A 6-week time period may not be sufficient to identify potential adverse events following COVID-19 vaccination

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Research Article

Keywords: Health, pharmacy, COVID-19, vaccination

Posted Date: November 30th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2327212/v1

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Abstract

Background

. Messenger RNA (mRNA) vaccines have been widely used as the main sanitary measure destined to fight the COVID-19 pandemic. Rapidly purported as being “safe and effective”, this new generation of vaccines is radically different from those developed traditionally and for which potentially associated adverse events (AEs) are considered through a standard 6-week post-vaccination period.

Hypothesis

. Here, we posited that the reporting period for AEs related to the COVID-19 vaccines may be different.

Method

. In this retrospective, observational study, we aimed to assess the chronology of new/worsening ailments occurring after the administration of COVID-19 vaccines based on the changes to the participants’ pharmacological records. Patients vaccinated against COVID-19 and experiencing health-related events during the study period (between September 30, 2021 and July 15, 2022) were included and the changes to their pharmacological records were analyzed.

Results

. One hundred and twelve (112) adult patients (63 men, 49 women; 67.54 ± 14.55 years-old; mean ± standard deviation) have reported changes to their pharmacological record following health-related events, which occurred 11.57 weeks (median; range 0.04–47.14) following their last COVID-19 injection of 3 doses (median; range 1–4). The most frequent medical ailments that appeared or worsened were cardiovascular diseases (CVD; N = 61), cancer (N = 31), respiratory diseases (RD; N = 22) and zona (N = 10), half of which occurred after the second dose. Nineteen (19) patients (10 men, 9 women; 78.2 ± 11.4 years-old) died on average 17.14 weeks (SD 13.71) after their last injection.

Conclusion

. Most (76.1%) of the health-related events experienced by patients vaccinated against COVID-19 occurred beyond the 6-week period prescribed by the health authorities. Our findings call for further investigations and an extension of the post-vaccination AE reporting period.

Introduction
Messenger RNA (mRNA) and adenoviral vaccines expressing the SARS-CoV-2 Spike protein have been widely promoted by pharmaceutical companies, government officials, medical associations and the medias worldwide as the main sanitary measure destined to fight the COVID-19 pandemic (Kis et al., 2021). The publicity campaigns rapidly purported this new generation of vaccines, authorized for emergency use, as being “safe and effective” against COVID-19. Currently in phase 3 clinical trials, which are available for public consultation at https://clinicaltrials.gov/ct2/show/study/NCT04368728?term=C4591001&draw=2&rank=1 (link to the Pfizer/BioNTech protocol: https://cdn.pfizer.com/pfizercom/2020-11/C4591001_Clinical_Protocol_Nov2020.pdf), the safety and efficacy of these injections remain to be confirmed, as their short, medium and long-term beneficial and side effects remain to be thoroughly documented and their link to the injections established and independently investigated (Fraiman et al., 2022).

Several hurdles remain to portray the precise nature and true incidence of the adverse events (AEs) associated with COVID-19 vaccination, including the guidelines of the professional orders, the awareness of the medical community, the passive surveillance of AEs and their reporting (Lazarus et al., 2010), which may constitute the blind spot of the COVID-19 crisis (Provost, manuscript submitted). According to Tom Shimabukuro of the Atlanta CDC and co-authors, the underreporting rate can be as low as less than 1% depending on the type of AE and the type of vaccine (Shimabukuro et al., 2015). Once reported by a member of the medical staff to the Quebec's Public Health Agency, the "Institut national de santé publique du Québec (INSPQ)”, AEs are then screened for follow-up and those occurring more than 6 weeks after vaccination are not considered, based on what is known about traditional vaccines.

However, mRNA and adenoviral vector vaccines have a content and mechanisms of action (i.e., pharmacodynamics) very different from that of traditional vaccines, and there is no precedent of an optimal minimal period of surveillance post-vaccination necessary to capture AEs related to these new vaccine technologies. The novelty of these approaches alone, now applied to the population on a global scale, should call into question the 6-week post-vaccination reporting period to consider the occurrence of a new or worsening ailment as a potential AE worth investigating. The consideration of a relatively short period of 6 weeks precludes the possibility of detecting slowly developing, or more insidious health problems that take longer than 6 weeks to become symptomatic, and that could affect patients in the long term. If new/worsening ailments that occur later than 6 weeks post-vaccination are systematically discarded by health agencies, they may go unnoticed and leave scientists unable to perform any observational and descriptive analysis, and, if necessary, alert the authorities.

Consequently, we explored an alternative source of health data, recorded by pharmacists following the reception of new prescriptions or modifications of previous prescriptions related to the occurrence of a new ailment or worsening of an existing one. Our rationale to consider this source of data is the following: people who are worried about their health and/or experience significant changes in their health condition usually consult their physician or visit a health care facility or hospital. The patients are then given a diagnosis and, depending on whether the existing and/or new ailment can be treated pharmacologically or not, a new drug prescription, or modification of an existing one (e.g., changes in the
dose of a drug) is then transmitted to their local pharmacy. Therefore, this peripheral component of the Quebec health care system represents a valuable source of health information provided indirectly by practicing physicians and used by pharmacists, which may yield a unique perspective in the descriptive analysis of post-vaccination AEs.

The present study aims to present the incidence of new and/or worsening ailments, recorded through a pharmacy's prescriptions of new drugs, or modifications of existing prescriptions, in relation to the vaccination dates. We hypothesized that an important number of new/worsening ailments may manifest beyond the currently used 6-week time period after vaccination against COVID-19.

Method

Study design

Our study is a retrospective, observational analysis that aimed to assess the chronology of new/worsening ailments occurring after the administration of COVID-19 vaccines.

Participants

We used a convenience sample of patients of a community pharmacy located in the Bas-St-Laurent-Gaspésie region of the province of Quebec, Canada, who had new prescriptions or modifications of existing prescriptions because of the diagnosis of a new ailment or worsening of an existing ailment, as well as patients who had their pharmacy files closed following death. The study period considered was between September 30, 2021 and July 15, 2022. A written informed consent was obtained from all the patients or from their legal representatives.

Variables of interest

We considered the following variables: age, sex, type of vaccine received, number of doses received, number and type of a new/worsening ailment (as per new/modification of drug prescription), time elapsed between last vaccination date and date of start of new/worsening ailment, number of comorbidities, PCR or antigenic COVID-19 testing results, diagnosis (i.e., type of disease) of a new/worsening ailment and cause of death.

All the variables were collected from the pharmaceutical records, the Quebec Health System (faius.santepublique.rtss.qc.ca) to record COVID-19 vaccine lot numbers, the death certificates’ information, and from the patients themselves or their closest relative or legal representative.

Statistical analysis

We used descriptive statistics to present all quantitative variables, as either mean and standard deviation (SD), or median and range, according to their distribution, and all qualitative variables as proportions. We used T-test to compare demographic quantitative variables, Chi square to compare the frequency of events, Mann-Whitney and Kruskal-Wallis tests to assess differences of quantitative variables across
categories, Spearman’s correlation coefficient to explore correlations, and a generalized linear model to assess associations with specific variables of interest.

All the statistical analyses were corrected for multiple comparisons using Bonferroni correction and were performed using SPSS statistics software (26.0.0 version).

Results

Participants

One hundred and twelve (112) adult patients who reported new or worsening ailments following vaccination against COVID-19 were included in this study, comprising 63 men (56.25%) and 49 women (43.75%) (Supplementary Table S1). The mean age of the population was 67.54 years-old (y.o.), SD 14.55, and there was no significant difference in the mean age of men (mean 66.40, SD 12.93) and women (mean 69.04, SD 16.45).

COVID-19 vaccine administration

All patients received at least one dose of a COVID-19 vaccine, but not all received the complete series of two doses or continued to receive a third or fourth dose (Note: we have used throughout this manuscript third and fourth dose instead of first and second booster, just to better depict the chronology of the administrations). At the end of the observation period, 2 patients had received only one dose (1.8%), whereas the majority (N = 110, 98.2%) received at least 2 doses: thirty-five (35) patients received 2 doses (31.3%), 62 patients received 3 doses (55.4%), and 13 patients received 4 doses (11.6%).

The patients received at least one of the following vaccines: Pfizer/BioNTech (pb; N = 76), Moderna (mod; N = 55) or AstraZeneca (AZ; N = 7)/CoviShield (CS; N = 2). Patients received one (N = 2), two (N = 35), three (N = 62) or four (N = 13) doses of the same vaccine (N = 88; 78.6%), and two (N = 22; 19.6%) or three (N = 2; 1.8%) doses of different vaccines.

Forty-nine (49) different vaccine lots were administered to these patients, the most frequent representative being Pfizer/BioNTech #EW3344 (N = 20), Moderna #3001658 (N = 14) and 043D21A (N = 14), AstraZeneca #MT0056 (N = 5) and CoviShield #4120Z003 (N = 2) (Supplementary Table S2).

Post-vaccination occurrence of new/worsening ailments

The most frequent medical conditions that appeared or worsened in vaccinated patients were cardiovascular diseases (CVD; N = 61), cancer (N = 31, including two pending biopsy confirmation), respiratory diseases (RD; N = 22) and zona (N = 10, including two bilateral cases). Other medical conditions (N = 10) include intense fatigue, infection, lymph node inflammation or hemorrhage.

Most patients experienced one new/worsening ailment (N = 100, 89.3%) and 10 patients (8.9%) experienced 2 new/worsening ailments, 1 patient (0.9%) experienced 3, and 1 patient (0.9%) experienced
4. There was not a significant difference in the number of new/worsening ailments occurring in men and women (Fig. 1).

The median time elapsed between the last administered dose and the occurrence of the first new/worsening ailment was 11.57 weeks (range 0.04–47.14). The majority of patients (N = 83, 76.1%) experienced the occurrence of the new/worsening ailment after 6 weeks post-vaccination, and only 26 (23.9%) before 6 weeks. In the group of patients experiencing the new/worsening ailment after 6 weeks post-vaccination, the median time elapsed was 15.0 weeks (range 6.43–47.14), and in the group experiencing the new/worsening ailment before 6 weeks post-vaccination, the median time elapsed was 4.28 weeks (range 0.04–5.57).

There was not a significant difference in age between the patients with a first new/worsening ailment starting before 6 weeks post-vaccination (mean 66.64, SD 16.90) and those with a first new/worsening ailment starting after 6 weeks post-vaccination (mean 67.61, SD 13.99). There was not a significant difference in the proportion of men and women experiencing a first new/worse ailment before or after 6 weeks post-vaccination (Fig. 2).

The median time elapsed between the last administered dose and the occurrence of the second new/worsening ailment was 18.21 weeks (range 8.57-60), all of them occurring after 6 weeks post-vaccination. The mean age of these patients was 68.83 (SD 11.85), and 75% were men (N = 9) and 25% were women (N = 3). One 61 y.o. man experienced a third new ailment, which occurred 30 weeks post-vaccination, and one 82 y.o. man experienced a fourth new ailment 21.43 weeks post-vaccination (Note: when referring to post-vaccinations, we always refer to the latest administered dose).

The number of doses administered before the occurrence of a first new/worsening ailment was 1 dose to 14 patients (12.5%), 2 doses to 64 patients (57.1%), 3 doses to 24 patients (21.4%), and 4 doses to 7 patients (6.3%) (Fig. 3). Additionally, 6 patients (5.3%) experienced a second new/worsening ailment after receiving 2 doses, and 5 patients (4.5%) after receiving 3 doses. The patient experiencing a third new/worsening ailment received 3 doses, and the patient experiencing a fourth new/worsening ailment received 4 doses. The number of new/worsening ailments occurring before 6 weeks was significantly higher in patients receiving four doses, while most new/worsening ailments in people receiving two and three doses occurred after 6 weeks (Chi square 12.97, p < 0.001 after Bonferroni correction) (Fig. 4). Regarding the number of new/worsening ailments that occurred in patients receiving 1, 2, 3 or 4 doses, we found no significant differences across groups.

When assessing the number of new/worsening ailments per vaccine type, we did not find any significant difference. Also, the number of weeks until the occurrence of a first or second new/worsening ailment was not significantly different across vaccine types.

Finally, we assessed the number of comorbidities (e.g., hypertension, diabetes, hypercholesterolemia, etc.), finding a median number of comorbidities of 4 (range 0–11), with a significantly higher number of comorbidities in women (median 4, range 0–9) than men (median 3, range 0–11) (p = 0.04). The number
of comorbidities was also significantly higher in participants developing a first new/worsening ailment before 6 weeks post-vaccination (median 5, range 0–11) than after 6 weeks post-vaccination (median 3, range 0–9). We also find a small but significantly negative correlation (Spearman's rho correlation coefficient: -0.3; p = 0.02) between the number of comorbidities and the number of new/worsening ailments of the participants, which was confirmed using a generalized linear model, correcting for sex, age, and vaccine type (p = 0.01).

**COVID-19 test results**

Among the 112 patients included in the study, 33 tested positive to a COVID-19 PCR or antigenic test during the study period, 48 were negative and 31 did not provide the information (unknown).

Of the 38 health-related events that occurred in 33 patients who tested positive for COVID-19, 26 (68.4%) occurred after vaccination but before COVID-19 infection, whereas 12 (31.6%) occurred after vaccination and infection.

**Deceased patients**

Nineteen (19) patients with a mean age of 78.2 y.o. (SD 11.4) (10 men, 9 women) died on average 17.14 weeks (SD 13.71) after their last injection. The known causes of death were cancer (N = 9) or cardiovascular diseases (N = 8). One patient died consecutively to a hip fracture, and the probable cause of death of one patient is not available. Only two of the 19 deceased patients tested positive for COVID-19 (in the month preceding their death) (Supplementary Table S3).

**Discussion**

Our study aimed to characterize the chronology of new and/or worsening ailments that occurred post-vaccination and that could be considered as potential AE. We explore these characteristics in a group of men and women without significant differences in age, who had received at least one dose of an approved COVID-19 vaccine.

The health authorities have assumed that COVID-19 vaccination-associated AEs would occur as shortly as with traditional vaccines. Our results suggest that, whereas some AEs do occur within 6 weeks, most AEs do not, proving this assumption is wrong and would need to be revisited. The current use of the narrow 6-week time window, which was implemented for traditional vaccines, leaves a majority (76.1%) of potential AEs beyond the scope of any investigations, thereby justifying the need to extend that time window, so that (i) it encompasses most, if not all, health-related events possibly related to COVID-19 vaccination, (ii) it is specifically designed for this new generation of vaccines, and (iii) it allows thorough investigation of the relationship between health-related events and COVID-19 vaccination.

**Observational time window**
Our data showed that the median time for a first new/worsening ailments to appear was 11.57 weeks after the last COVID-19 injection. This is two times later than the 6-week period that is currently used by the Quebec's Public Health Agency, the “Institut national de santé publique du Québec (INSPQ)” (https://www.inspq.qc.ca/), which neither considers nor investigates AEs reported beyond that period. Notably, less than a quarter (23.9%) of the new/worsening ailments that we documented occurred within 6 weeks and could be used to establish a possible relationship, if any, to the COVID-19 vaccines. With the current 6-week reporting period, post-vaccination AEs might be underestimated at least by a factor of 4, provided that they are systematically declared to the authorities and investigated, which is very unlikely for several reasons discussed elsewhere (Provost, manuscript submitted). The overall AE underreporting may be much more important, as an assessment of the VAERS database previously showed that fewer than 1% of vaccine AEs are reported to the Food and Drug Administration (FDA) (Lazarus et al., 2010).

In our study, the median time elapsed to the occurrence of a first new/worsening ailment that was happening after 6 weeks post-vaccination was 15 weeks, with a range between 6 and 47 weeks. Also, the time elapsed to the occurrence of a second new/worsening ailment was 18 weeks, with a range between 8 and 60 weeks. These delays would then justify extending the reporting time window to record new/worsening ailments as potential AEs to at least 15 to 18 weeks, up to a maximum of 60 weeks, to provide a picture closer to the reality of the COVID-19 vaccines.

Our study also assessed the potential differences between the participants developing a new/worse ailment before and after 6 weeks post-vaccination, since this information could influence the time window during which people with certain characteristics are followed to record potential AEs. We did not find any difference in the age nor sex of participants developing new/worsening ailments before or after 6 weeks post-vaccination. However, we did find a significantly higher number of new/worsening ailments occurring before 6 weeks, in participants receiving their 4th dose, and in participants with a higher number of comorbidities. If this observation is reproduced in larger cohorts of vaccinated participants, it could be used to optimize the follow-up period of people with fewer comorbidities.

Most participants, either men or women, receiving any number of doses of any vaccine type, experienced only one new/worsening ailments. Interestingly, we found a small, albeit significant correlation between the number of new/worsening ailments and the number of comorbidities, which was confirmed when applying a generalized linear model correcting for age, sex, and vaccine type (p = 0.01). This suggests that patients with an increased number of comorbidities, who are deemed at higher risk of complications to COVID-19, are also more susceptible to experience post-vaccination AEs.

**Causal relationship of post-vaccination AEs**

Assessment of the causal relationship (or absence of) between COVID-19 vaccines and the occurrence of new/worsening ailments requires thorough investigations, whose success directly depends on the amount and quality of the data. This is why as much information as possible needs to be collected for the longest period of time, reported to the authorities, processed, filtered, sorted and thoroughly analyzed until the safety profile of this new generation of vaccines is determined. This is of particular sense for
drugs, including vaccines, that modulate the adaptive immune systems. Indeed, unlike many drugs with classical dose/exposure/toxicity relationships, therapeutics that modulate the immune system can trigger pathological processes that further evolve independently of the exposure and can be revealed later, for instance following a “second hit” (encounter of a similar antigen) (Kostoff et al., 2020). If proven to be similar to traditional vaccines, then the observational period would be deemed appropriate. If it is not, then we would need to consider that the underlying mechanism(s) at play may be different from traditional vaccines and that the observational period should be adjusted/extended accordingly. This is instrumental, as the occurrence, nature, severity and persistence of the symptoms directly influence the evaluation of the risk-benefit ratio of the injections – not to mention the long-term side effects, the unknown in this equation, that will need to be monitored and taken into account. This influence may be such that, for a population in which the vaccination has only limited benefits (e.g., healthy children) (Banoun, 2022), the recognized risks may tilt the balance away from vaccination, which may also be for ethical reasons (Kraaijeveld et al., 2022). If the risks are such that the risk-benefit ratio becomes unfavorable to the vaccination of young or healthy individuals, then targeted vaccination campaigns would be more indicated. If the risks are found to weigh even more, then the application of mRNA technology as a vaccine platform may be reconsidered.

**Vaccine lot-to-lot variations**

We did not attempt an analysis regarding the association between specific vaccine lots and the number and/or type of new/worsening ailment because of the small number of patients per vaccine lot in our sample, which precludes a valid statistical analysis.

Nevertheless, COVID-19 vaccine lot-to-lot variations have been reported previously ([www.howbadismybatch.com](http://www.howbadismybatch.com)), suggesting that some lots may be more problematic than others. Some batches are associated with several health-related events, whereas others are not. Some of the discrepancies between vaccine lots may be due to their accelerated production by different suppliers as well as their storage time and conditions, leading to variable quality and control issues.

Part of the problems may lie in lot-to-lot variations in the mRNA intactness (Gutschi, 2022). Regulatory agencies (FDA, Health Canada and EMA) had major concerns over unexpectedly low quantities of intact mRNA in batches of the vaccine developed for commercial production, but no threshold – in terms of percentage mRNA integrity they consider acceptable for vaccines against COVID-19 – has been specified by Pfizer, Moderna, and CureVac, as well as several regulators (Tinari, 2021). Obviously, the complete, intact mRNA molecule is essential to its potency as a vaccine, as even a minor degradation reaction, anywhere along a mRNA strand, can severely slow or stop proper translation performance of that strand and thus result in the incomplete expression of the encoded antigen (Crommelin et al., 2021). Therefore, one may speculate that the lack of efficacy or increased AEs associated with certain vaccine lots may be related, respectively, to mRNA degradation or the presence of mRNA fragments, some of which may encode for truncated forms of the antigen with different bioactivity and properties. In this regard, the detection of mutant Spike S1 peptides in patients who experience post-acute sequelaes of COVID-19 (PASC)-like symptoms more than 4 weeks post-vaccination (Patterson et al., 2022) also raises concerns...
regarding the authenticity of the vaccine mRNA sequence and the fidelity of its translation into Spike proteins.

**Post-vaccination AEs**

In Canada, as of October 28, 2022 (with data up to and including October 14, 2022) ([https://health-infobase.canada.ca/covid-19/vaccine-safety/](https://health-infobase.canada.ca/covid-19/vaccine-safety/)), there has been a total of 51,714 reports of AEs (57.1 reports per 100,000 doses administered), of which 10,501 (20.3%) were considered serious (life-threatening; 11.6 reports per 100,000 doses administered). A total of 382 reports with an outcome of death were reported following vaccination. The prevalence of AEs following immunization for females was 77.1 reports per 100,000 doses administered, compared to 31.1 per 100,000 doses administered for males. The combined rate of AEs totaled 108.2 reports per 100,000 doses administered, i.e., ~ 1 report per 1,000 doses and ~ 1 serious report per 5,000 doses, which is substantial. This rate of post-vaccination AEs may be largely underestimated since – as suggested by the results of the present study – most AEs may occur beyond the limited 6-week time window during which the occurrence of a new/worsening ailment is currently being considered by the authorities. To the timeframe factor, we may also add the lack of patients’ awareness, the self-treatable nature of new/worsening ailments, and the lack of reporting by physicians, as discussed elsewhere (Provost, manuscript submitted). The authentic rate of AEs, either non-serious or serious, may thus reach a level that can hardly be ignored, especially since long-term AEs remain unknown.

**Post-vaccination cardiovascular AEs**

The most frequent medical ailment that appeared or worsened among the participants of our study was cardiovascular diseases. In Canada, cardiac complications, such as myocarditis/pericarditis, account for 1.53 reports of AEs of special interest (AESI) per 100,000 injections, and complications of the circulatory system total 1.65 per 100,000 injections (Table 1; [https://health-infobase.canada.ca/covid-19/vaccine-safety/](https://health-infobase.canada.ca/covid-19/vaccine-safety/)). Together, the cardiac/circulatory (cardiovascular) complications account for half (3.18 or 50.8%) of the 6.26 reports per 100,000 injections for all AESI categories. This proportion is very similar to that observed in our study (61 reports of a total of 136; 44.8%), despite the relatively small number of patients. The similarity between these two proportions is in favor of attributing the causality of the observed AEs to the vaccine, regardless of the time elapsed since vaccination. This relatively high proportion of cardiovascular complications may be related to the drainage of the vaccine components from the injected site into the bloodstream and their contact with the vasculature. Further investigations, such as blood analyses (e.g., troponin levels), histological and immunohistochemical analyses of tissue biopsies, and autopsies, should be conducted to confirm or infirm any causal link with COVID-19 vaccination (Maiese et al., 2022). Analysis of the US Vaccine Adverse Events Reporting System (VAERS) and of the European Database of Suspected Adverse Drug Reaction (EudraVigilance) found, for an equivalent number of individuals vaccinated, a risk of cardiovascular AEs that is 154 higher for COVID-19 vaccines compared to influenza vaccines (Montano, 2022).
In France in 2021, the difference in myocarditis rate with 2019 and 2020 coincided with the vaccination campaign in young individuals (Boudemaghe et al., 2022). In a retrospective Israeli study based on a cohort of 196,992 adults, no increased incidence of pericarditis or myocarditis was observed after COVID-19 infection (Tuvali et al., 2022). In a cohort of 23 million people, in men over 12 years of age, the incidence of myocarditis/pericarditis in the unvaccinated was 0.261/100,000 people and shown to vary according to the vaccination schedule: between 0.322/100,000 people (1 dose of Moderna) and 2.402/100,000 people (1 dose of Pfizer followed by one dose of Moderna) (Karlstad et al., 2022). A similar or higher prevalence of post-vaccination myocarditis/pericarditis was reported elsewhere: in 2021, the CDC reported a rate of 3.23/100,000 injections for 18–39 years in the Vaccine Safe Datalink (Klein, 2021) and a study from Israel reported a rate of 3.83/100,000 men of all ages after their 2nd dose (Mevorach et al., 2021), whereas recent public health data from Ontario, Canada, reported a rate of 13 per 100,000 injections, all ages combined (Buchan et al., 2022). The real incidence of post-vaccination myocardial lesions, however, may be as high as 2.8% (as estimated by increased troponin levels), which is 800 times more than the 0.0035% of myocarditis reported in retrospective studies (https://www.cardio-online.fr/Actualites/A-la-une/ESC-2022/Incidence-non-negligeable-myocardites-apres-3-dose-vaccin-ARN-messager-anti-COVID-19).

Window of vaccinal protection

We noticed that a patient (#41; Supplementary Table S1) tested positive for COVID-19 and was hospitalized ten days after his 4th dose of Pfizer-BioNTech vaccine. This case is compatible with the hypothesis of a reduced protection from the disease in the first 14 days following injection and highlights the need to constitute a distinct group of patients (0 to 14-day post-vaccination) for use in comparative analyses to other groups of non-vaccinated and vaccinated patients. Antibody-dependent enhancement (ADE) may be involved in facilitating or worsening a COVID-19 infection occurring within days of vaccination (Shimizu et al., 2022; Sridhar et al., 2022).

Limitations

The longer delay before the occurrence of the AEs (11.57 weeks instead of 6) makes it more difficult to establish a causal link with the COVID-19 injections. This may be circumvented by increasing the number of vaccinated patients and by including a control group of non-vaccinated patients in a larger retrospective study that would also cover a similar pre-COVID-19 and/or pre-COVID-19 vaccination period to correct for changes that may have occurred in the absence of vaccination.

Only patients with symptomatic AEs or major health-related events that led to changes in their prescriptions were included in our study. Patients who experienced changes in their health or medical condition following vaccination against COVID-19 that went unnoticed, were minor, could be self-treated or did not require changes to their medications or pharmacy record could not be identified and were not included in this study, thereby contributing to AE underreporting.

During the Spring of 2022, PCR testing became restricted to health care workers and patients had to be registered to the “Régie de l’assurance-maladie du Québec” (https://www.ramq.gouv.qc.ca/en) to obtain
an antigenic COVID-19 detection kit. Therefore, we cannot exclude the possibility that some of our patients may have had COVID-19 without testing positive for it or without knowing it (asymptomatic).

**Conclusion**

The main finding of our study is that most of the health-related events, as recorded as changes in patients’ pharmaceutical records, occurred beyond the 6-week observational period, which is currently used by the Quebec’s Public Health Agency, the “Institut national de santé publique du Québec (INSPQ)”, thereby calling for an extension of that period and a review of the guidelines set for post-vaccination AE reporting and analyses.

Association between COVID-19 vaccination and the ensuing occurrence of AEs does not necessarily equal causation. However, the new/worsening ailments that we observed in vaccinated patients of a Quebec pharmacy, the period of time after which they occurred and their faster occurrence in association with the number of doses received and the number of comorbidities, raise public health issues that are serious and important enough to warrant wider, larger and more thorough collaborative investigations by independent groups of pharmacists and researchers. Independent research funding opportunities should be launched to promote well-controlled, retrospective studies aimed to characterize the nature, occurrence and severity of the AEs associated with this new vaccine generation, and hopefully determine any possible causal link, if any, before their use is expanded even further to fight COVID-19 variants and other infectious diseases.

**Declarations**

**Acknowledgments**

We thank our Apothicaire collaborator for data collection. We also thank all the patients or their parents or siblings for having shared their personal and medical information that has made this study possible.

**Author Contributions**

Conceptualization, P.P.; methodology, P.P.; formal analysis, P.P.; supervision, P.P.; writing—original draft preparation, P.P.; writing—review and editing, H.B., P.P.; approved submission, all authors. All authors have read and agreed to the published version of the manuscript.

**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Funding

This research was not funded.

Data Availability Statement

All data presented in this study are included in this published article and are available in the accompanying Supplementary Information files.

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Figures

![Graph showing sex distribution of counts for different numbers of new/worsening ailments](image)

**Figure 1**
Bar chart presenting the number of new/worsening ailments occurring in men and women following COVID-19 vaccination.

![Bar chart](image)

**Figure 2**

Bar chart presenting the proportion of men and women experiencing a first new/worse ailment before or after 6 weeks post-vaccination.
Figure 3

Bar chart presenting the number of COVID-19 vaccine doses administered before the occurrence of a first new/worsening ailment.
Figure 4

Bar chart showing that most new/worsening ailments in people receiving two and three doses of a COVID-19 vaccine occurred after 6 weeks.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MSProvostAEreportingtimeperiodSupplementaryTableS1.xlsx
- MSProvostAEreportingtimeperiodSupplementaryTableS2.xlsx
- MSProvostAEreportingtimeperiodSupplementaryTableS3.xlsx