

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

## Steroid use post COVID-19 vaccination

### Evidence check question

Does the use of steroids post COVID-19 vaccination impact vaccine efficacy?

### In brief

- Phase 3 trials for Pfizer/BioNTech, Moderna and Oxford/AstraZeneca excluded individuals receiving corticosteroids or immunosuppressant medication at specific doses and time periods. No subgroup analysis for those who were on these medications at eligible doses was provided.<sup>1-4</sup>
- Two peer-reviewed articles from the American Society of Pain and Neuroscience and Spine Intervention Society's Patient Safety Committee summarise the literature on steroid medications and their impact on vaccine safety and efficacy. Key findings are outlined below.
  - American Society of Pain and Neuroscience<sup>5</sup>
    - There is no evidence that patients receiving epidural steroid therapy for the management of pain are at increased risk of adverse outcomes from COVID-19 vaccination.
    - There is no evidence that bolus steroids in the epidural space will impact vaccine responsiveness.
    - Neuraxial steroid injections do not need to be deferred when indicated in the context of COVID-19 vaccination.
    - No specific guidance suggests withholding nonsteroidal anti-inflammatory drugs or other anti-inflammatories prior to receiving vaccination.
  - Spine Intervention Society's Patient Safety Committee<sup>2</sup>
    - There is currently no direct evidence to suggest that a corticosteroid injection before or after the administration of an mRNA COVID-19 vaccine decreases the efficacy of the vaccine.
    - Physicians should consider timing an elective corticosteroid injection, such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible.
    - Physicians may consider the use of dexamethasone or betamethasone rather than triamcinolone or methylprednisolone when administering a corticosteroid injection in close

temporal proximity as advised in recommendation above. This recommendation is based on evidence of reduced hypothalamic-pituitary-adrenal axis suppression associated with dexamethasone and betamethasone, compared to triamcinolone or methylprednisolone. However, it must be acknowledged that the differential effects of these specific corticosteroids on adaptive immunity, immunological memory, and mRNA vaccine efficacy have not been studied.

- Limited prospective cohort studies (small sample sizes, one preprint) of individuals who had received mRNA vaccines found that use of steroids associated with reduced antibody response.
  - In one study, high dose steroids during the 12 months prior to vaccination was associated with reduced immunogenicity (odds ratio 1.8; 95% confidence interval 1.58-4.61; p=0.041) in liver transplant patients.<sup>6</sup> Low dose steroid use showed a trend towards reduced immunogenicity, but the difference was not significantly different (odds ratio 1.5; 95% confidence interval 0.91-4.1; p=0.089).<sup>6</sup>
  - In a pre-print study, participants who were on glucocorticoids (prednisone, mean mg/day  $\pm$  standard deviation=6.5 $\pm$  5.8) had a 10-fold reduction in anti-S immunoglobulin G and neutralisation titers (p<0.0001), fewer circulating plasma blasts and reduced seropositivity (65% versus 98%) when compared to immunocompetent controls.<sup>7</sup>
  - In one study, current use of steroid medications at low dose (<20mg daily) or short-term (<10 days) was associated with reduced antibody response (p=0.07) after the vaccination.<sup>8</sup>
- The Australian Rheumatology Association advises that for people on stable chronic glucocorticoid therapy, modification of dose is not necessary.<sup>9</sup> For people on higher doses who are planning to taper, the advice is to consider deferring vaccination until the dose is lower (e.g. <10mg/day), depending on the individual disease, comorbidities, likely trajectory of glucocorticoid therapy and an estimate of the risk of COVID-19.<sup>9</sup>
- The US Centres for Disease Control and Prevention advises that COVID-19 vaccines may be administered without regard to timing of corticosteroid treatment, including topical or intraarticular, bursal, or tendon injection.<sup>10</sup>
- Versus Arthritis (UK) advises that people who are on steroids can have COVID-19 vaccination, however, may need to follow guidance on shielding and social distancing after receiving the vaccination.<sup>11</sup>

## Limitations

Currently available evidence that is specific to steroid use impact on COVID-19 vaccine efficacy is limited and of low quality. Evidence is continuing to emerge on patients taking steroid medications.

## Background

Currently two COVID-19 vaccines, Pfizer/BioNTech and Oxford/AstraZeneca, are approved to be used in Australia. Moderna and Johnson & Johnson have also received provisional approval.<sup>12</sup> The evidence on various medication impact, including steroids, on vaccine efficacy is still emerging.

Critical Intelligence Unit had previously produced a rapid evidence check on immunocompromised patients and COVID-19 vaccines and maintains a living table on COVID-19 vaccines.<sup>13, 14</sup>

## Methods (Appendix 1)

PubMed and Google searches were conducted on 07 July 2021.

## Results

Table 1

Source	Summary
<b>Peer reviewed sources</b>	
<p><a href="#">Recommendations and guidance for steroid injection therapy and COVID-19 vaccine administration from the American Society of Pain and Neuroscience (ASPN)</a></p> <p>Chakravarthy, et al. 2021<sup>5</sup></p>	<ul style="list-style-type: none"> <li>• This guidance paper from the American Society of Pain and Neuroscience provides an overview of the literature on:                             <ul style="list-style-type: none"> <li>○ the impact of epidural steroids and immunocompetence</li> <li>○ COVID-19 vaccine clinical trial data</li> <li>○ other vaccines on horizon</li> <li>○ the key conclusion from vaccine trial data exclusion criteria</li> <li>○ safety of vaccination in a setting of systemic steroid use</li> <li>○ efficacy of vaccination in a setting of systemic steroid use</li> <li>○ broader considerations on the impact of nonsteroidal anti-inflammatory drugs and COX-inhibitors on immunity and vaccine efficacy</li> <li>○ ethical considerations and timing of therapeutic pain interventions.</li> </ul> </li> <li>• Based on currently available evidence, this paper recommends the following.                             <ul style="list-style-type: none"> <li>○ There is no evidence that patients receiving epidural steroid therapy for the management of pain are at increased risk of adverse outcomes from COVID-19 vaccination.</li> <li>○ There is no evidence that bolus steroids in the epidural space will impact vaccine responsiveness.</li> <li>○ Neuraxial steroid injections do not need to be deferred when indicated in the context of COVID-19 vaccination.</li> <li>○ No specific guidance suggests withholding nonsteroidal anti-inflammatory drugs or other anti-inflammatories prior to receiving vaccination.</li> </ul> </li> </ul>
<p><a href="#">Do corticosteroid injections for the treatment of pain influence the efficacy of mRNA COVID-19 vaccines?</a></p> <p>Lee, et al. 2021<sup>2</sup></p>	<ul style="list-style-type: none"> <li>• This paper discusses the current state of evidence on corticosteroid injection before and after mRNA COVID-19 vaccine administration and its impact on subsequent vaccine efficacy.</li> <li>• Recommendations:                             <ul style="list-style-type: none"> <li>○ Based on the known timeline of hypothalamic-pituitary-adrenal axis suppression following epidural and intraarticular corticosteroid injections, as well as the timeline of the reported peak efficacy of the PfizerBioNTech and Moderna vaccines,</li> </ul> </li> </ul>

Source	Summary
<b>Peer reviewed sources</b>	
	<p>physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible.</p> <ul style="list-style-type: none"> <li>○ Physicians may consider the use of dexamethasone or betamethasone rather than triamcinolone or methylprednisolone when administering a corticosteroid injection in close temporal proximity as advised in recommendation 1. This recommendation is based on evidence of reduced hypothalamic-pituitary-adrenal axis suppression associated with dexamethasone and betamethasone compared to triamcinolone or methylprednisolone. However, it must be acknowledged that the differential effects of these specific corticosteroids on adaptive immunity, immunological memory, and mRNA vaccine efficacy have not been studied.</li> <li>○ A shared decision-making process is used, with each unique patient in the context of his or her indications for injection, as well as risk factors for a reduced adaptive immune response to vaccine exposure and risks for morbidity and mortality associated with COVID-19.</li> <li>○ These recommendations may change as more direct evidence regarding the effect of corticosteroid injection on COVID-19 mRNA vaccine efficacy becomes available.</li> </ul>
<p><a href="#">Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients</a> Rabinowich, et al. 2021<sup>6</sup></p>	<ul style="list-style-type: none"> <li>• Prospective cohort study from Israel.</li> <li>• 80 liver transplant recipients and 25 healthy volunteers were followed after receiving the second dose of Pfizer mRNA vaccine.</li> <li>• Results:             <ul style="list-style-type: none"> <li>○ Compared to healthy volunteers, liver transplant recipients had:                 <ul style="list-style-type: none"> <li>▪ significantly lower positive serology (47.5% versus 100%)</li> <li>▪ significantly lower antibody titer in recipients with positive serological response (mean 95.41 AU/ml versus 200.5 AU/ml)</li> </ul> </li> <li>○ Treatment with high dose steroids in the last 12 months were among the predictors of negative serology response.</li> </ul> </li> <li>• Conclusion: treatment with high dose steroids, along with other factors, such as age and renal function, impairs the serological antibody response after the vaccination.</li> </ul>
<p><a href="#">Glucocorticoids and B cell depleting agents substantially impair</a></p>	<ul style="list-style-type: none"> <li>• Pre-print, not peer reviewed.</li> </ul>

Source	Summary
<b>Peer reviewed sources</b>	
<p><a href="#">immunogenicity of mRNA vaccines to SARS-CoV-2</a></p> <p>Deepak, et al. 2021 <sup>7</sup></p>	<ul style="list-style-type: none"> <li>• A prospective assessment of mRNA-based vaccine immunogenicity in 133 adults with chronic inflammatory diseases and 53 immunocompetent controls.</li> <li>• Results:                             <ul style="list-style-type: none"> <li>○ Compared to immunocompetent controls, chronic inflammatory disease participants had a:                                     <ul style="list-style-type: none"> <li>▪ 3-fold reduction in antibody titers</li> <li>▪ 2.7-fold decrease in neutralisation of viral infection.</li> </ul> </li> <li>○ Compared to immunocompetent controls, participants who were on glucocorticoids (prednisone mean mg/day ± SD=6.5± 5.8) had:                                     <ul style="list-style-type: none"> <li>▪ a 10-fold reduction in anti-S immunoglobulin G and neutralisation titers (p&lt;0.0001)</li> <li>▪ fewer circulating plasmablasts</li> <li>▪ reduced seropositivity (65% versus 98%).</li> </ul> </li> </ul> </li> <li>• Conclusion: patients with chronic inflammatory disease on glucocorticoids have reduced vaccine induced immunity compared to immunocompetent controls.</li> </ul>
<p><a href="#">Antibody responses after mRNA-based COVID-19 vaccination in residential older adults: implications for reopening</a></p> <p>Nace, et al. 2021 <sup>8</sup></p>	<ul style="list-style-type: none"> <li>• Prospective observational study from the United States.</li> <li>• Sera were collected to measure immunoglobulin G anti-SARS-CoV-2 antibody level in 70 older adults living in residential living communities. All participants had received two doses of mRNA-based COVID-19 vaccine within the prior 50 days.</li> <li>• Results:                             <ul style="list-style-type: none"> <li>○ All individuals demonstrated detectable and functionally neutralising antibody responses</li> <li>○ Male gender, advanced age, current use of steroids and longer length of time from vaccination were associated with lower antibody level.</li> </ul> </li> <li>• Conclusion: the older adults in this study are relatively healthy and the vaccination was able to mount protective responses.</li> </ul>
<p><a href="#">Australian clinician guide for the use of immunomodulatory drugs in autoimmune rheumatic diseases at the time of COVID-19 vaccination</a></p> <p>Australian Rheumatology Association 2021<sup>9</sup></p>	<ul style="list-style-type: none"> <li>• Australian Rheumatology Association advises the following for clinicians with patients using glucocorticoids medications.                             <ul style="list-style-type: none"> <li>○ Do not routinely modify dose for people on stable chronic glucocorticoid therapy.</li> <li>○ In people on higher doses who are planning to taper, consider deferring vaccination until the dose is lower (e.g. &lt;10mg/day), depending on the individual disease, comorbidities, likely</li> </ul> </li> </ul>

Source	Summary
<b>Peer reviewed sources</b>	
	trajectory of glucocorticoid therapy and an estimate of the risk of COVID-19.
<a href="#">Vaccines for COVID-19 – your questions answered</a> Versus Arthritis UK 2021 <sup>11</sup>	<ul style="list-style-type: none"> <li>• Versus Arthritis advice:                             <ul style="list-style-type: none"> <li>○ It is fine to have the vaccination while taking steroids.</li> <li>○ People who are on steroids may be advised to follow guidance on shielding and social distancing after receiving the vaccination.</li> <li>○ It is important not to stop taking steroids in order to get the vaccination without speaking with a healthcare team.</li> </ul> </li> </ul>
<a href="#">Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States</a> Centers for Disease Control and Prevention, US 2021 <sup>10</sup>	<ul style="list-style-type: none"> <li>• The guidance advises that: COVID-19 vaccines may be administered without regard to timing of corticosteroid treatment, including topical or intraarticular, bursal, or tendon injection.</li> </ul>

## Appendix

### PubMed search terms

("COVID-19"[Title/Abstract] OR "COVID-19"[MeSH Terms] OR "sars cov 2"[Title/Abstract] OR "sars cov 2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Title/Abstract] OR "2019 NCOV"[Title/Abstract] OR "Covid19"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "sars cov 2"[Title/Abstract] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept]) AND ("covid-19 vaccines"[MeSH Terms] OR "vaccin\*"[Title/Abstract] OR "immuniz\*"[Title/Abstract] OR "vaccination"[MeSH Terms]) AND ("steroid\*"[Title/Abstract] OR "steroids"[MeSH Terms]) AND 2020/01/01:3000/12/31[Date - Publication]

120 hits on 7 July 2021.

### Google search terms

COVID-19, vaccine efficacy, steroid

### Inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>• Published in English</li> <li>• Published since January 2020</li> </ul>	<ul style="list-style-type: none"> <li>• Not in English</li> <li>• Does not meet PICO criteria</li> </ul>

Inclusion	Exclusion
<ul style="list-style-type: none"> <li><b>Population:</b> individuals on steroid medications</li> <li><b>Intervention:</b> COVID-19 vaccination</li> <li><b>Comparator:</b> nil</li> <li><b>Outcomes:</b> COVID-19 vaccine efficacy including immune response after vaccination</li> </ul>	

## References

- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020 2020/12/31;383(27):2603-15. DOI: 10.1056/NEJMoa2034577
- Lee H, Punt JA, Miller DC, et al. Do corticosteroid injections for the treatment of pain influence the efficacy of mRNA COVID-19 vaccines? *Pain Med.* 2021 Apr 20;22(4):994-1000. DOI: 10.1093/pm/pnab063
- Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med.* 2020. DOI: 10.1056/NEJMoa2035389
- Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet.* 2021;397(10269):99-111. DOI: 10.1016/S0140-6736(20)32661-1
- Chakravarthy K, Strand N, Frosch A, et al. Recommendations and guidance for steroid injection therapy and COVID-19 vaccine administration from the American Society of Pain and Neuroscience (ASPN). *J Pain Res.* 2021;14:623.
- Rabinowich L, Grupper A, Baruch R, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol.* 2021 Apr 21. DOI: 10.1016/j.jhep.2021.04.020
- Deepak P, Kim W, Paley MA, et al. Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. *medRxiv.* 2021 Apr 9. DOI: 10.1101/2021.04.05.21254656
- Nace DA, Kip KE, Mellors JW, et al. Antibody responses after mRNA-Based COVID-19 vaccination in residential older adults: implications for reopening. *J Am Med Dir Assoc.* 2021 Jun 12. DOI: 10.1016/j.jamda.2021.06.006
- Australian Rheumatology Association. Australian clinician guide for the use of immunomodulatory drugs in autoimmune rheumatic diseases at the time of COVID-19 vaccination 2021 [cited 2021 14 July]. Available from: <https://rheumatology.org.au/gps/documents/20210629%20Clinician%20guide%20for%20the%20Use%20of%20immunomodulatory%20drugs%20in%20autoimmune%20rheumatic%20diseases%20at%20the%20time%20of%20COVID-19%20vaccination%20v1.0.pdf>.
- Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States [Internet]. 2021 [cited 2021 14 July]. Available from: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>.
- Versus Arthritis. Vaccines for COVID-19 – your questions answered [Internet]. 2021 [cited 2021 14 July]. Available from: <https://www.versusarthritis.org/covid-19-updates/vaccines-for-covid-19-your-questions-answered/>.
- Department of Health. COVID-19 vaccines [Internet]. Canberra: Australian Department of Health,; 2021 [cited 2021 15 July]. Available from: <https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines>.
- COVID-19 Critical Intelligence Unit. Immunocompromised patients and COVID-19 vaccines [Internet]. Sydney: Agency for Clinical Innovation; 2021 [cited 2021 14 July]. Available from:

[https://aci.health.nsw.gov.au/\\_data/assets/pdf\\_file/0009/645750/Evidence-check-Immunocompromised-patients-COVID-19-vaccines.pdf](https://aci.health.nsw.gov.au/_data/assets/pdf_file/0009/645750/Evidence-check-Immunocompromised-patients-COVID-19-vaccines.pdf).

14. COVID-19 Critical Intelligence Unit. Living evidence - COVID-19 vaccines [Internet]. Sydney: NSW Agency for Clinical Innovation; 2021 [cited 2021 15 July]. Available from: <https://aci.health.nsw.gov.au/covid-19/critical-intelligence-unit/covid-19-vaccines>.

**Evidence checks are archived a year after the date of publication**

SHPN: (ACI) 210732 | ISBN: 978-1-76081-883-8 | TRIM: ACI/D21/695-28 | Edition 1