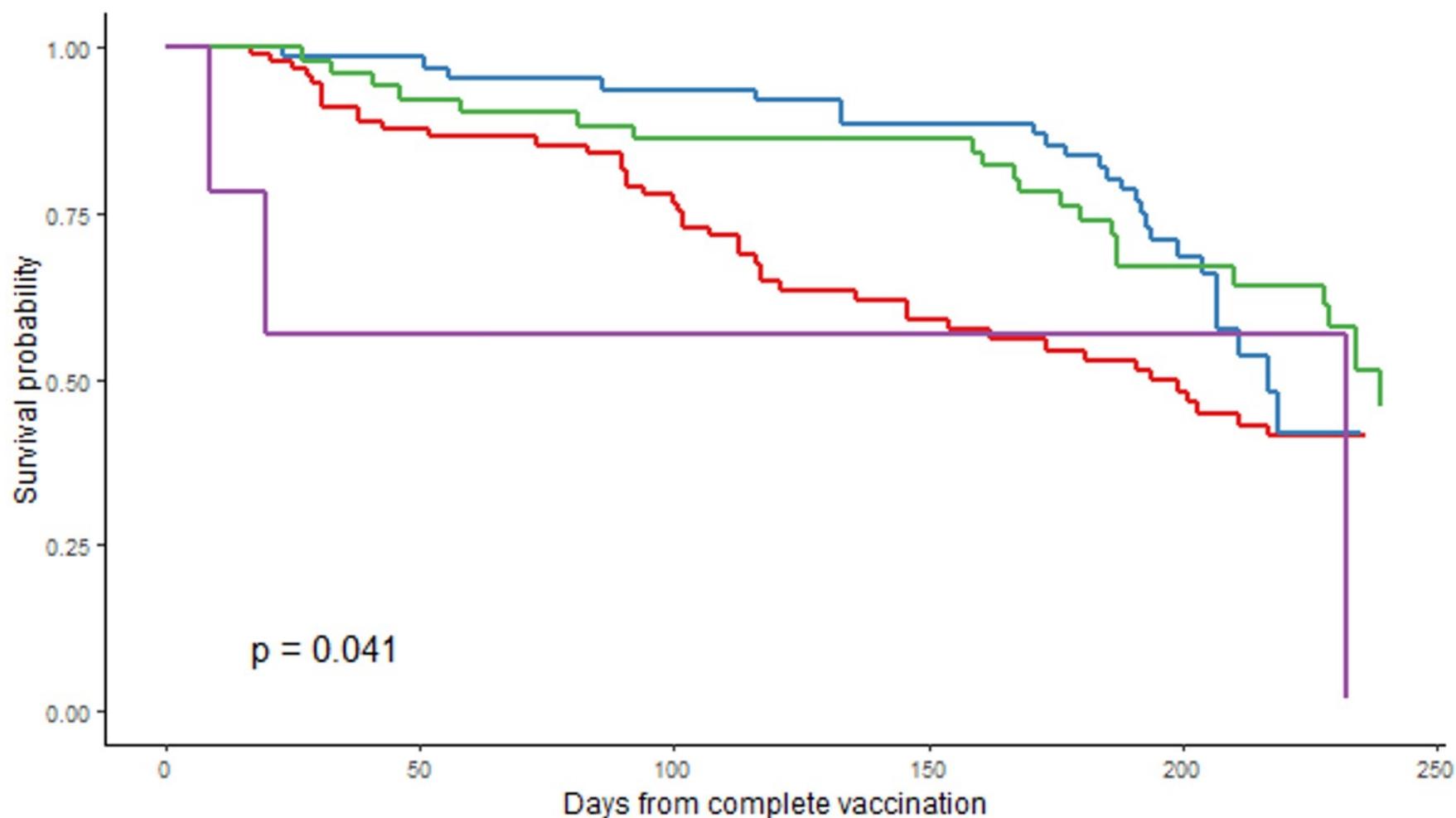
Supp1

Covariate Balance



Distributional Balance for "prop.score"





Type of vaccine

mRNA-BNT162b2	2711	2542	2246	1683	1531
ChAdOx1 nCoV-19 or MIXTE	2258	2245	2233	2206	1210
mRNA-1273	1910	1905	1902	1899	1169
RNA MIXTE	77	52	35	13	6

Efficiency