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1 **Risk of relapse after COVID-19 vaccination among patients with multiple sclerosis in**
2 **France: a self-controlled case series.**

3
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33

34 **Abstract**

35 **Background and objectives**

36 People with multiple sclerosis (MS) have an increased risk of severe coronavirus infection
37 due to their level of motor disability or exposure to certain immunosuppressive treatments.
38 Thus, MS patients have had priority access to COVID-19 vaccination. However, relapses
39 following vaccination have been reported, leading some patients to not seek the recommended
40 booster doses. The main objective was to estimate the risk of severe relapse after one, two,
41 and three (booster) doses of COVID-19 vaccination in patients with MS. The secondary
42 objectives were to assess the risk of relapse in clinically meaningful subgroups according to
43 the type of vaccine, the characteristics of the patients, and the use of disease modifying
44 treatments (DMTs).

45 **Methods**

46 We conducted a nationwide study using data from the French national health data system. MS
47 patients were identified according to ICD codes, specific treatments, and reimbursement data
48 up to March 31, 2022. Relapses requiring treatment with high-dose corticosteroids were
49 identified. A self-controlled case series method was used to evaluate the risk of relapse
50 associated with COVID-19 vaccines in the 45 days after vaccination. The associated risk was
51 evaluated after one, two, or three (booster) doses and is expressed as overall incidence rate
52 ratios (IRRs) and in subgroups of interest.

53 **Results**

54 Overall, 124,545 patients with MS were identified on January 1, 2021, and 82% received at
55 least one dose of a COVID-19 vaccine (n=102,524) until December 31, 2021, for a total of
56 259,880 doses. The combined IRR for MS relapse was 0.97 [0.91–1.03], p=0.30. The same
57 absence of risk was confirmed in various subgroups (age <50 years, duration of MS <10
58 years, use of DMT). A small increase in the relapse risk cannot be excluded after a booster
59 dose (IRR =1.39 [1.08–1.80]) for patients with high MS activity, especially when not treated.

60 **Discussion**

61 There is no increased risk of relapse requiring corticosteroid therapy after COVID-19
62 vaccination for almost all patients. We cannot exclude an increased risk following the booster
63 dose for patients who have had at least two relapses in the previous two years.

64 **Classification of Evidence**

65 This study provides Class III evidence that COVID-19 vaccination does not increase the risk
66 of severe relapse in patients with multiple sclerosis.

67

68 **Introduction**

69 During the COVID-19 pandemic, it was shown that patients with multiple sclerosis (MS) had
70 a risk of severe infection due to severe acute respiratory syndrome coronavirus-2 (SARS-
71 CoV-2) that was more than twice that of the general population¹. Such excess risk is mainly
72 explained by the level of disability and comorbidities (hypertension, diabetes, cancer,
73 obesity). A residual increase in such risk can be attributed to immunosuppressants, especially
74 anti-CD20 therapies. Because of the higher risk of severe infection, patients with MS were
75 given priority for vaccination in France.

76 However, case series of relapses following COVID-19 vaccination have been reported^{2,3} and
77 the analysis of a cohort of 1661 patients with MS recently concluded that there was a small
78 increase in the incidence of relapse after COVID-19 vaccination⁴. First episodes of acute
79 inflammatory central nervous system diseases (neuromyelitis optica spectrum disorder and
80 myelin oligodendrocyte glycoprotein antibody-associated disease) have also been reported⁵. A
81 systematic review and meta-analysis of 19 observational studies involving nearly 15,000
82 patients with MS concluded that there was no excess risk⁶. However, certain elements could
83 not be properly considered. Each series had potential selection biases and lacked an
84 appropriate control group or control period. In addition, potential risk factors for relapse
85 merited assessment, in particular the patients' age and disease duration, as younger patients
86 with shorter disease duration are at a higher risk of relapse. Disease modifying treatments
87 (DMTs) also needed to be considered. Finally, the type of vaccine used and the number of
88 doses received could also influence the risk of relapse. Such risk factors have never been
89 assessed in sufficiently large samples of patients with MS.

90 If there is an increase in the risk of relapse, such information would be of major importance
91 for both clinicians and patients with MS, as some patients are already reluctant to be

92 vaccinated^{7,8}, despite clear guidelines⁹. The absence of such a risk would be reassuring for
93 patients, especially if booster shots are to be repeated in the future.

94 The main objective of the present study was to estimate the risk of severe relapse after one,
95 two, and three (booster) doses of COVID-19 vaccination for patients with MS in a
96 comprehensive nationwide cohort sufficiently large to explore a small increase in the risk of
97 relapse. The secondary objectives were to assess the risk of relapse in clinically meaningful
98 subgroups according to the type of vaccine, the characteristics of the patients (age, disease
99 duration, previous relapses), and the use of DMTs.

100

101 **Methods**

102 *Data source*

103 The study was carried out using the French National Health Data System (SNDS)^{10,11}, which
104 covers approximately 99% of the French population, i.e. 66 million inhabitants. It contains
105 exhaustive anonymous individual data concerning reimbursed outpatient health expenditures
106 (SNIIRAM), such as consultations, drugs dispensed by pharmacies, laboratory tests, etc.
107 Information about long-term diseases (LTDs) with 100% coverage is recorded using the
108 International Classification Diseases 10th Revision (ICD-10), with reference to the date of
109 onset of the disease. Sociodemographic data are available, such as the sex, age, and postal
110 code of residence. This information is linkable to the national hospital database (PMSI),
111 which contains inpatient data with dates of admission and discharge, diagnoses (coded using
112 ICD-10), procedures, and expensive drugs or medical devices. This database is also linked to
113 the National COVID-19 Vaccination Database (VAC-SI), which includes the brand name of
114 the vaccine, the date of injection, and the dose number.

115 The SNDS database covering from January 1, 2009, to March 31, 2022 was explored.

116 *Standard protocol approvals*

117 The Clermont-Ferrand University Hospital has had permanent access to the SNDS since the
118 governmental decision published on June 29, 2021 (decree number 2021-848 and French data
119 protection authority decision CNIL-2016-316). The study was approved by local Ethics
120 Committee (IRB00013412, “CHU de Clermont Ferrand IRB #1”, IRB number 2023-CF115)
121 with compliance to the French policy of individual data protection.

122 *Study population*

123 Patients with MS were identified in the database as having a LTD for MS (ICD-10 code G35),
124 having been hospitalised for MS, or receiving a DMT specific for MS (at least one

125 reimbursement for beta-interferons, glatiramer acetate, oral teriflunomide, dimethyl fumarate,
126 fingolimod, oral cladribine, natalizumab, or ocrelizumab) over the study period^{12,13}. Patients
127 that were identified by only one hospitalisation (without specific treatment or LTD for MS)
128 were excluded. Patients identified with neuromyelitis optica (ICD-10 G360 or eculizumab or
129 tocilizumab administration in the absence of rheumatoid arthritis) were also excluded from
130 the selection. The remaining patients were assigned a MS identification date according to the
131 earliest date for which there was information indicating MS among the LTDs, hospitalisation,
132 and treatment data. For the main analysis, patients with an onset of MS after December 31,
133 2019, were excluded. Patients who died before January 1, 2021, were also excluded. For the
134 complementary analysis of new MS cases identified in 2021, the same identification
135 algorithm has been applied, focusing solely on the year 2021.

136 *Outcomes*

137 The primary outcome was treated MS relapse. Because relapse as a clinical event was not
138 directly available in the database, we used a specific recently published algorithm based on
139 hospital admissions and the use of high-dose corticosteroids (either oral or intravenous)¹²⁻¹⁴.
140 This highly efficient algorithm was shown to have a positive predictive value of 95% and a
141 negative predictive value of 96%. Relapses were retrieved from January 1, 2019, to March
142 31, 2022.

143 *Exposure*

144 For each patient, only the first three vaccine injections were considered, whereas the French
145 recommendations were to give four doses of vaccine to people at high risk of severe infection,
146 including patients on immunosuppressive therapy for MS.

147 A 45-day time frame was chosen to define the risk period, as potential vaccine-induced
148 relapses are believed to generally occur within the first 28 days after vaccination⁶ and as

149 treatment was used as a proxy and could have been slightly delayed after clinical onset of the
150 relapse.

151 *Other data*

152 Patient comorbidities (cardio or neurovascular disease, diabetes mellitus, respiratory disease,
153 cancer) were determined using LTD, hospitalization, and treatment data. The patient status
154 concerning DMT (specific to MS and used for patient identification or not) was considered as
155 follows: for intravenous anti-CD20 treatment (ocrelizumab and rituximab), patients were
156 considered to have been treated for nine months following the last dispensation. For other
157 treatment (mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, glatiramer
158 acetate, dimethylfumarate, interferon beta, cladribine, teriflunomide, anti-S1P, ofatumumab,
159 and natalizumab), patients were considered to have been treated for 42 days after the last
160 dispensation.

161 *Overall study design*

162 Based on the main objective, we focused on self-controlled study designs, which are well
163 suited for vaccine safety evaluation. Three self-controlled designs are used to control
164 unmeasured confounding factors: case-crossover (CCO), case-time control (CTC) and self-
165 controlled case series (SCCS). We decided to use the two most appropriate methods in our
166 context (SCCS and CTC) to evaluate the potential risk of relapse associated with COVID-19
167 vaccination¹⁵ and to check their concordance. CCO was avoided because of potential temporal
168 bias: vaccination was not uniform during 2021 (**Figure S1**) and relapses could be linked to a
169 certain level of seasonal variation¹⁶. In such situation, CTC is recommended over the CCO.

170 Major validity assumptions for using such methods were satisfied in the present study:
171 vaccination is an intermittent/transient type of exposure and MS relapse is an abrupt, possibly
172 recurrent, and rare event. Minor validity assumptions were not all met, but the study design
173 was adapted to account for this, as explained below.

174 *SCCS study*

175 The SCCS method allows investigation of the association between transient exposure and an
176 adverse event and is especially suited to study adverse reactions to vaccines¹⁷. The method
177 uses only subjects that are exposed to the COVID-19 vaccine. No separate controls (subjects
178 unexposed to the COVID-19 vaccine) are required, as the cases act as their own controls. For
179 each patient, time was divided into control and risk periods (**Figure 1**). As recommended,
180 neurologists generally avoid proposing vaccination to MS patients in the month following a
181 relapse. Thus, a 30-day pre-vaccination period with a lower probability of relapse was
182 expected, which violated the minor event-independent exposure assumption. We therefore
183 decided to consider a 30-day “pre-exposure” period that was discarded from the control
184 period. As the vaccination scheme involved a potential overlap between exposure and pre-
185 exposure periods (particularly for the 1st and 2nd dose of vaccine) and because the pre-
186 exposure period was expected to contain fewer relapses due to the practice of neurologists, we
187 decided to consider the overlap and to divide the periods to make them suitable for combined
188 period evaluation. Due to the potential modifying effect of DMTs on relapse risk and the
189 possible alternation between treatment and nontreatment periods, we considered treatment as
190 a time varying covariate. Because of the non-uniformity of the temporal distribution of
191 vaccination during 2021 (violating the time-trend minor validation assumption), we created a
192 seasonal time varying covariate by dividing the time periods according to the month of the
193 year (**Figure S1**). Other minor assumptions can be considered to have been satisfied: MS
194 relapse can be considered to be independent when recurrent and MS relapse is not responsible
195 for censoring (death). However, the data was censored at the date of death (when applicable),
196 at the date of the 4th vaccine injection (minus 30 days to properly exclude the 4th dose pre-
197 exposition period), or otherwise on March 31, 2022. The starting date was the date of the 1st

198 vaccination injection for the 1st patient, minus 30 days (for pre-exposition purpose), that is
199 November 30, 2020.

200 *CTC study*

201 The first step of the CTC study was a CCO, in which cases were patients with a MS relapse.
202 The date of the relapse defined the end of the risk period, for which the beginning was set to
203 45 days before. Control periods were considered immediately (with no overlap) prior to the
204 risk period, for the same duration. The timeframe considered to identify cases spanned from
205 April 1, 2021 (so that the earliest beginning of a control period was still after the date of the
206 1st patient vaccination, considering 45 days of exposure) until March 31, 2022. The second
207 step of the CTC study was to select the control subjects, i.e., patients without a MS relapse.
208 The purpose of this group was to correct for the time trend bias in the CCO analysis of the
209 cases. The control group was selected using propensity score matching. After matching, an
210 index date was attributed to each control, corresponding to the relapse date of his/her matched
211 case, thus making it possible to compute the risk and control periods for the control subjects
212 in the same way as for the cases.

213 *Statistical analysis*

214 The data for the study population is described using means \pm standard deviations (SDs) and
215 medians and interquartile ranges for continuous variables and crude numbers and proportions
216 for categorical variables. Patients who received a COVID-19 vaccine before December 31,
217 2021, were compared to unvaccinated patients for the same date using appropriate statistical
218 tests. The distribution of vaccinations and of relapses over the study period are shown using a
219 histogram to evaluate the time trend of vaccination and seasonality of MS relapses.

220 The time between a relapse and vaccination was plotted to assess the event-independent
221 exposure assumption.

222 For the SCCS study, the incidence rate ratio (IRR) of MS relapse was computed using a
223 conditional Poisson regression model. Exposition and pre-exposition periods for each dose of
224 vaccine (1st to 3rd) were considered to estimate the main effects. The model was adjusted to
225 control for the seasonal effect (month) and the effect of DMT. Results are shown as IRRs and
226 their 95% confidence intervals, but only for periods with a time contribution >0.7% (the time
227 contribution was calculated as the sum of the time periods of interest divided by the total time
228 of each period).

229 For the CTC study, the propensity score was computed by logistic regression, with group
230 (case / control) as the dependant variable and sex, age, MS duration, cardio neurovascular
231 disease, diabetes mellitus, respiratory disease, cancer, and MS treatments as covariates. The
232 four nearest control neighbours were paired to each case using the difference in the logit of
233 the propensity score with a calliper constraint set <0.1. After matching, a conditional logistic
234 regression was used considering the interaction term between vaccine exposure and the
235 subject's group (case or control). The CTC OR corresponds to the ratio between the OR of
236 CCO analysis of cases and the that of CCO analysis of controls. The CTC OR is shown with
237 its 95% confidence interval.

238 ***Subgroup and sensitivity analyses***

239 Sensitivity analyses were systematically performed with a 90-day risk period for the SCCS
240 study to consider potential delays in the initiation of corticosteroids after symptoms onset. As
241 there is a risk of pseudo-outbreaks following vaccination, we proposed a sensitivity analysis,
242 dividing the 45-day period analysed into two parts: D1 to D4, then D5 to D45. Indeed,
243 according to the available data, this risk almost exclusively concerns the first four days
244 following vaccination¹⁸.

245 The main analyses were repeated in subgroups of patients with a higher risk of relapse:
246 patients <50 years of age and those with a duration of MS <10 years. Interactions between the

247 vaccine exposure period and the treatment status (No DMT / moderate-efficacy DMT / high-
248 efficacy DMT) was tested for patients with high inflammatory activity (≥ 2 relapses) in the
249 previous two years.

250 Analyses were also performed separately for each type of vaccine manufacturer. For this
251 analysis, only patients who received the same type of vaccine for each dose were considered.

252 An additional specific analysis was carried out for patients whose MS was identified in 2021.

253 For these incident cases during the year in question, the date of identification of MS was
254 analysed on the basis of the rate of vaccination carried out in the general population (non-MS)
255 and on the basis of the date of vaccination in these people newly identified with MS.

256 Finally, at least partial data on the results of tests for Covid-19 infection have been available
257 since the beginning of 2024, covering the whole of 2021. An analysis aimed at identifying the
258 link between Covid-19 infection proven by a positive test and the risk of a relapse has also
259 been carried out.

260

261 **Data availability**

262 The authors are unable to share the data with individuals outside their team. Data from the
263 French administrative healthcare databases (SNDS) were on the SNDS portal. However,
264 legitimate entities, whether they belong to the public or private sector, have the opportunity to
265 request access to the data directly, provided that their research objectives align with the
266 broader interests of public health. Requests to access these datasets should be directed to
267 <https://www.health-data-hub.fr/>.

268 **Results**

269 Overall, 124,545 patients with MS were identified on January 1, 2021. Patients who received
270 at least one dose of a COVID-19 vaccine before the end of 2021 (n=102,524, 82.3%) are
271 presented in **Table 1** and compared to those who did not.

272 ***Risk of relapse after a first, second, and booster dose of vaccine in the overall population***

273 Overall, 102,524 patients with MS received at least one dose of vaccine, for a total of 259,880
274 doses. The second dose was received by 96,990 (94.6%) of those who received a first dose
275 and 60,366 (58.9%) received a booster dose during the year 2021. The time between
276 vaccination and relapse are shown in weeks from the time of vaccination (**Figure 2A**),
277 negative values corresponding to relapses that occurred before vaccination. There was a lower
278 number of relapses during the four weeks before vaccination. We observed a similar effect
279 just before the 2nd and booster doses (**Figure 2B, 2C**). The exposure period included the 45
280 days after vaccination. For the messenger RNA vaccines, the first two doses were most often
281 given three to four weeks apart. Thus, it is possible that a period that counted as exposure to
282 the first dose counted as pre-exposure to the second. The days considered for the analysis are
283 presented in **Table S1**.

284 There was no increase in relapse risk following the first vaccine dose (IRR=1.01 [0.88 - 1.15],
285 p=0.93) (**Figure 3**). Similarly, there was no increased risk of relapse following the second
286 (IRR=1.02 [0.94 - 1.12], p=0.61) or booster doses (IRR=1.00 [0.90 - 1.11], p=0.79). The
287 combined IRR for all three doses was 0.97 [0.91 - 1.03], p=0.30, excluding the pre-exposure
288 periods. Taking DMT into account, a slight excess risk of relapse was observed following the
289 booster dose in patients not receiving any DMT (**Table S2**).

290 ***Risk of relapse in specific sub-groups***

291 We analysed subgroups of MS patients with a higher risk of inflammation (**Figure 4**),
292 consisting of those under 50 years of age, those with MS diagnosed <10 years before, and

293 those with at least two relapses in the two years before vaccination. There was an increase in
294 the risk of relapse following the booster dose for patients who had had two or more relapses in
295 the previous two years (IRR=1.28 [1.07 - 1.53], p=0.006). Among these patients with high
296 levels of inflammation, the increased relapse risk was mainly observed for those who were
297 untreated (**Figure S2**). No other subgroup showed an increased risk of relapse.

298 Similarly, we performed an analysis according to the type of vaccine used (**Table S3, Figure**
299 **S3**). Both types of mRNA vaccine (BNT162b2 and mRNA-1273) were analysed (**Table S4**).
300 The two viral vector vaccines (ChAdOx1 nCoV-19 and Ad26.COV2) were also analysed
301 (**Table S5**). There was no excess risk of relapse for any type of vaccine.

302 *Verification and confirmation with the CTC design*

303 The CTC study confirmed the results of the SCCS study, showing no increase in the risk of
304 relapse after any of the three vaccine doses. Overall, there was even a small decrease in the
305 risk of relapse, with an OR of 0.90 [95%CI 0.83 – 0.98], p=0.01.

306 *Sensitivity analysis*

307 The results were similar for the SCCS design using a 90-day risk period as those using a 45-
308 day risk period (**Figure S4**). By splitting the 45-day period following vaccination in two,
309 there was a reduced risk of relapse treated in the four days following vaccination (**Table S6,**
310 **Figure S5**). This result does not support the inclusion of a significant number of pseudo-
311 relapses. There has been no increase in the number of incident cases of MS identified during
312 2021 in connection with the implementation of the Covid-19 vaccination in the general
313 population (**Figure S6**). Moreover, the identification of MS in these newly diagnosed patients
314 most often preceded vaccination (**Figure S7**). In fact, the fact of being diagnosed gave
315 priority access to vaccination in France and could encourage vaccination in the following
316 weeks. The delay between the identification of a Covid-19 infection (positive test) and the
317 identification of a relapse was studied (**Figure S8**). A significant peak was seen at D0 and D1,

318 corresponding to the simultaneous identification of a Covid-19 infection and the initiation of
319 treatment for a relapse.

320 **Classification of evidence**

321 This study provides Class III evidence that COVID-19 vaccination does not increase the risk
322 of severe relapse in patients with multiple sclerosis.

323

324 **Discussion**

325 In this nationwide study, we did not find any significant increase in the risk of treated relapse
326 requiring the use of corticosteroid therapy after Sars-Cov2 vaccination for >100,000 patients
327 with MS in France by the end of March 2022. This result was confirmed for clinically
328 meaningful subgroups at a higher risk of relapse due to younger age or shorter disease
329 duration. However, we did observe an increase in relapse risk after the booster dose for
330 patients with high inflammatory activity in the previous two years, especially those who went
331 untreated. The type of vaccine was not associated with relapse risk. These findings are
332 reassuring and have direct implications for the management of patients with MS in the context
333 of pandemics.

334
335 Many case reports and case series have been published suggesting a possible risk of relapse
336 just after COVID-19 vaccination, the largest study indicating a small increase in relapse risk⁴.
337 Other cases of post-vaccination inflammatory outbreaks have also been reported^{19,20}.
338 However, no population-based study has been conducted to date to assess such risk while
339 limiting the risk of selection bias and including the entire population at a national level. In
340 addition, the studies conducted to date have not addressed the specific risk of the initial
341 vaccination and the booster dose. In the current study, the sufficient size of the population
342 allowed for an independent analysis of each dose, leading to the conclusion that there is no
343 excess risk for either of the two doses of the initial vaccination or the booster dose, except in
344 the small sub-group of patients with very high inflammatory activity, especially those who
345 went untreated.

346 The sample size also allowed analysis for each type of vaccine. The data presented are highly
347 reliable for the vaccines BNT162b2 and mRNA-1273, which have been administered to
348 thousands of patients. In contrast, the ChAdOx1 nCoV-19 and Ad26.COV2 vaccines have
349 been less widely used for patients with MS in France and the confidence intervals are wider. It

350 is more difficult to draw conclusions on vaccine combinations, as some patients did not
351 always receive the same brand of vaccine and some combinations were used by very few
352 patients. However, there are no indications of an excess risk, regardless of the vaccine or
353 combination of vaccines.

354 Several studies have shown that the risk of relapse can be increased by infections. For
355 example, patients with MS experienced significantly increased relapse rates and enhanced
356 lesion activity shortly after a bacterial urinary tract infection, a viral respiratory infection, or
357 gastroenteritis, as measured by MRI²¹. Another study found that infection increased the risk of
358 relapse approximately twofold²². Of note, the annualised relapse rate (ARR) outside the risk
359 periods was approximately one in these two studies, indicating that the patients had high
360 inflammatory activity and were not receiving highly active DMT. In the present study, the
361 ARR was approximately 0.1 and there was no increase following COVID-19 vaccination,
362 except after the booster dose for patients with high inflammatory activity, especially those
363 who went untreated. It has long been known that previous inflammatory activity is one of the
364 main predictors of the risk of a new relapse²³. Thus, patients who had experienced two or
365 more relapses in the previous two years were naturally most at risk of relapse, in particular if
366 no DMT had been initiated in the interim. It is likely that the induced immune response (either
367 after natural infection or vaccination) can be a trigger of a relapse for these patients with
368 highly active inflammation. However, this does not mean that a highly effective DMT should
369 always be applied before the necessary vaccines are administered. In fact, several treatments,
370 notably anti-CD20s, are known to limit or even prevent the vaccine reaction. This parameter
371 must be taken into account when initiating DMT. Some clinicians suggest using natalizumab
372 for a few months, to allow time for the necessary vaccinations, before initiating anti-CD20
373 therapy in a highly active patient.

374 These results are consistent with those of previous studies concerning vaccination²⁴, although
375 controversies have existed for years, notably for the yellow fever^{9,25,26} and rabies²⁷ vaccines.
376 French guidelines and those of the American Academy of Neurology for immunization are
377 reassuring for many vaccines^{9,28}. However, they were both published in 2019 and obviously
378 could not have had any data regarding COVID-19 vaccination. The results of this study show
379 that it is possible to vaccinate the vast majority of the MS patient population without a
380 subsequent increased risk of relapse. Thus, the recommended booster doses should be
381 administered without any ulterior motive. For patients with high inflammatory activity, it is
382 justified to have highly effective DMT before performing the booster doses, while
383 emphasizing that the humoral response is very limited following certain treatments, notably
384 anti-CD20.

385 **Limitations**

386 The main limitation of this study was the type of data used. The data available corresponded
387 to the total care provided in the hospital or the drugs reimbursed. Certain long-term
388 conditions, such as MS, are easily identifiable. However, very little clinical data are available.
389 To identify MS relapses, we relied on a recent algorithm based on five criteria that allowed
390 the identification of relapses requiring hospital admission or corticosteroid therapy. This
391 signifies that benign relapses (i.e., not seen by neurologists or not needing the use of
392 corticosteroid therapy) were not considered in the outcomes, which would imply that the ARR
393 may have been underestimated, whereas the impact on the IRR would be low. A limitation of
394 identifying hospitalisations is that it is not possible to know with certainty the cause of the
395 hospitalisation and whether it is actually related to a relapse, although the positive predictive
396 value of the algorithm is around 95%. In fact, a hospitalisation for another reason (e.g.
397 pyelonephritis) may be incorrectly counted as a hospitalisation for a relapse, although Z512
398 code (part of the algorithm for relapse identification) is normally not used in such situation.

399 However, the impact on the IRR is a priori very small, as this type of hospitalisation can occur
400 in both the post-vaccination and control periods.

401 Another point is that pseudo-relapses may have been treated and thus identified as relapses.
402 Pseudo-relapses are common in the post-vaccination phase¹⁸, affecting around 3% of patients.
403 However, all symptoms generally resolve within 4 days. As the sensitivity analysis did not
404 reveal any increase in the number of relapses treated in the first few days following
405 vaccination, this phenomenon is probably marginal and does not seem to affect the overall
406 interpretation of the results. Data on the results of Covid-19 screening tests have recently been
407 added to the database. An analysis of these data shows no link between the occurrence of a
408 Covid-19 infection and the risk of subsequent relapses. However, these data suggest that
409 pseudo-relapses induced by Covid-19 infections may have been treated as relapses.

410 In the coming months, all data for the year 2022 will be available for analysis. Thus, it will be
411 possible to assess whether the excess risk is confirmed for the patients with the most active
412 inflammation based on a larger number of patients who received the first booster dose. It will
413 also be possible to determine whether the second booster dose amplifies such risk.

414

415 In conclusion, there is no increased risk of relapse requiring corticosteroid treatment
416 following coronavirus vaccination for the vast majority of patients with MS. Data for the
417 mRNA vaccines were acquired for very large populations and are robust. These vaccines can
418 be used without any worry about the risk of relapse to provide booster doses to patients for
419 whom they are warranted. However, particular caution is needed for patients with the highest
420 inflammatory activity in the previous two years, who should first receive DMT.

421

422 **Declaration of interests**

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438

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519

520

	Not vaccinated N = 22 021	Vaccinated N = 102 524
Female sex, n (%)	15 516 (70.5)	73 637 (71.8)
Age (years), mean \pm SD	52.6 \pm 16	54.3 \pm 14.2
\geq 50 years, n (%)	12 310 (55.9)	64 139 (62.6)
Duration of MS (years), mean \pm SD	13.5 \pm 8.9	13.5 \pm 8.8
< 10 years, n (%)	9 111 (41.4)	42 054 (41.0)
Number of relapses in the previous 2 years, n (%)		
0	19 046 (88.1)	87 954 (85.8)
1	1 890 (8.6)	10 617 (10.4)
\geq 2	725 (3.3)	3 953 (3.9)
Comorbidities, n (%)		
Cardio-neurovascular	3 348 (15.2)	16 189 (15.8)
Cancer	1 880 (8.5)	9 563 (9.3)
Respiratory	2 704 (12.3)	13 053 (12.7)
Diabetes mellitus	1 262 (5.7)	6 818 (6.7)
Disease modifying treatments (DMT), n (%)		
No DMT	15 409 (70.0)	53 652 (52.3)
Any moderate efficacy DMT	3 871 (17.6)	29 974 (29.2)
Teriflunomide	1038 (4.7)	8 870 (8.7)
Dimethyl fumarate	1 021 (4.6)	7 719 (7.5)
Beta interferon	875 (4.0)	6 425 (6.3)
Glatiramer acetate	579 (2.6)	4 375 (4.3)
Mycophenolic mofetil	140 (0.6)	1 063 (1.0)
Methotrexate	117 (0.5)	966 (0.9)
Azathioprine	99 (0.5)	550 (0.5)
Cyclophosphamide	2 (0.01)	6 (0.01)
Any high efficacy DMT	2 741 (12.4)	18 898 (18.4)
Fingolimod	1 186 (5.4)	8 098 (7.9)
Ocrelizumab	650 (3.0)	4 602 (4.5)
Natalizumab	599 (2.7)	3 883 (3.8)
Rituximab	306 (1.4)	2 315 (2.3)

522 **Table 1. Comparison of patients with MS vaccinated at least once against COVID-19, or not, during the**
523 **year 2021.** The values for age, comorbidities, and DMT are as of January 1, 2021. Data are presented as the
524 mean (SD), median (IQR), or n (%).

526 **Figure legends**

527

528 **Figure 1. 45-day periods considered, for each vaccine dose, in measuring the risk of a**
529 **relapse. The pre-exposure period (30 days) is excluded from the control period.**

530

531 **Figure 2. Number of relapses counted each week relative to the date the first (A), second**
532 **(B) or booster (C) dose of vaccine administered.**

533

534 **Figure 3. Incidence rate ratio (IRR) and 95% confidence intervals for each observation**
535 **period.** The global exposure to each of the three doses is noted on the right of the figure.

536 * Exp. Dose 1 (all) = All Dose 1 expositions in combination with Dose 2 or Booster dose (exposition or pre-
537 exposition)

538 Exp. Dose 2 (all) = All Dose 2 expositions in combination with Dose 1 or Booster dose (exposition or pre-
539 exposition)

540 Exp. Booster dose (all) = All Booster dose expositions in combination with Dose 1 or Dose 2 (exposition or pre-
541 exposition)

542

543 **Figure 4. Incidence rate ratio (IRR) and 95% confidence intervals for each dose and**
544 **subgroup of interest.** Only the “pure” exposure period without any pre-exposure to another
545 dose is presented.