Saskatchewan Health Authority

University of Saskatchewan

## COVID-19 Evidence Support Team
# RAPID REVIEW REPORT

What are the harmful/adverse effects of multiple doses of COVID-19 mRNA vaccines?


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**Version:** 1 **Review History:**

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Full author statement available at the end of report.

## Key Findings

- Evidence to date of adverse events associated with mRNA COVID-19 vaccines are largely local reactions such as pain and swelling of the injection site, and systemic reactions of an allergic nature
- Increased incidences of myocarditis and pericarditis have been observed, most often occurring in men under 30 years of age, and most often after the second dose of mRNA vaccine, with more occurrences following the Moderna COVID-19 vaccine versus Pfizer, however all cases appear to resolve
- To date, there is no evidence indicating a negative effect on the immune system from the administration of multiple doses of mRNA COVID-19 vaccines

## Limitations

- As the mRNA COVID-19 vaccines have only been available since December 2020, long term safety data are not yet available

## Strength of Evidence

☐Mature evidence ☐Emerging Supportive evidence
☐Mixed evidence ☒Weak evidence

## Quality of Evidence Assessment

1. **Adequacy of primary studies**:

Clinical trials and surveillance data from around the world have captured adverse events occurring with the administration of mRNA COVID-19 vaccines.

2. **Methodological limitations**:

The effect of vaccines on the immune system long term is not yet fully understood. In addition, as the mRNA COVID-19 vaccines have only been in use since December 2020, there is no long term data yet available.

3. **Relevance to review question**:

Existing literature on the adverse events associated with vaccines are limited to local and systemic reactions. Due to the limited time frame of vaccine use, long term safety data Is not yet available.

4. **Generalizability of findings**:

To date, given the volume of mRNA COVID-19 vaccinations administered around the world, there does not appear to be an immediate safety concern in the effect of the mRNA vaccines on the immune system function.

## Background/Context

**1. Clinical Context**

With over 10 billion doses of COVID-19 vaccines administered worldwide to date, concerns around the long term safety, particularly of mRNA vaccines have arisen.

**2. Purpose**

To determine whether there are any safety concerns, particularly long-term of the administration of multiple doses of mRNA COVID-19 vaccines.

**3. Review Question(s)**

- Is there evidence that there are potential harms associated with multiple doses of mRNA COVID-19 vaccines?

## Method

For each Rapid Review, the initial question is posed by a decision-maker in the health care system seeking the evidence base for a specific policy decision. According to the subject of the question, the COVID Evidence Support Team (CEST) Intake Committee allocates the question to the appropriate Working Group. Each Working Group may be comprised of a librarian, researcher, 1-2 clinicians, 1-2 subject matter experts, and a group leader. A reference interview is conducted to establish the parameters of the question to ensure it is articulated in a clear, searchable manner. The librarians assigned to the team then conduct a thorough search of the indexed literature, grey literature, news sources, or other sources as agreed upon. Some reference lists for especially pertinent articles are also reviewed. An Evidence Search Report is thereby created. See Appendix for more details on the search strategy. A Rapid Review of the identified literature is then performed by the researcher using

the approach of a systematic review, but without a double review, formal assessment of quality of reported study, or meta-analysis. Importantly, the review is completed in a time-sensitive manner. Relevant evidence is summarized in both tabular and narrative form, key findings and limitations articulated, and the quality of the body of evidence evaluated using a four-point grading system that assesses the methodologies, adequacy of the included studies, the direct relevance to the question and the generalizability of the findings related to the question. The draft Rapid Review Report is reviewed and edited by the Working Group clinicians, experts, and leader. Once revisions are complete, the Rapid Review is submitted to the requesting decision-maker and placed in the COVID-19 repository and database. For certain topics with rapidly changing evidence, after a period of time an updated evidence search is performed, the review process repeated, and an updated Rapid Review released.

## Summary of Evidence

As of December 30th 2021, more than 51 million doses of Pfizer and 22 million doses of Moderna's mRNA COVID-19 vaccines have been administered in Canada[1]. Up to January 22, 2022 there have been 15,753 non-serious and 5,138 serious adverse events reported to Health Canada associated with the Pfizer vaccine and 9,255 and 1,407 reported for the Moderna vaccine, respectively[2]. The majority of non-serious adverse events for all vaccines reported were local reactions such as vaccination site redness, pain, swelling and itching and systemic reactions such as headache, fatigue, chest pain dizziness, and nausea. Adverse events of special interest reported include 116 cases of Guillain-Barré Syndrome and 1,680 cases of myocarditis/pericarditis reported for all COVID-19 vaccines. The Canadian Pediatric Society[3] provided an evaluation of the Canadian COVID-19 vaccine safety data and found that most cases of myocarditis/pericarditis associated with COVID-19 mRNA vaccines and are in males under 30 years, after the second dose, and mild. NACI[4] further determined that in Canada, cases of myocarditis have been more frequently associated with the Moderna COVID-19 vaccine compared to the Pfizer vaccine.

The CDC[5] has reported similar findings from the COVID-19 vaccination campaign in the US with the most common systemic reactions reported being fatigue, headache and myalgia – with most being mild to moderate in severity within the first three days of vaccination, and often resolving within one or two days of onset. The CDC has also found an increased rate of reports of myocarditis/pericarditis and noted that it occurred most predominantly in males 12-29 years of age within the first week of the second dose, and also more commonly found following vaccination with the Moderna COVID-19 vaccine compared to the Pfizer vaccine – and that until additional safety are available those who develop pericarditis or myocarditis after a dose do not receive a subsequent dose of any COVID-19 vaccine.

For doses in addition to the primary two dose series of mRNA COVID-19 vaccines, the safety data is still emerging. A review of several large trials[6] of almost 22,000 participants who had received the Pfizer vaccine, and over 22,000 participants who had received the Moderna vaccine found that post-vaccination fever cases dropped to about half for the 3rd/booster dose for both vaccines, and that the occurrence of other adverse events was similar to that of the preceding dose. Of note, this review also determined that the 'nocebo' (a phenomenon where adverse events are seemingly elicited by placebos[7] – in this case, the physical act of injection) effect appears to significantly contribute to the differences in the frequencies of various systemic adverse events across vaccine types. An Israeli study[8] of self-reported adverse events of healthcare workers >60 years who had received the booster had 1,056 respondents and found no serious adverse events.

A recent article in the Globe and Mail by Dr. Norman Doidge[9], a Canadian psychiatrist criticizing COVID-19 vaccination campaigns, cited the European Union as coming out against regular, continuing boosters in fear that they will weaken the immune response. This statement has not been found in publications from the European Medical agency, and is only referred to in another journal article in Bloomberg[10] – with the only direct quote from Marco Cavaleri, the EMA head of biological threats and vaccine strategy being that "[boosters] can be done once, maybe twice, but it's not something that we can think should be repeated constantly" and another journalistic article in DW[11] which references a press conference by Cavaleri where he is said to indicate a lack of data on the effectiveness of multiple booster doses, and that frequent boosting could have a negative impact on immune response to COVID-10, causing "fatigue in the population" that has received multiple shots. To date, there has been no evidence to either support or refute these claims. Physicians and scientists from the University of Toronto[12], the Canadian Coronavirus Variants Rapid Response Network (CoVaRR-Net)[13], as well as the Editorial Board of the Globe and Mail[14]disagreed with numerous aspects of the arguments forwarded by Dr. Doidge. Citing the evidence from Alberta and Quebec, the editorial board of the Globe and Mail highlights the documented effectiveness of vaccines in reducing hospitalizations and death from COVID-19.

## Conclusions

With over 70 million doses of mRNA COVID-19 vaccines having been administered in Canada alone, short term safety data has been thoroughly investigated. To date, adverse events associated with COVID-19 vaccines are largely local reactions such as injection site swelling and pain, and systemic reactions associated with immune responses such as fever, headache and myalgia. New research has indicated that many of these systemic reactions may be attributable to a 'nocebo' effect due to the act of the injection itself. More serious adverse events include a slight increase in risk of myocarditis/pericarditis, often in men under 30 years of age and most often after the second dose, with the majority of cases being mild and resolving with minimal intervention. A number of journal articles in recent weeks have indicated that there is a possibility of "immune fatigue" associated with multiple doses of, in particular, mRNA COVID-19 vaccines. To date, these claims have not been supported by any scientific evidence and the overwhelming consensus is that COVID-19 vaccines are safe and effective when used according to manufacturer instructions.

## Table 1: Summary of Evidence

Consult the Summary of Evidence table using the following link:

- https://covid19evidencereviews.saskhealthauthority.ca/en/permalink/coviddoc437

This link provides access to the database where it is possible to view the spreadsheet for review.

## Reference List


1. COVID-19 Tracker. Updated December 30, 2021. https://covid19tracker.ca/vaccinationtracker.html
2. Health Canada. Reported side effects following COVID-19 vaccination in Canada. 21 January, 2022. https://health-infobase.canada.ca/covid-19/vaccine-safety/#a3
3. Canadian Pediatric Society. Clinical guidance for youth with myocarditis and pericarditis following mRNA COVID-19 Vaccination. 1 September 2021.

https://cps.ca/en/documents/position/clinical-guidance-for-youth-with-myocarditis-and-pericarditis

4. PHAC. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) Interim guidance on booster COVID-19 vaccine doses in Canada. 29 October 2021 https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines/statement-guidance-booster-doses/statement-guidance-booster-doses.pdf
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11. DW. COVID: Do multiple boosters 'exhaust' our immune response? January 18, 20222. https://www.dw.com/en/covid-do-multiple-boosters-exhaust-our-immune-response/a-60447735
12. The Globe & Mail. We should debate the best COVID treatments. But let's eschew revisionist history. January 28, 2022. https://www.theglobeandmail.com/opinion/article-we-should-debate-the-best-covid-treatments-but-lets-eschew-revisionist/
13. HealthyDebate. Let evidence be our guide: Misinformation most insidious when it comes from health-care professionals. January 27, 2022. https://healthydebate.ca/2022/01/topic/covid-misinformation-from-health-care-professionals/
14. The Globe & Mail. Vaccines are our most powerful pandemic-fighting tool. Yes, they're silver bullets. January 29, 2022. https://www.theglobeandmail.com/opinion/editorials/article-vaccines-are-our-most-powerful-pandemic-fighting-tool-yes-theyre/

## Appendix 1: Evidence Search Details

**Note:** To view full search strategy details, please consult the associated Evidence Search Report.

| | |
|---|---|
| **Filters, Limits & Exclusions:** | English only<br>[Month Day, Year – Month Day, Year]<br>… |
| **Sources Searched:** | [Alphabetical]<br>• BCCDC<br>• CDC COVID-19 Website<br>• COVID-End<br>• CPS<br>• Evidence Check Australia<br>• FDA (US)<br>• Google<br>• Google Scholar<br>• Government of Canada: COVID-19 Vaccines and Treatments Portal<br>• Health Canada<br>• HSE Ireland<br>• IBM Micromedex<br>• MedRxiv<br>• Lexicomp<br>• L-OVE<br>• McMaster Plus Evidence Alerts<br>• NCCMT<br>• PHAC<br>• Pharmacist's Letter Canada<br>• Public Health Ontario<br>• SPOR Evidence Alliance<br>• TRIP Pro<br>• Veteran's Affairs Database<br>• WHO<br>• WHO Global Research Database |
| **Librarian(s):** | Lukas Miller, Clinical Librarian, Saskatchewan Health Authority<br>Mark Mueller, Clinical Librarian, Saskatchewan Health Authority |

## Appendix 2: Evidence Search Strategies

**Ovid MEDLINE(R) ALL <1946 to January 24, 2022>**

| # | Searches | Results |
|---|---|---|
| 1 | COVID-19/ or exp COVID-19 Testing/ or SARS-CoV-2/ | 136025 |
| 2 | (coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/) | 40116 |
| 3 | (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ot,ox,rx,px. | 212937 |
| 4 | ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,ot. | 62111 |
| 5 | (longCOVID* or postCOVID* or postcoronavirus* or postSARS*).ti,ab,kf,ot. | 26 |

| | | |
|---|---|---|
| 6 | ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot. | 11155 |
| 7 | ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot. | 382 |
| 8 | or/1-7 [CADTH COVID-19 Hedge September 2020] | 223363 |
| 9 | (exp *Immunization/ or exp *Vaccines/ or *Immunity, Herd/ or COVID-19 Vaccines/) and exp RNA, Messenger/ | 1768 |
| 10 | (((messenger adj2 "RNA") or "mRNA") and (vaccinat* or vaccine? or revaccinat* or re-vaccinat* or inoculat* or immunization? or immunize? or immunity or immunogenicity or variolation?)).ti,ab,kf,ot. | 18270 |
| 11 | (pfizer-biontech or biontech or pfizer or comirnaty or "BNT162b1" or "BNT162b2" or "BNT162b3" or "BNT162b2SA" or "BNT162a1" or "BNT162c2" or tozinameran).ti,ab,kf,nm,ot,ox,rx,px. | 5275 |
| 12 | (moderna or modernaTX or spikevax or "mrna-1273" or "mrna 1273" or "mrna1273" or "mrna-1273.351").ti,ab,kf,nm,ot,ox,rx,px. | 1885 |
| 13 | or/9-12 | 24013 |
| 14 | exp *"Drug-Related Side Effects and Adverse Reactions"/ or Nocebo effect/ or Patient Harm/ | 88479 |
| 15 | (adverse effect? or adverse event? or adverse reaction? or side effect or harm* or injur* or unsafe or un-safe or accident* or misuse? or danger* or poison* or overdos* or contraindicat* or contra-indicat* or drug interact* or toxic* or cardiotoxic* or myotoxic*).ti,kf. or (adverse effect? or adverse event? or adverse reaction? or side effect or harm* or injur* or unsafe or un-safe or accident* or misuse? or danger* or poison* or overdos* or contraindicat* or contra-indicat* or drug interact* or toxic* or cardiotoxic* or myotoxic*).ab. /freq=2 | 1359328 |
| 16 | nocebo?.tw,kf. | 970 |
| 17 | exp RNA, Messenger/ and COVID-19 Vaccines/ae | 37 |
| 18 | or/14-17 | 1419021 |
| 19 | 8 and 13 and 18 | 490 |
| 20 | boost*.ti,kf. or boost*.ab. /freq=2 | 25159 |
| 21 | (multiple adj3 (administrations or inoculations or vaccinations or vaccines or re-vaccinations or revaccinations or immunizations or doses or injections)).tw,kf. | 14036 |
| 22 | ("more than" adj3 (administration? or inoculation? or vaccination? or vaccine? or re-vaccination? or revaccination? or immunization? or dose? or injection?)).tw,kf. | 5228 |
| 23 | (numerous adj3 (administrations or inoculations or vaccinations or vaccines or re-vaccinations or revaccinations or immunizations or doses or injections)).tw,kf. | 305 |

| | | |
|---|---|---|
| 24 | ((three or third or "3" or "3rd" or four or fourth or "4" or "4th" or five or fifth or "5" or "5th") adj3 (dose? or inoculation? or vaccination? or vaccine? or re-vaccination? or revaccination? or immunization? or boost*)).tw,kf. | 145186 |
| 25 | 20 or 21 or 22 or 23 or 24 | 184050 |
| 26 | 19 and 25 | 98 |
| 27 | from 26 keep 1, 3-9, 12-20, 22, 24, 27... | 35 |

Search history sorted by search number ascending

**Embase <1974 to 2022 January 24>**

| # | Searches | Results |
|---|---|---|
| 1 | Sars-Related Coronavirus/ | 484 |
| 2 | (Coronavirinae/ or Betacoronavirus/ or Coronavirus Infection/) and (Epidemic/ or Pandemic/) | 10699 |
| 3 | (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).tw,kw,hw,ot. | 219350 |
| 4 | ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).tw,kw,hw,ot. | 191853 |
| 5 | (longCOVID* or postCOVID* or postcoronavirus* or postSARS*).tw,kw,hw,ot. | 70 |
| 6 | ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).tw,kw,ot. | 12804 |
| 7 | ((Wuhan or Hubei) adj5 pneumonia).tw,kw,ot. | 431 |
| 8 | or/1-7 | 238140 |
| 9 | (exp SARS-CoV-2 vaccine/ or exp *vaccination/) and exp messenger RNA/ | 1427 |
| 10 | (((messenger adj2 "RNA") or "mRNA") and (vaccinat* or vaccine? or revaccinat* or re-vaccinat* or inoculat* or immunization? or immunize? or immunity or immunogenicity or variolation?)).ti,ab,kf,ot. | 24135 |
| 11 | (pfizer-biontech or biontech or pfizer or comirnaty or "BNT162b1" or "BNT162b2" or "BNT162b3" or "BNT162b2SA" or "BNT162a1" or "BNT162c2" or tozinameran).ti,ab,kf,ot. | 14139 |
| 12 | (moderna or modernaTX or spikevax or "mrna-1273" or "mrna 1273" or "mrna1273" or "mrna-1273.351").ti,ab,kf,ot. | 1623 |
| 13 | 9 or 10 or 11 or 12 | 37769 |
| 14 | exp adverse event/ or exp side effect/ or patient harm/ or nocebo effect/ | 901322 |

| | | |
|---|---|---|
| 15 | (adverse effect? or adverse event? or adverse reaction? or side effect or harm* or injur* or unsafe or un-safe or accident* or misuse? or danger* or poison* or overdos* or contraindicat* or contra-indicat* or drug interact* or toxic* or cardiotoxic* or myotoxic*).ti,kf. or (adverse effect? or adverse event? or adverse reaction? or side effect or harm* or injur* or unsafe or un-safe or accident* or misuse? or danger* or poison* or overdos* or contraindicat* or contra-indicat* or drug interact* or toxic* or cardiotoxic* or myotoxic*).ab. /freq=2 | 1715245 |
| 16 | nocebo.tw,kf. | 1278 |
| 17 | 14 or 15 or 16 | 2431689 |
| 18 | 8 and 13 and 17 | 1082 |
| 19 | boost*.ti,kf. or boost*.ab. /freq=2 | 33102 |
| 20 | (multiple adj3 (administrations or inoculations or vaccinations or vaccines or re-vaccinations or revaccinations or immunizations or doses or injections)).tw,kf. | 20293 |
| 21 | ("more than" adj3 (administration? or inoculation? or vaccination? or vaccine? or re-vaccination? or revaccination? or immunization? or dose? or injection?)).tw,kf. | 7678 |
| 22 | (numerous adj3 (administrations or inoculations or vaccinations or vaccines or re-vaccinations or revaccinations or immunizations or doses or injections)).tw,kf. | 362 |
| 23 | ((three or third or "3" or "3rd" or four or fourth or "4" or "4th" or five or fifth or "5" or "5th") adj3 (dose? or inoculation? or vaccination? or vaccine? or re-vaccination? or revaccination? or immunization? or boost*)).tw,kf. | 213122 |
| 24 | or/19-23 | 265806 |
| 25 | 18 and 24 | 211 |
| 26 | limit 25 to (english language and yr="2021 -Current") | 201 |
| 27 | limit 26 to medline | 24 |
| 28 | 26 not 27 | 177 |

Search history sorted by search number ascending

**Search Terms Used in Other Resources**

mRNA, pfizer, biontech, BNT162b2, mrna-1273
Vaccine, vaccination, immunization, immunisation, inoculation
Multiple, second, booster
Dose, shot
Nocebo, harm, danger, adverse, unsafe, negative, risk

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The authors declare they have no conflicts of interest to report.