Saskatchewan Health Authority

University of Saskatchewan

COVID-19 Evidence Support Team
RAPID REVIEW REPORT

What are the risks or benefits of extended intervals between doses of COVID-19 vaccines compared to recommended dosing in extremely vulnerable populations?

Review Code: EOC210302 RR **Review Date:** April 21, 2021
Version: 1 **Review History:**

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Full author statement available at the end of report.

Key Findings

- The group designated in Saskatchewan as Clinically Extremely Vulnerable (CEV) is a heterogenous clinical population with factors that impair their immune response to differing degrees.
- Very Limited evidence is currently available to assess the immune response following vaccination is selected clinical populations; no evidence is available to assess vaccine efficacy or effectiveness in these populations. The clinical relevance of measured immune response with respect to protection from disease is still uncertain.
- In considering the immune response of the CEV population, it is recommended that the absolute difference in immune response between 1 and 2 doses be considered, as it is possible some patient groups will have lowered protection regardless of vaccine strategy.
- In terms of clinical subgroups:
    - Organ transplantation recipients on immunosuppressive medication: solid organ transplant recipients receiving anti-metabolite maintenance immunosuppression therapy were less likely to develop an antibody response to an mRNA vaccine, compared to those receiving other types of therapies (37% vs 63%). In a study of 242 kidney transplant recipients on immunosuppressive therapy only 10.8% became seropositive at 28 days after a single dose of mRNA vaccine.
    - Cancer: A study of 151 elderly patients with solid and hematological malignancies and 54 healthy controls who received one or two doses of BNT162b2 (Pfizer-BioNTech)

vaccine shows approximately 39% of solid cancer patients, 13% of hematological cancer patients, and 97% of healthy controls ($p<0.0001$) developed anti-S IgG 21 days following a single dose vaccine. However, response in solid cancer patients increased to 95% within 2 weeks of the second dose at 21 days.

- Other immunocompromising conditions (e.g., auto-immune disorders and therapy): some level of immunity is generated with vaccination; however, what this means clinically is unknown. It seems that ensuring the dosing is properly timed around biologic therapy is important.

Limitations

- Studies assessed the efficacy and safety of COVID-19 vaccines in patients with inflammatory diseases or cancers were small size studies. Further research is needed to validate the findings of these studies.
- Additionally, the immunology of COVID-19 is still largely unknown, compounded with limited evidence, our knowledge of the field is very limited. Studies showing only a decreased immune response to one dose is not truly useful as the main consideration is the ability to improve immune response with 2 doses. Very limited evidence is available to answer this question.
- Due to the nature of the rapid review, the methodology or findings of the studies were not critically appraised.

Strength of Evidence

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

Quality of Evidence Assessment

1. **Adequacy of primary studies**:
   Limited primary studies on CEV population
2. **Methodological limitations**:
   No RCT on CEV population was reviewed.
3. **Relevance to review question**:
   Limited evidence is available.
4. **Generalizability of findings**:
   Limited findings to generalize to all CEV individuals.

Background/Context

1. Clinical Context

Due to shortage of COVID-19 vaccine, some jurisdictions around world have decided to extend the interval between COVID-19 vaccine doses. At the time of this review, the Canadian National Advisory Committee on Immunization (NACI) recommends extending the interval for the second dose of COVID-19 vaccines up to four months after the first. However, the impact of this recommendation has not been thoroughly studied in vulnerable populations.

2. Purpose
To understand current recommendations and findings about extended COVID-19 vaccines intervals, especially in vulnerable populations.

3. Review Question(s)

- What do current studies suggest for extending intervals between vaccine doses?
- What are the impacts (risks or benefits) of extended intervals in vulnerable populations?

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

Clinically extremely vulnerable (CEV) population

The Government of Saskatchewan has developed a list of underlying health conditions that are believed to make an individual clinically extremely vulnerable (CEV) to severe COVID-19 (1). The list is a heterogeneous set of conditions each with a different underlying pathophysiology. In the evidence search for this review, no studies assessing vaccine efficacy or effectiveness for these conditions were identified. Studies measuring the immune response of individuals in this group are available, however there remains some uncertainty regarding the relationship between immune response and protection from COVID-19 disease (2).

Immune response

Elderly

A study of 12 COVID-19 seronegative residents of long-term care facilities (median age, 82 years), 18 seronegative health care workers (HCW; median age, 36 years), and 4 convalescent HCW, assessing

antibody responses to SARS-CoV-2 nucleocapsid (N) and spike protein receptor binding domain (S/RBD) after one BNT162b2 mRNA (Pfizer-BioNTech) vaccine shows that binding antibodies against S/RBD, inhibition of ACE2 binding, and pseudovirus neutralizing activity were, respectively, 4-, 3-, and 2-fold lower in elderly individuals compared to HCW (3).

Solid organ transplant recipients on immunosuppressive medications

Studies have shown that the immune response to COVID-19 vaccines depends on a patient's immunocompetency, type of immunosuppressive therapy, length of disease, and age (4–8). A prospective cohort study in the US assessed humoral response to the first dose of mRNA vaccines (52% received Pfizer-BioNTech and 48% received Moderna) among 436 solid organ transplant recipients (median age: 55.9 [IQR, 41.3 – 67.4 years]) (4). The study shows that recipients receiving anti-metabolite maintenance immunosuppression therapy were less likely to develop an antibody response, compared to other types of therapies (37% vs 63%, adjusted multivariable incidence rate ratio [IRR], 0.22 [95% CI, 0.15 – 0.34], p<0.001) (4). Older participants were less likely to develop an antibody response (adjusted multivariable IRR, 0.83 [95% CI, 0.73 – 0.93] per 1 year, p=0.002). Recipients of Moderna vaccine were more likely to develop an antibody response than Pfizer-BioNTech vaccine recipients (69% vs 31%, adjusted multivariable IRR, 2.15 [95% CI, 1.29 – 3.57], p=0.003) (4). A study of 242 kidney transplant recipients (KTRs) on immunosuppressive therapy with a negative history and laboratory test for COVID-19 assessed their anti-SARD-CoV-2 antibody response against the spike protein 28 days after administration of their first dose of Moderna mRNA-1273 vaccine (5). The study shows a weak anti-SARS-CoV-2 antibody response among the KTR participants (only 10.8% became seropositive at 28 days after injection) (5). Patients with longer time from transplantation, less immunosuppression, and better kidney function had a greater likelihood of seroconversion (5).

Cancer patients

A study in the UK on 151 mostly elderly (median: 73 years) patients with solid (63%) and hematological (37%) malignancies and 54 healthy controls (primarily health care workers) who received one or two doses of BNT162b2 (Pfizer-BioNTech) vaccine shows approximately 39% of solid cancer patients, 13% of hematological cancer patients, and 97% of healthy controls (p<0.0001) were "responders" (developed anti-S IgG) at 21 days following a single dose vaccine (9). However, the immune response in solid cancer patients was increased to 95% within 2 weeks of a booster at 21-days (9).

Immunocompromised individuals

In patients with inflammatory arthritis on immunosuppressive therapy, the impact of therapy on COVID-19 vaccine responses is unclear (7). However, it has been recommended that vaccination be avoided during disease flare or before withholding anti-CD20 therapy such as rituximab for 6 months (7). Another study reports that 74% of patients with rheumatic and musculoskeletal diseases (RMD) show detectable antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein at a median 22 days after the first mRNA vaccine dose (6). In a study, antibody titres were assessed in 26 patients with chronic inflammatory diseases (CID) and 42 healthy controls (mean age 50.5 years vs 37.5) after two doses of mRNA vaccines (Pfizer-BioNTech or Moderna) with 35 days interval (8). The vaccines showed immunogenicity in all participants, but the anti-SARS-CoV2-IgG titre 7 days after the second dose in patients with CID was significantly lower than that of healthy participants (2053 binding antibody units (BAU)/mL ± 1218 vs 2685 ± 1102 [p=0.037]) (8). Neutralizing antibodies had significantly lower inhibitory activity level in patients with CID than in healthy controls (87.42% vs 96.04% [p=0.0442]) (8). No significant response difference in CID patients in various therapeutic groups (TNF blockade vs conventional disease-modifying anti-rheumatic drugs [cDMARDs]) was detected (8). Mild side effects were slightly more frequent in CID patients, but systemic side effects were less frequent in those

patients compared with healthy individuals (8). A non-systematic review has found that low-degree immunosuppression may not interfere with antibody response to vaccines, but patients on rituximab should receive vaccine at least 4 weeks before or 6 months after treatment (10). The authors also recommend that vaccinations should be made during remission in patients with autoimmune/autoinflammatory rheumatological disease (AIIRD) or before the initiation of any biological disease-modifying antirheumatic drugs (DMARDs) (10).

National/provincial guidelines

NACI recommends that COVID-19 vaccines be administered according to schedules recommended in product monographs, however that the interval between doses may be extended up to 4 months in jurisdictions facing limited vaccine supply given the expected public health benefits of doing so. NACI makes no broad recommendation regarding the CEV population but to indicate that the decision to vaccinate and timing of vaccination should be dealt with on a case-by-case basis.(2). The World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) recommend the vaccine doses be given according to the schedules employed in the products' clinical trials, but Britain and Canada have modified vaccine dose intervals (11–14). Ontario's Vaccine Clinical Advisory Group (VCAG) recommends that the following groups should receive the COVID-19 vaccines at the dose interval indicated in the products monographs (15): transplant recipients, individuals with malignant hematologic disorders and non-hematologic malignant solid tumors receiving active treatment, except those who receive solely hormonal therapy or radiation therapy. On the other hand, the VCAG supports the extended dose intervals for older individuals and pregnant women (15). The Australian Technical Advisory Group on Immunisation (ATAGI) recommends that Pfizer-BioNTech be given at least 3 weeks apart and AstraZeneca vaccine be given preferably 12 weeks apart, although the interval can be shortened to as little as 4 weeks if required, for immunocompromised individuals (16).
The Korean College of Rheumatology (KCR) considers current COVID vaccine safe and effective in patients with autoimmune inflammatory rheumatic disease (AIIRD) (17). KCR states that corticosteroids should be reduced to the lowest dose possible without aggravating the AIIRD and methotrexate can be withheld for 1-2 weeks after each vaccination (17). The Department of Hospital Epidemiology and Infection Prevention (HEIP) at the University of California San Francisco (UCSF) recommends COVID immunization for immunocompromised patients and provides patient-specific factors for delay of vaccines in their vaccine guidelines document (18). For example, they recommend delaying vaccine 30 days prior and 90 days post allogenic stem cell transplantation (18).

Conclusions

Evidence is mixed and limited about the efficacy of extended vaccine intervals in older individuals and clinically extremely vulnerable (CEV) population. Further studies are needed.

Table 1: Summary of Evidence

Consult the Summary of Evidence table using the following link:
https://covid19evidencereviews.saskhealthauthority.ca/en/permalink/coviddoc300
This link provides access to the database where it is possible to view the spreadsheet for review.

Reference List

1. Vaccine Delivery Phases [Internet]. Government of Saskatchewan. [cited 2021 Apr 14]. Available from: https://www.saskatchewan.ca/government/health-care-administration-and-provider-resources/treatment-procedures-and-guidelines/emerging-public-health-issues/2019-novel-coronavirus/covid-19-vaccine/vaccine-delivery-phases#clinically-vulnerable
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16. Provider guide to COVID-19 vaccination of people with immunocompromised. [30 March 2021] [Internet]. Australian Technical Advisory Group on Immunisation (ATAGI). [cited 2021 Apr 14]. Available from: https://www.health.gov.au/sites/default/files/documents/2021/03/atagi-provider-guide-to-covid-19-vaccination-of-people-with-immunocompromise.pdf
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Appendix 1: Evidence Search Details

Filters, Limits & Exclusions:	English only	
Sources Searched:	Embase LitCOVID Medline MedRvix ECRI Alberta Health Services BCCDC BC Health Manitoba Health Ontario Health Google Google Scholar COVID-NMA European CDC	WHO Global Literature on Novel Coronavirus WHO Website CDC Website FDA Website CPG Infobase TRIP CADTH CEP Health Canada Government of Canada McMaster NCCMT CEBM (UK) NICE Guidance (UK) Australian Gov't
Librarian(s):	**Brianna Howell-Spooner, Clinical Librarian, Saskatchewan Health Authority** **Lukas Miller, Clinical Librarian, Saskatchewan Health Authority**	

Appendix 2: Evidence Search Strategies

Medline – March 30, 2021

#	Searches	Results
1	(coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)	39965
2	(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.	113729
3	((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.	37346
4	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf.	7126
5	((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf.	318
6	or/1-5	119380
7	limit 6 to yr="2019 -Current"	117912

8	exp *Immunosuppression/ or exp *Immunocompromised Host/ or (immunocompromised or immunosuppress* or (weak* adj2 immun*)).ti,kf,kw.	66052			
9	risk factors/ or exp age factors/ or exp comorbidity/ or race factors/ or sex factors/ or exp diabetes mellitus/ or exp cardiovascular diseases/ or hypertension/ or exp smoking/ or exp lung diseases, obstructive/	4172400			
10	(risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer* or renal disease? or kidney disease? or heart failure? or pulmonary disease? or peripheral vascular disease? or stroke? or dementia? or alzheimer* or myocardial infarction? or liver disease? or rheumatologic* disease? or hemiplegia? or paraplegia? or peptic ulcer? or ((extremely or clinical* or medical*) adj1 vulnerable)).ti,kf,tw.	4626596			
11	8 or 9 or 10	7035395			
12	(vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ti,kf. or (vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ab. /freq=2	337745			
13	7 and 12	4870			
14	(moderna? or mrna-1273 or mrna1273).mp.	1121			
15	(pfizer* or biontech* or tozinameran or BNT162b2).mp.	3208			
16	(astrazeneca or astra zeneca or "ChAdOx1-S" or ChAdOx1* or COVISHIELD or (oxford adj3 astrazeneca)).mp.	1328			
17	(janssen? or "ad26.cov2.s" or ad26cov2s or ad26cov2* or (johnson adj2 johnson)).mp.	16191			
18	or/14-17	21513			
19	13 or 18	26114			
20	time/ or time factors/ or (interval? or timing? or time? or period* or week? or day? or month?).ti,kf,tw.	8477447			
21	7 and 11 and 19 and 20	128			

Medline – March 31, 2021

#	**Searches**	**Results**			
1	(coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)	39966			
2	(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.	114058			

3	((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.	37437			
4	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf.	7141			
5	((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf.	318			
6	or/1-5	119713			
7	limit 6 to yr="2019 -Current"	118245			
8	exp *Immunosuppression/ or exp *Immunocompromised Host/ or (immunocompromised or immunosuppress* or (weak* adj2 immun*)).ti,kf,kw.	66070			
9	risk factors/ or exp age factors/ or exp comorbidity/ or race factors/ or sex factors/ or exp diabetes mellitus/ or exp cardiovascular diseases/ or hypertension/ or exp smoking/ or exp lung diseases, obstructive/	4173239			
10	(risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer* or renal disease? or kidney disease? or heart failure? or pulmonary disease? or peripheral vascular disease? or stroke? or dementia? or alzheimer* or myocardial infarction? or liver disease? or rheumatologic* disease? or hemiplegia? or paraplegia? or peptic ulcer? or ((extremely or clinical* or medical*) adj1 vulnerable)).ti,kf,tw.	4627454			
11	8 or 9 or 10	7036632			
12	(vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ti,kf. or (vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ab. /freq=2	337823			
13	7 and 12	4908			
14	(moderna? or mrna-1273 or mrna1273).mp.	1125			
15	(pfizer* or biontech* or tozinameran or BNT162b2).mp.	3215			
16	(astrazeneca or astra zeneca or "ChAdOx1-S" or ChAdOx1* or COVISHIELD or (oxford adj3 astrazeneca)).mp.	1329			
17	(janssen? or "ad26.cov2.s" or ad26cov2s or ad26cov2* or (johnson adj2 johnson)).mp.	16193			
18	or/14-17	21522			
19	13 or 18	26154			
20	time/ or time factors/ or (interval? or timing? or time? or period* or week? or day? or month?).ti,kf,tw.	8478879			
21	7 and 11 and 19 and 20	132			
22	hiv/ or acquired immunodeficiency syndrome/ or exp *Immunosuppression/ or exp	1797837			

	*Immunocompromised Host/ or abatacept/ or adalimumab/ or "Interleukin 1 Receptor Antagonist Protein"/ or Certolizumab pegol/ or etanercept/ or infliximab/ or rituximab/ or tocilizumab/ or Ustekinumab/ or Azathioprine/ or cladribine/ or cyclophosphamide/ or cyclosporine/ or Fingolimod Hydrochloride/ or Leflunomide/ or methotrexate/ or Mycophenolic Acid/ or Sirolimus/ or prednisone/ or exp leukemia/ or exp immune system diseases/				
23	(abatacept or orencia or adalimumab or humira or Interleukin 1 Receptor Antagonist Protein or kineret or Brodalumab or siliq or Certolizumab pegol or cimzia or etanercept or enbrel or simponi or etanercept or infliximab or remicade or atumumab or ocrevus or ocrelizumab or rituxan or rituximab or kevzara or sarilumab or cosentyx or secukinumab or tocilizumab or atlizumab or actemra or satralizumab or ustekinumab or stelara or Azathioprine or imurel or imuran or immuran or cladribine or mavenclad or cyclophosphamide or sendoxan or procytox or cyclosporine or neoral or Fingolimod Hydrochloride or gilenya or gilenia or Leflunomide or arava or methotrexate or Mycophenolic Acid or cellcept or Mycophenolate Mofetil or myfortic or Sirolimus or rapamune or rapamycin or xeljanz or tasocitinib or tofacitinib or prednisone or leukemia? or immunodeficienc* or immunocompromised or immunosuppress* or (weak* adj2 immun*) or immune system disease? or immune system disorder? or immune disorder? or immunologic disease? or immunologic disorder? or immune disease? or graves disease or addison disease).ti,ab,kf.	742454			
24	22 or 23	2107271			
25	7 and 19 and 20 and 24	68			

#	**Searches**	**Results**			
1	(coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)	39966			
2	(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kw,nm,rx,px.	112763			
3	((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.	37437			
4	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf.	7141			
5	((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf.	318			
6	or/1-5	118996			

7	limit 6 to yr="2019 -Current"	117528			
8	exp *Immunosuppression/ or exp *Immunocompromised Host/ or (immunocompromised or immunosuppress* or (weak* adj2 immun*)).ti,kf,kw.	66070			
9	risk factors/ or exp age factors/ or exp comorbidity/ or race factors/ or sex factors/ or exp diabetes mellitus/ or exp cardiovascular diseases/ or hypertension/ or exp smoking/ or exp lung diseases, obstructive/	4173239			
10	(risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer* or renal disease? or kidney disease? or heart failure? or pulmonary disease? or peripheral vascular disease? or stroke? or dementia? or alzheimer* or myocardial infarction? or liver disease? or rheumatologic* disease? or hemiplegia? or paraplegia? or peptic ulcer? or ((extremely or clinical* or medical*) adj1 vulnerable)).ti,kf,tw.	4627454			
11	8 or 9 or 10	7036632			
12	(vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ti,kf. or (vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ab. /freq=2	337823			
13	7 and 12	4880			
14	(moderna? or mrna-1273 or mrna1273).mp.	1125			
15	(pfizer* or biontech* or tozinameran or BNT162b2).mp.	3215			
16	(astrazeneca or astra zeneca or "ChAdOx1-S" or ChAdOx1* or COVISHIELD or (oxford adj3 astrazeneca)).mp.	1329			
17	(janssen? or "ad26.cov2.s" or ad26cov2s or ad26cov2* or (johnson adj2 johnson)).mp.	16193			
18	or/14-17	21522			
19	13 or 18	26126			
20	time/ or time factors/ or (interval? or timing? or time? or period* or week? or day? or month?).ti,kf,tw.	8478879			
21	7 and 11 and 19 and 20	132			
22	hiv/ or acquired immunodeficiency syndrome/ or exp *Immunosuppression/ or exp *Immunocompromised Host/ or abatacept/ or adalimumab/ or "Interleukin 1 Receptor Antagonist Protein"/ or Certolizumab pegol/ or etanercept/ or infliximab/ or rituximab/ or tocilizumab/ or Ustekinumab/ or Azathioprine/ or cladribine/ or cyclophosphamide/ or cyclosporine/ or Fingolimod Hydrochloride/ or Leflunomide/ or methotrexate/ or Mycophenolic Acid/ or Sirolimus/ or prednisone/ or exp leukemia/ or exp immune system diseases/	1797837			

23	(abatacept or orencia or adalimumab or humira or Interleukin 1 Receptor Antagonist Protein or kineret or Brodalumab or siliq or Certolizumab pegol or cimzia or etanercept or enbrel or simponi or etanercept or infliximab or remicade or atumumab or ocrevus or ocrelizumab or rituxan or rituximab or kevzara or sarilumab or cosentyx or secukinumab or tocilizumab or atlizumab or actemra or satralizumab or ustekinumab or stelara or Azathioprine or imurel or imuran or immuran or cladribine or mavenclad or cyclophosphamide or sendoxan or procytox or cyclosporine or neoral or Fingolimod Hydrochloride or gilenya or gilenia or Leflunomide or arava or methotrexate or Mycophenolic Acid or cellcept or Mycophenolate Mofetil or myfortic or Sirolimus or rapamune or rapamycin or xeljanz or tasocitinib or tofacitinib or prednisone or leukemia? or immunodeficienc* or immunocompromised or immunosuppress* or (weak* adj2 immun*) or immune system disease? or immune system disorder? or immune disorder? or immunologic disease? or immunologic disorder? or immune disease? or graves disease or addison disease).ti,ab,kf.	742454			
24	22 or 23	2107271			
25	7 and 19 and 20 and 24	68			
26	autoimmune.tw,kf.	159934			
27	7 and 19 and 21 and 26	5			
28	((first adj5 second) and ((first or second) adj1 dose?)).ti,ab,kf.	736			
29	11 or 24 or 26	8459820			
30	7 and 19 and 28 and 29	1			
31	7 and 28 and 29	2			
32	19 and 28 and 29	1			

Embase

#	Searches	Results			
1	(coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)	2380			
2	[(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kw,ox,rx,px.]	0			
3	((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,kw.	36205			
4	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kw.	6919			
5	((Wuhan or Hubei) adj5 pneumonia).ti,ab,kw.	373			

6	or/1-5	39768			
7	limit 6 to yr="2019 -Current"	38514			
8	exp *Immunosuppression/ or exp *Immunocompromised Host/ or (immunocompromised or immunosuppress* or (weak* adj2 immun*)).ti,ab,kw.	314084			
9	risk factors/ or exp age factors/ or exp comorbidity/ or race factors/ or sex factors/ or exp diabetes mellitus/ or exp cardiovascular diseases/ or hypertension/ or exp smoking/ or exp lung diseases, obstructive/	6456618			
10	(risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer* or renal disease? or kidney disease? or heart failure? or pulmonary disease? or peripheral vascular disease? or stroke? or dementia? or alzheimer* or myocardial infarction? or liver disease? or rheumatologic* disease? or hemiplegia? or paraplegia? or peptic ulcer? or ((extremely or clinical* or medical*) adj1 vulnerable)).ti,ab,kw.	6631397			
11	8 or 9 or 10	10130227			
12	[(vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ti,kf. or (vaccinat* or vaccine? or inoculat* or immunization? or immunize? or immunogenicity).ab. /freq=2]	0			
13	7 and 12	0			
14	(moderna? or mrna-1273 or mrna1273).mp.	833			
15	(pfizer* or biontech* or tozinameran or BNT162b2).mp.	52295			
16	(astrazeneca or astra zeneca or "ChAdOx1-S" or ChAdOx1* or COVISHIELD or (oxford adj3 astrazeneca)).mp.	22224			
17	(janssen? or "ad26.cov2.s" or ad26cov2s or ad26cov2* or (johnson adj2 johnson)).mp.	57566			
18	or/14-17	121255			
19	13 or 18	121255			
20	time/ or time factors/ or (interval? or timing? or time? or period* or week? or day? or month?).ti,ab,tw.	10960758			
21	7 and 11 and 19 and 20	22			

Other Search Terms:
COVID vaccine schedule immunocompromised

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