A Systematic Review of the Impact of Vaccination on Long COVID

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BACKGROUND

- Long-term morbidity following illness with coronavirus disease 2019 (COVID-19) is a growing public health concern[1]
- The perpetuation or development of new symptoms after acute COVID-19 infection is known as "long COVID" and is characterised by prolonged symptoms and illness[2]
  - Long COVID can include ongoing symptomatic COVID-19 (from 4-12 weeks) and post–COVID-19 syndrome (≥12 weeks)[3]
- Results from clinical studies have indicated that COVID-19 vaccination is highly efficacious at preventing the initial occurrence of symptomatic and severe COVID-19,[4-7] with more recent observational evidence suggesting that vaccination may also be associated with an improvement in existing long COVID symptoms and a decreased likelihood of developing self-reported long COVID[8]
  - However, the various stages of the vaccine rollout coincided with the emergence of variants of the virus, which complicates these findings; thus, additional research is needed to elucidate the protective role of vaccination versus the differential risk of long COVID by different variants
- This systematic literature review summarises published studies evaluating the relationship between vaccines, circulating variants (estimated from the time course of the study), and outcomes related to long COVID

OBJECTIVES

- To evaluate the impact of vaccination (pre-infection) on the prevalence of long COVID and associated outcomes
- To evaluate the impact of vaccination on health and economic outcomes of long COVID

METHODS

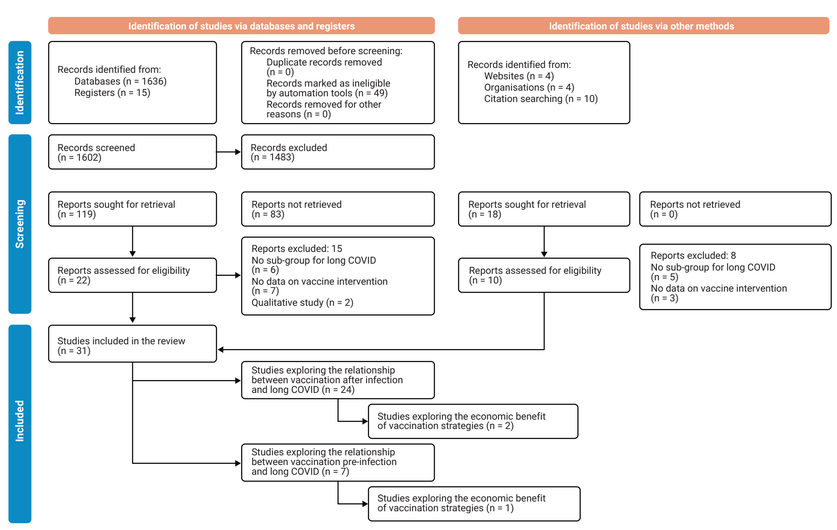
- The protocol for this systematic literature review was registered on PROSPERO (registration number: CRD42021288753)
- A comprehensive search of electronic literature databases was conducted using COVID-19 search terms
  - Databases included MEDLINE, EMBASE, Scopus, Epistemonikos COVID-19 evidence, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane COVID-19 Study Register, Web of Science Core Collection, the World Health Organization COVID-19 database, the COVID-19 Evidence Reviews resource, the Campbell Collaboration and grey literature, and the pre-print servers medRxiv and bioRxiv
  - No language restrictions were applied
- Studies that met the protocol-defined eligibility criteria were considered for inclusion
- Any vaccine types delivered in a hospital or community setting were included
- The quality of studies was assessed using the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I)
- Results were reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)

RESULTS

Characteristics of Studies

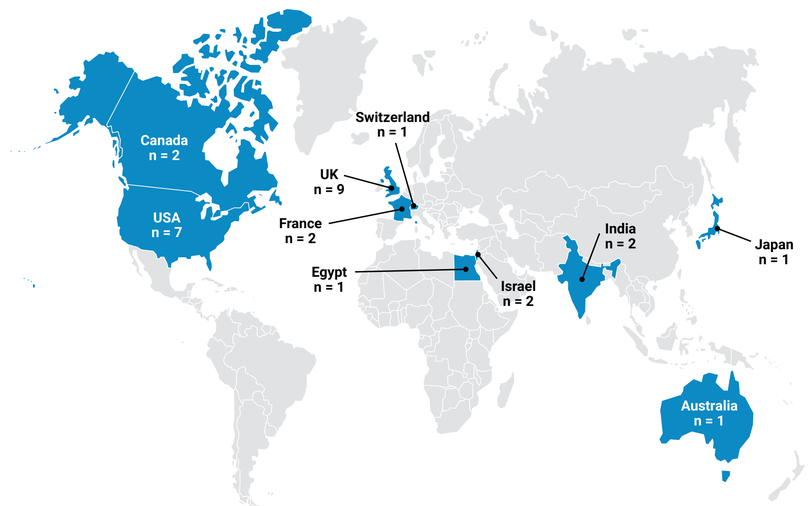
- The eligibility assessments conducted during each stage of the systematic review are illustrated in **Figure 1**
- Of the 1669 records initially identified by databases/registers or other methods, 31 publications were included in the final analysis, representing studies from 10 individual countries; 3 studies included results from multiple countries (**Figure 2**)
- Of the 31 total identified studies, this presentation shows findings from 7 studies that evaluated the impact of vaccination on long COVID symptoms after breakthrough infection and 3 studies that evaluated health and economic outcomes related to vaccination
  - The vaccines evaluated in these studies included mRNA-1273 (Moderna, Inc.; n = 3 studies), BNT162b2 (Pfizer/BioNTech; n = 3 studies), ChAdOx1 nCoV-19 (AstraZeneca/Oxford; n = 3 studies), Ad.26.COV2.5 (Janssen; n = 2 studies), and others/unspecified (n = 5 studies)

Figure 1. Study Selection Flow Diagram



COVID, coronavirus disease.

Figure 2. Global Map of the Location and Number of Included Studies



Impact of Vaccination on the Symptoms of Long COVID

- Seven studies explored the relationship between vaccination before breakthrough infection and the symptoms of long COVID (**Table 1**)
  - 6 studies provided evidence that vaccination before infection was associated with less severe or less frequent symptoms of long COVID
  - 1 study found no association of vaccination with long COVID

Health Economic Outcomes

- Specific measures of economic benefit could not be evaluated, as most studies did not report costs associated with healthcare
- Three studies included an economic evaluation of vaccination strategy outcomes on long COVID, which generally showed vaccination had a positive impact on outcomes (**Table 2**)

Table 1. Studies Evaluating the Effects of Vaccination Before Infection on Long COVID

Study	Study Type	Country	Population and Sample Size	COVID-19 Vaccine Type	Variants of Concern	Key Results
Studies Identifying Vaccination Associated With Less Severe or Less Frequent Symptoms of Long COVID						
Adibi A, et al. *medRxiv*. 2021. doi: 10.1101/2021.04.11.21255138	Prevalence	Canada	N = 246,700 doses; frontline workers and the entire population	ChAdOx1 nCoV-19	Alpha, beta, gamma, delta	• Population-level model demonstrated that a reduction in long COVID cases was associated with community vaccine distribution
Kim S, et al. *Int J Infect Dis*. 2022. doi: 10.1016/j.ijid.2021.12.142	Economic loss in production	Canada	Not reported	Unspecified	Unspecified	• Model predicted that a vaccination strategy prioritising administration of a first vaccine dose would result in: – Reduction of 67,130,775 doses of vaccine administered – 20 lives saved
Ayoubkhani D, et al. *medRxiv*. 2022. doi: 10.1101/2022.02.23.22271388	Prevalence/ odds ratio	United Kingdom	Random selection from 500,000 participants (aged 18-69 years) of the UK COVID-19 Infection Survey	ChAdOx1 nCoV-19, BNT162b2, or mRNA-1273	Alpha, beta, gamma, delta	• Symptoms of any severity of long COVID – Prevalence: 9.5% of double-vaccinated vs 14.6% of unvaccinated participants (aOR: 0.59; 95% CI, 0.50-0.69) • Activity-limiting symptoms of long COVID – Prevalence: 5.5% of double-vaccinated vs 8.7% of unvaccinated participants (aOR: 0.59; 95% CI, 0.48-0.73)
Gurdasani D, et al. *J R Soc Med*. 2021. doi: 10.1177/01410768211052589	Prevalence	United Kingdom	N = 3,918,373; UK database noted COVID case rates of all 12- to 17-year-old participants	Unspecified	Mostly delta	• Vaccination was predicted to prevent 56,000, 16,000, or 8,000 cases, assuming incidence rates of 14%, 4%, or 2%, respectively
Tran V, et al. *SSRN*. 2021. doi: 10.2139/ssrn.3932953	Mean difference	France	Participants enrolled in the ComPaRe long COVID cohort • N = 455 vaccinated participants • N = 455 unvaccinated participants	BNT162b2, ChAdOx1 nCoV-19, mRNA-1273, Ad26.COV2.S	Unspecified	• Symptoms of long COVID were significantly less severe in vaccinated vs unvaccinated participants – Mean difference in long COVID severity score: -3.3 (95% CI, -6.2 to -0.5)
Blumberg Y, et al. *medRxiv*. 2021. doi: 10.1101/2021.12.30.21268538	Proportion	Israel	N = 15 vaccinated participants N = 28 unvaccinated participants	Unspecified	Alpha, beta, gamma (period before omicron variant was detected in Israel)	• Mean VO_2/kg at peak exercise was 95% and 83% of predicted values in vaccinated and unvaccinated participants, respectively (P<0.05) • Mean peak heart rate was higher in vaccinated vs unvaccinated participants
Study Identifying No Association Between Vaccination and the Symptoms of Long COVID						
Taquet M, et al. *Brain Behav Immun*. 2022. doi: 10.1016/j.bbi.2022.04.013	Hazard ratio	United States	N = 10,024; anonymised data from 59 healthcare organisations	BNT162b2, mRNA-1273, or Ad26. COV2.S	Unspecified	• Risk of long COVID outcomes was similar regardless of vaccination status (HR, 1.01; 95% CI, 0.96-1.05; P=0.83, Bonferroni corrected P=1.0)

aOR, adjusted odds ratio; CI, confidence interval; COVID, coronavirus disease; HR, hazard ratio, VO_2/kg; peak oxygen consumption per kilogram.

Table 2. Studies of Health Economic Outcomes Related to Long COVID

Study	Country	Population and Sample Size	COVID-19 Vaccine Type	Variants of Concern	Key Results
Kim S, et al. *Int J Infect Dis*. 2022. doi: 10.1016/j.ijid.2021.12.142	Canada	Not reported	Unspecified	Unspecified	• Model predicted that a vaccination strategy prioritising administration of a first vaccine dose would result in a $3.8 billion reduction in lost production due to long COVID using a modelling strategy with prioritisation of the first dose; or a reduction of $575,149 in lost production in a strategy that prioritised first dose and screening
Mohr NM, et al. *medRxiv*. 2022. doi: 10.1101/2022.02.16.22271092	USA	N = 180 vaccinated participants N = 239 unvaccinated participants	Unspecified	Unspecified	• Vaccinated participants returned to work a median of 2.0 days (95% CI, 1.0-3.0) earlier than unvaccinated participants • Vaccinated participants were less likely to have COVID symptoms on return to work (49.4% vs 66.2%; RR, 0.83; 95% CI, 0.67-1.03)
Angeles MR, et al. *BMC Public Health*. 2022. doi: 10.1186/s12889-022-13169-x	Australia	Not applicable	Unspecified	Delta	• Mortality impact (YLL) was the most significant contributor to the base case DALY burden (72%-74%), but long COVID (19%-22%) had the most impact on morbidity • In all scenarios, the total DALY burden was significantly higher in unvaccinated versus vaccinated individuals

CI, confidence interval; COVID, coronavirus disease; DALY, disability-adjusted life years; RR, rate ratio; YLL, years of life lost.

CONCLUSIONS

- This systematic review found evidence across multiple regions of an association between vaccination and the prevalence or incidence of the symptoms of long COVID
  - Few studies included an economic evaluation of vaccination strategy impact on long COVID, highlighting a need for additional studies on this important topic
- Due to the emergence of different strains and the need for adaptive vaccines, future information may alter confidence in these findings due to the possibility of selection bias and different diagnostic and reporting patterns
- Published prevalence statistics for long COVID may underestimate the burden of disease and the association between the impact of vaccines and nonpharmacologic public health measures

References

1. Adeloye D, et al. *Lancet Respir Med*. 2021;9(12):1467-1478. doi:10.1016/S2213-2600(21)00286-1
2. Centers for Disease Control and Prevention. Long COVID or Post-COVID Conditions. 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
3. National Institute for Health and Care Excellence, Royal College of General Practitioners, Healthcare Improvement Scotland SIGN. COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19. 2022. https://www.nice.org.uk/guidance/ng188/chapter/Update-information
4. Sadoff J, et al. *N Engl J Med*. 2021;384(23):2187-2201. doi:10.1056/NEJMoa2101544
5. Polack FP, et al. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577
6. Falsey AR, et al. *N Engl J Med*. 2021;385(25):2348-2360. doi:10.1056/NEJMoa2105290
7. Baden LR, et al. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389
8. Ayoubkhani D, et al. *BMJ*. 2022;377:e069676. doi:10.1136/bmj-2021-069676

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Disclosures

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ABSTRACT PLAIN LANGUAGE SUMMARY

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