A Living Evidence Synthesis on Variants of Concern and COVID-19 Vaccine Effectiveness

Initial Results for Outcomes related to Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

(Version 2.6: February 6, 2023)

Introduction

As part of the CIHR-funded project "A Living Evidence Synthesis on Variants of Concern and COVID-19 Vaccine Effectiveness", this report provides initial results on vaccine effectiveness against outcomes related to post-acute sequelae of SARS-CoV-2 infection (PASC). Results are reported from preprints released as of November 1, 2022, and published literature released as of August 16, 2022. In the future, the report will be updated with results on vaccine effectiveness and immunological outcomes, including humoral and cell-mediated immunity.

Methodology

A detailed methodology for the literature search and eligibility criteria is available in the protocol, which is registered on PROSPERO (CRD42022359790) and the Open Science Framework (https://osf.io/qacw4/).

In this report, vaccine effectiveness results are provided in tables separated by outcome. When a single study was available for an outcome, the vaccine effectiveness was calculated from the most adjusted estimate of effect provided in that study's results. If more than one study was available, then the vaccine effectiveness was calculated for each study and the range was given. All vaccine effectiveness estimates were rounded to the nearest whole number. Study results that were not able to be synthesized in the vaccine effectiveness tables are provided in Appendix 2.

We considered the overall prevalence of PASC, i.e. the presence of one or more symptoms at least 12 weeks after COVID-19 diagnosis [1] as a non-specific outcome. We considered specific PASC outcomes in the following outcome domains:

- Respiratory functioning, symptoms and conditions
- Fatigue or exhaustion
- Pain
- Nervous system functioning, symptoms and conditions
- Cognitive functioning, symptoms and conditions
- Mental functioning, symptoms and conditions
- Cardiovascular functioning, symptoms and conditions

These outcome domains were selected from the core outcome set for PASC [2], based on their relatively higher prevalence from systematic reviews [1, 3–9]. A complete list of all outcomes within these domains is provided in Appendix 3. The overall number of PASC symptoms, quality of life, overall functional impairment (ability to perform daily living activities) and ability to work at least 12 weeks after COVID-19 diagnosis were also outcomes of interest.

For each study, a risk of bias assessment was conducted using a modified version of the ROBINS-I tool [10], which was adapted specifically for studies on vaccine effectiveness against PASC outcomes. This modified tool is provided in Appendix 5. An overall risk of bias judgement was given for each study, ranging from Low, Moderate, Serious, or Critical. In the synthesis tables, the risk of bias judgement is colour-coded as follows:

Low risk of bias	Moderate risk of bias	Serious risk of bias	Critical risk of bias

Studies with three Serious domains were given a Serious overall risk of bias judgement, rather than Critical (as was done in the original living review [11]). Since we are in the early stages of collecting evidence on vaccination and PASC, it is helpful to provide insight into the domains that are rated as Serious.

Study characteristics, such as the study design, time period, and population, are provided in Appendix 4.

Overall Summary of Results

Overall, 11 studies that examine PASC outcomes have been included: 6 published studies and 5 preprints. For an overview of the study selection process, see Appendix 1.

We present data for the following outcomes: overall prevalence of PASC (Table 1.1-1.6); respiratory (Table 2.1-2.6); fatigue or exhaustion (Table 3.1-3.5); pain (Table 4.1-4.5); nervous system (Table 5.1-5.5); cognitive (Table 6.1-6.2); mental (Table 7.1-7.5); and cardiovascular functioning, symptoms and conditions (Table 8.1-8.4). We also present data for the overall number of PASC symptoms (Table 9).

None of the included studies provided data on the association between vaccination and quality of life or ability to work. For overall functional impairment, two studies reported “activity-limiting PASC” as an outcome (defined by the authors as PASC that limits daily activities) [12, 13], which we present in Table 1.1 and 1.6.

Across all included studies, the following vaccine types and brands were reported: mRNA, inactivated viral vaccine, viral vector vaccine, ChAdOx1 (AstraZeneca), BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen).

None of the included studies were conducted in Canada; four were done in the USA, two in the UK, two in Switzerland, one in Denmark, one in Indonesia, and one in South Africa.

1. Overall prevalence of PASC

Table 1.1. Vaccine effectiveness against the development of PASC among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**

PASC (any symptom/sequelae)							
mRNA	2	12+ weeks	Pre-infection	53%	**Unvaccinated**	wildtype, Alpha, Delta	[12]*
	2	6 months	Pre-infection	0-15%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
	2	8-12 months	Pre-infection	22%	**Unvaccinated**	wildtype, Alpha	[16]
	1 or 2	6 months	Pre-infection	47%	**Unvaccinated** and infected with wild-type	Delta	[17]
	1 or 2	6 months	Pre-infection	51%	**Unvaccinated** and infected with wild-type	Omicron	[17]
	3	6 months	Pre-infection	-84%**	**Unvaccinated** and infected with wild-type	Delta	[17]
	3	6 months	Pre-infection	70%	**Unvaccinated** and infected with wild-type	Omicron	[17]
Inactivated viral vaccine	2	3 months	Pre-infection	26%	1 dose or unvaccinated	Alpha, Beta, Delta	[18]
mRNA or viral vector vaccine	2 mRNA or 1 viral vector	4-10 months	Pre-infection	31%	**Unvaccinated**	Delta, Omicron	[19]
ChAdOx1	2	12+ weeks	Pre-infection	29%	**Unvaccinated**	wildtype, Alpha, Delta	[12]*
BNT or Janssen	2 BNT or 1 Janssen	6 months	Pre-infection	-3%	**Unvaccinated**	Beta, Delta, Omicron	[20]
Activity-limiting PASC							
mRNA	2	12+ weeks	Pre-infection	55%	**Unvaccinated**	wildtype, Alpha, Delta	[12]*
ChAdOx1	2	12+ weeks	Pre-infection	32%	**Unvaccinated**	wildtype, Alpha, Delta	[12]*

*Estimate is from the analysis that only examined the subset of participants with confirmed vaccination status. Almost all double-vaccinated individuals were infected during Delta dominance, while almost all unvaccinated individuals were infected before Delta dominance (with Alpha or wild-type).

**Estimate is statistically insignificant, with a very wide confidence interval (aOR 1.84, 0.08-19.84).

Table 1.2. Vaccine effectiveness against the development of PASC among individuals infected with Omicron

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**

PASC (any symptom/sequelae)						
mRNA	1 or 2	6 months	Pre-infection	51%	**Unvaccinated** and infected with wild-type	[17]
	3	6 months	Pre-infection	70%	**Unvaccinated** and infected with wild-type	[17]

Table 1.3. Vaccine effectiveness against the development of PASC among individuals infected with Delta

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
PASC (any symptom/sequelae)						
mRNA	1 or 2	6 months	Pre-infection	47%	**Unvaccinated** and infected with wild-type	[17]
	3	6 months	Pre-infection	-84%*	**Unvaccinated** and infected with wild-type	[17]
	2	6 months	Pre-infection	15%	**Unvaccinated**	[14]

*Estimate is statistically insignificant, with a very wide confidence interval (aOR 1.84, 0.08-19.84).

Table 1.4. Vaccine effectiveness against the development of PASC, stratified by care received during acute infection

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Not hospitalized							
mRNA	2	6 months	Pre-infection	7%	**Unvaccinated**	Delta	[14]
Hospitalized							
mRNA	2	6 months	Pre-infection	12%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	22%	**Unvaccinated**	Delta	[14]

Table 1.5. Vaccine effectiveness against the development of PASC, stratified by immunocompromised status

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during**	**References**

						infection period	
Immunocompromised*							
mRNA	2	6 months	Pre-infection	15%	**Unvaccinated**	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	13%	**Unvaccinated**	Alpha, Delta	[14]

*Immunocompromised was defined as "a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

Table 1.6. Vaccine effectiveness against the development of PASC, head-to-head vaccine brand comparison, by outcome

Vaccine brand 1, number of doses	Vaccine brand 2 (comparator), number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Dominant variant during infection period	References
PASC (any symptom/sequelae)						
BNT, 2 doses	Janssen, 1 dose	6 months	Pre-infection	11%	Alpha, Delta	[14]
	Moderna, 2 doses	6 months	Pre-infection	0%	Alpha, Delta	[14]
Moderna, 2 doses	Janssen, 1 dose	6 months	Pre-infection	11%	Alpha, Delta	[14]
ChAd, 2 doses	mRNA, 2 doses	9 months	Post-infection	0%	Alpha, Delta	[13]
Activity-limiting PASC						
ChAd, 2 doses	mRNA, 2 doses	9 months	Post-infection	11%	Alpha, Delta	[13]

2. Respiratory functioning, symptoms and conditions

Table 2.1. Vaccine effectiveness against respiratory functioning, symptoms and conditions among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Pulmonary disorders*							
mRNA	2	6 months	Pre-infection	49%	**Unvaccinated**	Delta	[14]
Cough							

Inactivated viral vaccine	2	3 months	Pre-infection	47%	1 dose or unvaccinated	Alpha, Beta, Delta	[18]
mRNA	3	4 months	Pre-infection	8%	2 doses	Omicron	[21]
Shortness of breath							
mRNA	2	6 months	Pre-infection	32%	**Unvaccinated**	Delta	[14]
	3	4 months	Pre-infection	-27%	2 doses	Omicron	[21]
Hypoxemia							
mRNA	2	6 months	Pre-infection	34-63%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Interstitial lung disease							
mRNA	2	6 months	Pre-infection	26-56%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Abnormal breathing							
mRNA	2	6 months	Pre-infection	11%	**Unvaccinated**	Alpha, Delta	[15]
Respiratory failure							
mRNA	2	6 months	Pre-infection	37%	**Unvaccinated**	Alpha, Delta	[15]
Pulmonary disease							
mRNA	2	6 months	Pre-infection	66%	**Unvaccinated**	Delta	[14]
Pleurisy or pleural effusion							
mRNA	2	6 months	Pre-infection	43%	**Unvaccinated**	Delta	[14]
Runny nose							
mRNA	3	4 months	Pre-infection	15%	2 doses	Omicron	[21]
Sore throat							
mRNA	3	4 months	Pre-infection	36%	2 doses	Omicron	[21]

*hypoxemia, interstitial lung disease, pleurisy or pleural effusion, pulmonary disease, shortness of breath

Table 2.2. Vaccine effectiveness against respiratory functioning, symptoms and conditions among individuals infected with Omicron

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Runny nose						
mRNA	3	4 months	Pre-infection	15%	2 doses	[21]
Sore throat						
mRNA	3	4 months	Pre-infection	36%	2 doses	[21]
Shortness of breath						
mRNA	3	4 months	Pre-infection	-27%	2 doses	[21]
Cough						

mRNA	3	4 months	Pre-infection	8%	2 doses	[21]

Table 2.3. Vaccine effectiveness against respiratory functioning, symptoms and conditions among individuals infected with Delta

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	References
Pulmonary disorders*						
mRNA	2	6 months	Pre-infection	49%	**Unvaccinated**	[14]
Hypoxemia						
mRNA	2	6 months	Pre-infection	63%	**Unvaccinated**	[14]
Interstitial lung disease						
mRNA	2	6 months	Pre-infection	56%	**Unvaccinated**	[14]
Pleurisy or pleural effusion						
mRNA	2	6 months	Pre-infection	43%	**Unvaccinated**	[14]
Pulmonary disease						
mRNA	2	6 months	Pre-infection	66%	**Unvaccinated**	[14]
Shortness of breath						
mRNA	2	6 months	Pre-infection	32%	**Unvaccinated**	[14]

*hypoxemia, interstitial lung disease, pleurisy or pleural effusion, pulmonary disease, shortness of breath

Table 2.4. Vaccine effectiveness against respiratory functioning, symptoms and conditions, stratified by care received during acute infection

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Not hospitalized							
mRNA	2	6 months	Pre-infection	33%	**Unvaccinated**	Delta	[14]
Hospitalized							
mRNA	2	6 months	Pre-infection	37%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	47%	**Unvaccinated**	Delta	[14]

Table 2.5. Vaccine effectiveness against respiratory functioning, symptoms and conditions, stratified by immunocompromised status

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Immunocompromised*							
mRNA	2	6 months	Pre-infection	42%	**Unvaccinated**	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	48%	**Unvaccinated**	Alpha, Delta	[14]

*Immunocompromised was defined as "a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

Table 2.6. Vaccine effectiveness against respiratory functioning, symptoms and conditions, head-to-head vaccine brand comparison, by outcome

Vaccine brand 1, number of doses	Vaccine brand 2 (comparator), number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Dominant variant during infection period	References
Pulmonary disorders*						
BNT, 2 doses	Janssen, 1 dose	6 months	Pre-infection	23%	Alpha, Delta	[14]
	Moderna, 2 doses	6 months	Pre-infection	-8%	Alpha, Delta	[14]
Moderna, 2 doses	Janssen, 1 dose	6 months	Pre-infection	28%	Alpha, Delta	[14]

*hypoxemia, interstitial lung disease, pleurisy or pleural effusion, pulmonary disease, shortness of breath

3. Fatigue or exhaustion

Table 3.1. Vaccine effectiveness against fatigue or exhaustion among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Fatigue							
mRNA	2	6 months	Pre-infection	14-28%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]

	3	4 months	Pre-infection	23%	2 doses	Omicron	[21]
Inactivated viral vaccine	2	3 months	Pre-infection	4%	1 dose or unvaccinated	Alpha, Beta, Delta	[18]
Fatigue/exhaustion							
mRNA	3	4 months	Pre-infection	31%	2 doses	Omicron	[21]
Physical exhaustion							
mRNA	3	4 months	Pre-infection	6%	2 doses	Omicron	[21]

Table 3.2. Vaccine effectiveness against fatigue or exhaustion among individuals infected with Omicron

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Fatigue						
mRNA	3	4 months	Pre-infection	23%	2 doses	[21]
Fatigue/exhaustion						
mRNA	3	4 months	Pre-infection	31%	2 doses	[21]
Physical exhaustion						
mRNA	3	4 months	Pre-infection	6%	2 doses	[21]

Table 3.3. Vaccine effectiveness against fatigue or exhaustion among individuals infected with Delta

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Fatigue						
mRNA	2	6 months	Pre-infection	28%	**Unvaccinated**	[14]

Table 3.4. Vaccine effectiveness against fatigue or exhaustion, stratified by care received during acute infection

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Not hospitalized							
mRNA	2	6 months	Pre-infection	13%	**Unvaccinated**	Delta	[14]

Hospitalized							
mRNA	2	6 months	Pre-infection	38%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	50%	**Unvaccinated**	Delta	[14]

Table 3.5. Vaccine effectiveness against fatigue or exhaustion, stratified by immunocompromised status

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Immunocompromised*							
mRNA	2	6 months	Pre-infection	41%	**Unvaccinated**	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	27%	**Unvaccinated**	Alpha, Delta	[14]

*Immunocompromised was defined as "a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

4. Pain

Table 4.1. Vaccine effectiveness against pain among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Musculoskeletal disorders*							
mRNA	2	6 months	Pre-infection	12%	**Unvaccinated**	Delta	[14]
Joint pain							
mRNA	2	6 months	Pre-infection	2-9%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Inactivated viral vaccine	2	3 months	Pre-infection	72%	1 dose or unvaccinated	Alpha, Beta, Delta	[18]
Muscle pain							
mRNA	2	6 months	Pre-infection	24%	**Unvaccinated**	Delta	[14]
Chest/throat pain							

mRNA	2	6 months	Pre-infection	8%	**Unvaccinated**	Alpha, Delta	[15]
Other pain (besides chest/throat or joint pain)							
mRNA	2	6 months	Pre-infection	15%	**Unvaccinated**	Alpha, Delta	[15]
Chest pain							
mRNA	3	4 months	Pre-infection	28%	2 doses	Omicron	[21]
Muscle/joint pain							
mRNA	3	4 months	Pre-infection	-21%	2 doses	Omicron	[21]
Abdominal pain							
mRNA	3	4 months	Pre-infection	33%	2 doses	Omicron	[21]

*joint pain, muscle pain

Table 4.2. Vaccine effectiveness against pain among individuals infected with Omicron

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Abdominal pain						
mRNA	3	4 months	Pre-infection	33%	2 doses	[21]
Muscle/joint pain						
mRNA	3	4 months	Pre-infection	-21%	2 doses	[21]
Chest pain						
mRNA	3	4 months	Pre-infection	28%	2 doses	[21]

Table 4.3. Vaccine effectiveness against pain among individuals infected with Delta

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Musculoskeletal disorders*						
mRNA	2	6 months	Pre-infection	12%	**Unvaccinated**	[14]
Joint pain						
mRNA	2	6 months	Pre-infection	2%	**Unvaccinated**	[14]
Muscle pain						
mRNA	2	6 months	Pre-infection	24%	**Unvaccinated**	[14]

*joint pain, muscle pain

Table 4.4. Vaccine effectiveness against pain, stratified by care received during acute infection

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Not hospitalized							
mRNA	2	6 months	Pre-infection	-5%	**Unvaccinated**	Delta	[14]
Hospitalized							
mRNA	2	6 months	Pre-infection	26%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	39%	**Unvaccinated**	Delta	[14]

Table 4.5. Vaccine effectiveness against pain, stratified by immunocompromised status

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Immunocompromised*							
mRNA	2	6 months	Pre-infection	12%	**Unvaccinated**	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	12%	**Unvaccinated**	Alpha, Delta	[14]

*Immunocompromised was defined as "a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

5. Nervous system functioning, symptoms and conditions

Table 5.1. Vaccine effectiveness against nervous system functioning, symptoms and conditions among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Neurologic disorders*							
mRNA	2	6 months	Pre-infection	21%	**Unvaccinated**	Delta	[14]
Smell loss (anosmia)							
mRNA	2	6 months	Pre-infection	32-37%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Seizure							

mRNA	2	6 months	Pre-infection	12-33%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Stroke							
mRNA	2	6 months	Pre-infection	21-23%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Neurocognitive decline							
mRNA	2	6 months	Pre-infection	18%	**Unvaccinated**	Delta	[14]
Acute hemorrhagic cerebrovascular disease							
mRNA	2	6 months	Pre-infection	-2%	**Unvaccinated**	Delta	[14]
Cerebral hemorrhage							
mRNA	2	6 months	Pre-infection	31%	**Unvaccinated**	Alpha, Delta	[15]
Headache							
mRNA	2	6 months	Pre-infection	0%	**Unvaccinated**	Alpha, Delta	[15]
	3	4 months	Pre-infection	42%	2 doses	Omicron	[21]
Inactivated viral vaccine	2	3 months	Pre-infection	68%	1 dose or unvaccinated	Alpha, Beta, Delta	[18]
Dysosmia (smell disturbance)							
mRNA	3	4 months	Pre-infection	24%	2 doses	Omicron	[21]
Dysgeusia (taste disturbance)							
mRNA	3	4 months	Pre-infection	18%	2 doses	Omicron	[21]
Dizziness							
mRNA	3	4 months	Pre-infection	25%	2 doses	Omicron	[21]
Nerve/nerve root/plexus disorder							
mRNA	2	6 months	Pre-infection	22%	**Unvaccinated**	Alpha, Delta	[15]
Peripheral neuropathy							
mRNA	2	6 months	Pre-infection	18%	**Unvaccinated**	Alpha, Delta	[15]

*smell loss, seizure, stroke, neurocognitive decline, acute hemorrhagic cerebrovascular disease

Table 5.2. Vaccine effectiveness against nervous system functioning, symptoms and conditions among individuals infected with Omicron

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Dysosmia (smell disturbance)						
mRNA	3	4 months	Pre-infection	24%	2 doses	[21]

Dysgeusia (taste disturbance)						
mRNA	3	4 months	Pre-infection	18%	2 doses	[21]
Headache						
mRNA	3	4 months	Pre-infection	42%	2 doses	[21]
Dizziness						
mRNA	3	4 months	Pre-infection	25%	2 doses	[21]

Table 5.3. Vaccine effectiveness against nervous system functioning, symptoms and conditions among individuals infected with Delta

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Neurologic disorders*						
mRNA	2	6 months	Pre-infection	21%	**Unvaccinated**	[14]
Acute hemorrhagic cerebrovascular disease						
mRNA	2	6 months	Pre-infection	-2%	**Unvaccinated**	[14]
Neurocognitive decline						
mRNA	2	6 months	Pre-infection	18%	**Unvaccinated**	[14]
Seizure						
mRNA	2	6 months	Pre-infection	12%	**Unvaccinated**	[14]
Smell loss (anosmia)						
mRNA	2	6 months	Pre-infection	37%	**Unvaccinated**	[14]
Stroke						
mRNA	2	6 months	Pre-infection	21%	**Unvaccinated**	[14]

*smell loss, seizure, stroke, neurocognitive decline, acute hemorrhagic cerebrovascular disease

Table 5.4. Vaccine effectiveness against nervous system functioning, symptoms and conditions, stratified by care received during acute infection

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Not hospitalized							
mRNA	2	6 months	Pre-infection	17%	**Unvaccinated**	Delta	[14]
Hospitalized							
mRNA	2	6 months	Pre-infection	20%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	25%	**Unvaccinated**	Delta	[14]

Table 5.5. Vaccine effectiveness against nervous system functioning, symptoms and conditions, stratified by immunocompromised status

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Immunocompromised*							
mRNA	2	6 months	Pre-infection	20%	**Unvaccinated**	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	18%	**Unvaccinated**	Alpha, Delta	[14]

*Immunocompromised was defined as "a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

6. Cognitive functioning, symptoms and conditions

Table 6.1. Vaccine effectiveness against cognitive functioning, symptoms and conditions among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Cognitive symptoms							
mRNA	2	6 months	Pre-infection	13%	**Unvaccinated**	Alpha, Delta	[15]
Cognitive complaints							
mRNA	3	4 months	Pre-infection	28%	2 doses	Omicron	[21]
Difficulties concentrating							
mRNA	3	4 months	Pre-infection	29%	2 doses	Omicron	[21]
Memory issues							
mRNA	3	4 months	Pre-infection	15%	2 doses	Omicron	[21]
Altered concentration							
Inactivated viral vaccine	2	3 months	Pre-infection	26%	1 dose or unvaccinated	Alpha, Beta, Delta	[18]

Table 6.2. Vaccine effectiveness against cognitive functioning, symptoms and conditions among individuals infected with Omicron

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	References
Cognitive complaints						
mRNA	3	4 months	Pre-infection	28%	2 doses	[21]
Difficulties concentrating						
mRNA	3	4 months	Pre-infection	29%	2 doses	[21]
Memory issues						
mRNA	3	4 months	Pre-infection	15%	2 doses	[21]

7. Mental functioning, symptoms and conditions

Table 7.1. Vaccine effectiveness against mental functioning, symptoms and conditions among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Mental health disorders*							
mRNA	2	6 months	Pre-infection	15%	**Unvaccinated**	Delta	[14]
Depression							
mRNA	3	4 months	Pre-infection	49%	2 doses	Omicron	[21]
Anxiety							
mRNA	2	6 months	Pre-infection	37%	**Unvaccinated**	Delta	[14]
	3	4 months	Pre-infection	51%	2 doses	Omicron	[21]
Anxiety disorder							
mRNA	2	6 months	Pre-infection	0%	**Unvaccinated**	Alpha, Delta	[15]
Anxiety/Depression							
mRNA	2	6 months	Pre-infection	-3%	**Unvaccinated**	Alpha, Delta	[15]
Alcohol related disorders							
mRNA	2	6 months	Pre-infection	5%	**Unvaccinated**	Delta	[14]
Opioid use							
mRNA	2	6 months	Pre-infection	17%	**Unvaccinated**	Delta	[14]
Other substance use disorders							

mRNA	2	6 months	Pre-infection	24%	**Unvaccinated**	Delta	[14]
Panic, stress, and trauma related disorders							
mRNA	2	6 months	Pre-infection	8%	**Unvaccinated**	Delta	[14]
Mood disorder							
mRNA	2	6 months	Pre-infection	-3%	**Unvaccinated**	Alpha, Delta	[15]
Psychotic disorder							
mRNA	2	6 months	Pre-infection	35%	**Unvaccinated**	Alpha, Delta	[15]
Mental exhaustion							
mRNA	3	4 months	Pre-infection	21%	2 doses	Omicron	[21]

*alcohol related disorders; anxiety; opioid use; other substance use disorders; panic, stress and trauma related disorders; adjustment disorder; atypical depressants; benzodiazepines; naloxone/naltrexone; sleep aids; sleep disorder

Table 7.2. Vaccine effectiveness against mental functioning, symptoms and conditions among individuals infected with Omicron

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Depression						
mRNA	3	4 months	Pre-infection	49%	2 doses	[21]
Anxiety						
mRNA	3	4 months	Pre-infection	51%	2 doses	[21]
Mental exhaustion						
mRNA	3	4 months	Pre-infection	21%	2 doses	[21]

Table 7.3. Vaccine effectiveness against mental functioning, symptoms and conditions among individuals infected with Delta

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**References**
Mental health disorders*						
mRNA	2	6 months	Pre-infection	15%	**Unvaccinated**	[14]
Alcohol related disorders						
mRNA	2	6 months	Pre-infection	5%	**Unvaccinated**	[14]
Opioid use						

mRNA	2	6 months	Pre-infection	17%	**Unvaccinated**	[14]
Other substance use disorders						
mRNA	2	6 months	Pre-infection	24%	**Unvaccinated**	[14]
Panic, stress, and trauma related disorders						
mRNA	2	6 months	Pre-infection	8%	**Unvaccinated**	[14]
Anxiety						
mRNA	2	6 months	Pre-infection	37%	**Unvaccinated**	[14]

*alcohol related disorders; anxiety; opioid use; other substance use disorders; panic, stress and trauma related disorders; adjustment disorder; atypical depressants; benzodiazepines; naloxone/naltrexone; sleep aids; sleep disorder

Table 7.4. Vaccine effectiveness against mental functioning, symptoms and conditions, stratified by care received during acute infection

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Not hospitalized							
mRNA	2	6 months	Pre-infection	5%	**Unvaccinated**	Delta	[14]
Hospitalized							
mRNA	2	6 months	Pre-infection	6%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	19%	**Unvaccinated**	Delta	[14]

Table 7.5. Vaccine effectiveness against mental functioning, symptoms and conditions, stratified by immunocompromised status

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Immunocompromised*							
mRNA	2	6 months	Pre-infection	13%	**Unvaccinated**	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	10%	**Unvaccinated**	Alpha, Delta	[14]

*Immunocompromised was defined as “a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

8. Cardiovascular functioning, symptoms and conditions

Table 8.1 Vaccine effectiveness against cardiovascular functioning, symptoms and conditions, among individuals infected with SARS-CoV-2 (Alpha, Beta, Delta, or Omicron)

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Cardiovascular disorders*							
mRNA	2	6 months	Pre-infection	13%	**Unvaccinated**	Delta	[14]
Acute coronary disease / Coronary disease							
mRNA	2	6 months	Pre-infection	8-15%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Atrial fibrillation							
mRNA	2	6 months	Pre-infection	21%	**Unvaccinated**	Delta	[14]
Heart failure / Cardiac failure							
mRNA	2	6 months	Pre-infection	2-5%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Hypertension							
mRNA	2	6 months	Pre-infection	-5% to 8%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Myocardial infarction							
mRNA	2	6 months	Pre-infection	30%	**Unvaccinated**	Delta	[14]
Myocarditis							
mRNA	2	6 months	Pre-infection	36-95%	**Unvaccinated**	Delta; Alpha, Delta	[14, 15]
Other dysrhythmias							
mRNA	2	6 months	Pre-infection	48%	**Unvaccinated**	Delta	[14]
Pericarditis							
mRNA	2	6 months	Pre-infection	18%	**Unvaccinated**	Delta	[14]
Tachycardia							
mRNA	2	6 months	Pre-infection	43%	**Unvaccinated**	Delta	[14]
Arrhythmia							
mRNA	2	6 months	Pre-infection	10%	**Unvaccinated**	Alpha, Delta	[15]
Cardiomyopathy							
mRNA	2	6 months	Pre-infection	15%	**Unvaccinated**	Alpha, Delta	[15]

*acute coronary disease, atrial fibrillation, heart failure, hypertension, myocardial infarction, myocarditis, other dysrhythmias, pericarditis, tachycardia

Table 8.2. Vaccine effectiveness against cardiovascular functioning, symptoms and conditions among individuals infected with Delta

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	References
Cardiovascular disorders*						
mRNA	2	6 months	Pre-infection	13%	**Unvaccinated**	[14]
Acute coronary disease						
mRNA	2	6 months	Pre-infection	8%	**Unvaccinated**	[14]
Atrial fibrillation						
mRNA	2	6 months	Pre-infection	21%	**Unvaccinated**	[14]
Heart failure						
mRNA	2	6 months	Pre-infection	2%	**Unvaccinated**	[14]
Hypertension						
mRNA	2	6 months	Pre-infection	8%	**Unvaccinated**	[14]
Myocardial infarction						
mRNA	2	6 months	Pre-infection	30%	**Unvaccinated**	[14]
Myocarditis						
mRNA	2	6 months	Pre-infection	95%	**Unvaccinated**	[14]
Other dysrhythmias						
mRNA	2	6 months	Pre-infection	48%	**Unvaccinated**	[14]
Pericarditis						
mRNA	2	6 months	Pre-infection	18%	**Unvaccinated**	[14]
Tachycardia						
mRNA	2	6 months	Pre-infection	43%	**Unvaccinated**	[14]

*acute coronary disease, atrial fibrillation, heart failure, hypertension, myocardial infarction, myocarditis, other dysrhythmias, pericarditis, tachycardia

Table 8.3. Vaccine effectiveness against cardiovascular functioning, symptoms and conditions, stratified by care received during acute infection

Outcome (and vaccine)	Number of doses	Time since infection	Vaccinated pre-or post-infection	Effectiveness	Comparator	Dominant variant during infection period	References
Not hospitalized							
mRNA	2	6 months	Pre-infection	-7%	**Unvaccinated**	Delta	[14]
Hospitalized							

mRNA	2	6 months	Pre-infection	10%	**Unvaccinated**	Delta	[14]
ICU							
mRNA	2	6 months	Pre-infection	22%	**Unvaccinated**	Delta	[14]

Table 8.4. Vaccine effectiveness against cardiovascular functioning, symptoms and conditions, stratified by immunocompromised status

Outcome (and vaccine)	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Effectiveness**	**Comparator**	**Dominant variant during infection period**	**References**
Immunocompromised*							
mRNA	2	6 months	Pre-infection	22%	Unvaccinated	Alpha, Delta	[14]
Not immunocompromised							
mRNA	2	6 months	Pre-infection	8%	Unvaccinated	Alpha, Delta	[14]

*Immunocompromised was defined as "a history of organ transplantation, advanced kidney disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m2 or end-stage renal disease), cancer, HIV or conditions with prescriptions of more than 30-day use of corticosteroids or immunosuppressants, including systemic lupus erythematosus and rheumatoid arthritis." [14]

9. Number of symptoms

Table 9. Vaccination and number of PASC symptoms among individuals infected with SARS-CoV-2 (Alpha, Delta, or Omicron)

Vaccine type	**Number of doses**	**Time since infection**	**Vaccinated pre-or post-infection**	**Key findings**	**Comparator**	**Dominant variant during infection period**	**References**
mRNA or ChAdOx1	2	9 months	Post-infection	A second ChAdOx1 or mRNA dose post-infection was not associated with a change in the odds of experiencing at least 3 of 21 PASC symptoms (aOR 0.931, 95%CI 0.852-1.016, p=0.11) or at least 5 of 21 PASC symptoms (aOR 0.982, 95%CI 0.886-1.088, p=0.73).	Same individuals before vaccination	Alpha, Delta	[13]
mRNA	3	4 months	Pre-infection	Among Omicron cases, 3 mRNA doses pre-infection was associated with 9% fewer post-acute physical symptoms, compared to 2 mRNA doses pre-infection (IRR 0.91, 95%CI 0.88-0.94).	2 doses	Omicron	[21]

	3+	3 months	Pre-infection	Among Omicron cases, no significant difference in the mean number of PASC symptoms between those vaccinated with 3+ mRNA doses pre-infection vs. unvaccinated individuals (mean 0.49 vs. 0.36, p=0.30).	Unvaccinated	Omicron	[22]
	1 or 2	3 months	Pre-infection	Among Omicron cases, those vaccinated with 1 or 2 mRNA doses pre-infection had a significantly higher mean number of PASC symptoms compared to those unvaccinated (mean 0.71 vs. 0.36, p=0.028).	Unvaccinated	Omicron	[22]

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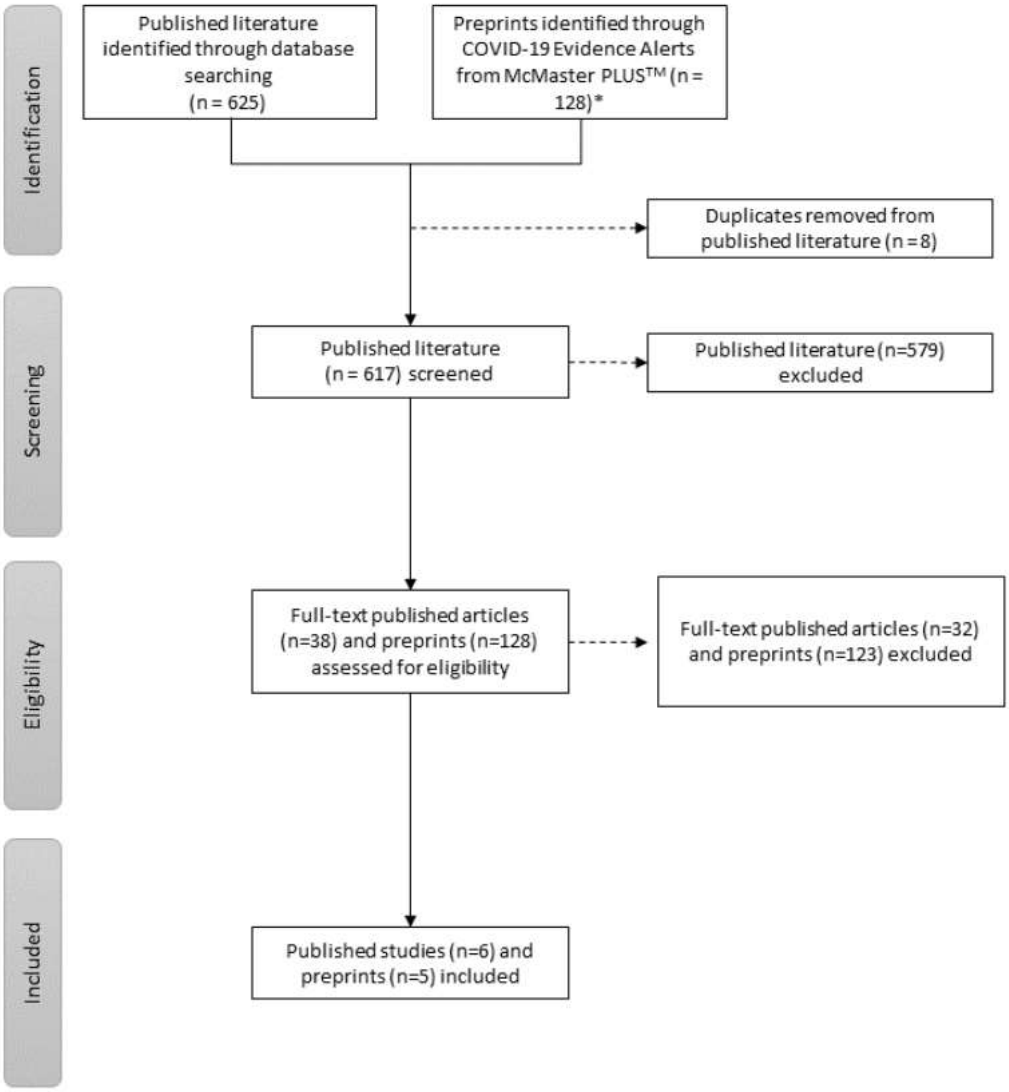
Appendix

Appendix 1: PRISMA Flow Chart

Figure 1. PRISMA flow chart for PASC published literature and preprints.



*Preprints had already gone through title/abstract screening and had been tagged as relevant to PASC before being uploaded to this database

Appendix 2: Summary of study findings not included in synthesis tables of vaccine effectiveness

Reference	Key findings	ROBINS-I	Study design	Reason for exclusion from VE synthesis tables 1-8
Ayoubkhani [13]	A second ChAdOx1 dose post-infection was associated with a 8.7% decrease (95%CI -15.4 to -1.4%) in the odds of experiencing long covid (no OR reported). A second mRNA dose post-infection was associated with a 8.9% decrease (95%CI -17.6 to 0.7%) in the odds of experiencing long covid (no OR reported). A second ChAdOx1 or mRNA dose post-infection was associated with a 9.7% decrease (95%CI -16.5 to -2.4%) in the odds of experiencing fatigue (aOR 0.903, 95%CI 0.835-0.976). A second ChAdOx1 or mRNA dose post-infection was not associated with a change in the odds of experiencing shortness of breath (aOR 1.012, 95%CI 0.921-1.111, p=0.81); muscle ache (aOR 0.948, 95%CI 0.860-1.044, p=0.28); headache (aOR 0.91, 95%CI 0.819-1.010, p=0.08); loss of smell (aOR 0.913, 95%CI 0.829-1.005, p=0.06); loss of taste (aOR 0.91, 95%CI 0.821-1.008, p=0.07); difficulty concentrating (aOR 0.954, 95%CI 0.866-1.052, p=0.35); memory loss or confusion (aOR 1.029, 95%CI 0.924-1.147, p=0.60); worry or anxiety (aOR 0.967, 95%CI 0.865-1.080, p=0.55).	Serious	- Prospective cohort study. - Participants were infected before September 2021 in the UK (wildtype, Alpha, or Delta). - An interrupted time series analysis was conducted to compare the odds of experiencing long covid in the same individuals before vs. after vaccination. - Final follow-up was median 267 days post-infection.	- These data were excluded from VE synthesis tables due to comparison of the same individuals before vs. after vaccination (individual-level interrupted time series analysis).
Jassat [20]	Among those vaccinated with 2 BNT doses or 1 Janssen dose, there was no significant difference in the risk of 1 or more persistent symptoms between individuals vaccinated after vs. before infection (aIRR 0.91, 95%CI 0.75-1.10, p=0.3413).	Serious	- Prospective cohort study. - Participants were infected between Nov 2020-Feb 2022 in South Africa (Beta, Delta, or Omicron). - Final follow-up was 6 months post-infection.	- These data were excluded from VE synthesis tables due to comparison of individuals vaccinated after vs. before infection.

Spiliopoulos [21]	Among Omicron cases, 3 mRNA doses pre-infection was associated with a 18% lower score on the depression scale HADS-D (IRR 0.82, 95%CI 0.77-0.88); 16% lower score on the anxiety scale HADS-A (IRR 0.84, 95%CI 0.80-0.89); 5% lower score on the fatigue scale FAS (IRR 0.95, 95%CI 0.93-0.97); and a 9% lower score on the cognitive complaints scale COBRA (IRR 0.91, 95%CI 0.88-0.94), compared to 2 mRNA doses pre-infection.	Serious	- Prospective cohort study. - Cases were classified as Omicron infection based on variant predominance in Denmark (infected Dec 28, 2021-Jan 15, 2022). - Final follow-up was 4 months post-infection.	- These data were excluded from VE synthesis tables due to continuous outcomes.

Appendix 3: Eligible PASC Outcome Domains

The following outcomes in each domain were taken directly from Table S4 in Supplementary Appendix 1 of the core outcome set for PASC [2].

Outcome Domain	Outcomes
Respiratory functioning, symptoms and conditions	Sore throat Sneezing New-onset Chronic obstructive pulmonary disease (COPD) Excessive sputum expectoration Nasal congestion Catarrh Wheezing Cough Lung fibrosis Pleurisy Pleural effusion Pain on breathing Pulmonary function abnormalities Hypoxaemia Respiratory failure Respiratory disease Bronchiectasis Asthma
Fatigue or exhaustion	
Pain	
Nervous system functioning, symptoms and conditions	Dizziness Headache Stroke Autonomic dysfunction Tremors Seizures Taste disturbance Smell disturbance Bradykinesia Dysmetria Speech difficulty/dysarthria Numbness Guillain-Barré syndrome Abnormal reflex status Trigeminal neuralgia Neuralgia/neuropathy Frontal release signs Parkinsonism Problems with balance Encephalitis Brain physiology changes Restless legs Abnormal muscle tone
Cognitive functioning, symptoms and conditions	Confusion Concentration impairment Memory impairment
Mental functioning, symptoms and conditions	Depression Anxiety Post-traumatic stress disorder (PTSD) Acute stress disorder

	Mood change Obsessive-Compulsive Disorder (OCD) Behaviour change Thoughts of self-harm/suicide Risk to self and/or others Psychosis Traumatic bereavement Substance abuse Smoking habit Hallucinations
Cardiovascular functioning, symptoms and conditions	Angina pectoris Acute coronary disease Heart rhythm issues Heart failure Palpitations Chest tightness Newly diagnosed hypertension Myocardial fibrosis Myo- or pericarditis Changes in cardiovascular fitness Signal variations in the Electrocardiogram (ECG) High blood pressure

Appendix 4: Study Characteristics

First Author	Peer Review Status	Country	Funding (public, private, combined)	Study Design	Population	Study Period	Timing of Outcome follow up	Vaccine Type/ Brand	Total Sample Size	Total Vaccinated	Age (mean/ median), years	Reported measure of effect	Risk of Bias
Spiliopoulos [21]	Preprint	Denmark	None	prospective cohort	General population	July 2021 - Jan 2022	4 months after testing positive for COVID	BNT, Moderna, Ad26, AZ	44,004	NR	Median(IQR)= 57 (46-70) males, 62 (52-71) females	Risk Difference (RD). Raw data in the study was used to calculate crude OR and then VE.	Serious risk
Herman [18]	Published	Indonesia	Public	case-control	General population	Jul 2021 - Dec 2021	90 days after COVID onset or diagnosis	inactivated viral vaccine	923	168	Mean(SD) = 32.77 (10.4)	Odds Ratio (OR)	Critical risk
Jassat [20]	Preprint	South Africa	combined	prospective cohort	General population	Nov 2020 - Feb 2022	6 months	BNT, Ad26	3700	2535	Median(IQR) for hospitalized = 49(37-60); for non-hospitalized = 37(28-47)	Incident Risk Ratio (IRR)	Serious risk
Ballouz [17]	Preprint	Switzerland	combined	retrospective cohort	General population	Aug 2020 – Feb 2022	median 183 days (IQR 182-186)	mRNA, Adenovirus vector	1350	NR	Median(IQR) = 48 (34-63)	Odds Ratio (OR)	Serious risk
Kahlert [22]	Preprint	Switzerland	combined	prospective cohort	HCWs	Aug 2020 - June 2022	median 3.1 months (IQR 2.6-4.0)	BNT, mRNA	2912	2698	Median= 44	Mean number of symptoms	Serious risk
Ayoubkhani (2) [12]	Published	UK	combined	prospective cohort	General population	Apr 2020 - Nov 2021	median 96 days (IQR 90-104) after infection for vaccinated and median 98 days (IQR 89-109) for unvaccinated	ChAd, Moderna, BNT	3090	3090	Mean(SD) = 49.0 (12.0)	Odds Ratio (OR)	Critical risk
Ayoubkhani [13]	Published	UK	combined	prospective cohort (interrupted time series analysis)	General population	Feb 2021- Sep 2021	Median 67 days (IQR 20-99) after second dose, median 267 days (IQR 219-431) after COVID infection	mRNA, ChAd	28,356	NR	Mean(SD)= 45.9 (13.6)	Odds Ratio (OR)	Serious risk
Taquet [15]	Published	USA	combined	retrospective cohort	General population	Jan 2021 - Aug 2021	6 months	BNT, Moderna, Ad26	18958	9479	Mean(SD)= 57.0 (17.9)	Hazard Ratio (HR)	Serious risk
Brannock [19]	Preprint	USA	NR	retrospective cohort	General population	Aug 2021 -	120-300 days after infection	mRNA, viral	47752	26567	Mean= 48.17	Odds Ratio (OR) and Hazard	Serious risk

						Jan 2022		vector vaccine				Ratio (HR). The OR was used to calculate VE.	
Ioannou [16]	Published	USA	Public	retrospective cohort	Veterans	Feb 2020 - Dec 2021	8 to 12 months after COVID infection	BNT, Moderna	198,601	2447 (3.6%)	Mean(SD) = 60.4 (17.7)	Odds Ratio (OR)	Serious risk
Al-Aly [14]	Published	USA	combined	retrospective cohort	Veterans	Jan 2021- Oct 2021	6 months	BNT, Moderna, Ad26	13,369,073	33940	Mean = 66.63	Hazard Ratio (HR)	Serious risk

Appendix 5. Critical Appraisal Process for Studies on Vaccination and PASC Outcomes

ROBINS-I Domain	Study characteristic that may introduce bias
ROBINS-I: Bias in selection of participants into study	• Study design • Method for confirming previous COVID infection
ROBINS-I: Bias in classification of interventions	• Method for confirming vaccination
ROBINS-I: Bias due to confounding	• Accounting for non-immune period • Accounting for calendar time • Adjustment for prognostic factors • Accounting for re-infections • Accounting for period of time between vaccination and infection
ROBINS-I: Bias in measurement of outcomes	• Detection of PASC in vaccinated vs. unvaccinated • Systematic COVID testing
ROBINS-I: Bias due to deviations from intended interventions	*Not applicable for vaccination as intervention*
ROBINS-I: Bias due to missing data	• Missing data in vaccinated vs. unvaccinated
ROBINS-I: Bias in selection of the reported result	• Discrepancies in methods vs. results sections

ROBINS-I: Bias in selection of participants into study

Study design
Prospective cohort = low

Case-control/retrospective cohort/data-linkage = moderate

If any concerns about case-control/cohort/data-linkage = serious

Surveillance cohort = moderate

Surveillance cross-sectional or any cross-sectional or ecological = serious

Survey = critical

Method for confirming previous COVID infection
National or state or provincial registry/surveillance database, EMRs = low

Self-reported previous COVID infection without laboratory or clinical confirmation, for some or all participants = serious

ROBINS-I: Bias in classification of interventions

Method for confirming vaccination
Vaccine/immunization database/onsite vaccinations/prison or military records = low

Questionnaire with subset confirmed with registry/EHR = moderate

Self-report = serious

Not reported/estimated vaccine coverage = critical

ROBINS-I: Bias due to confounding

Accounting for non-immune period following vaccination (first 14 days after 2nd dose and first 7 days after any booster dose) **only applicable to those infected after vaccination*
Clearly stated that infection occurred beyond non-immune period for last dose of vaccine = low

No clear statement about timing of infection post vaccination but at least 2 doses of vaccine administered = moderate

No statement about timing of infection post vaccination and only 1 dose of vaccine administered = serious

Accounting for calendar time
Use of time-varying statistics without explicit mention of adjustment for calendar time (e.g. results stratified by dominant variant wave) = moderate

Not taken into account but short time frame (e.g. ≤ 2 months) = serious

Not taken into account and time frame >2 months = critical

Adjustment for prognostic factors
No or insufficient adjustment for occupation (number of tests as surrogate for exposure risk) = moderate – occupation not relevant for LTCF

No or insufficient adjustment for socioeconomic factors (neighborhood or income as surrogate; municipality= serious because could include all income brackets), race, ethnicity = serious

No or insufficient adjustment for age or chronic medical conditions/comorbidities (any study population) = critical

Accounting for re-infections
Accounted for number of previous COVID infections = low

Not accounted for/unclear that re-infections were considered = serious

ROBINS-I: Bias in measurement of outcomes

Detection of PASC in vaccinated vs. unvaccinated
Symptoms assessed prospectively using standardized report forms with clear statement or criteria that symptoms only began after infection = low

Symptoms assessed retrospectively using EHRs and pre-specified checklist of PASC symptoms, and recorded as new after infection = moderate

Symptoms assessed at a PASC clinic = moderate

No method of verifying symptoms were new after infection, or symptoms were reported before infection = critical

One group assessed by a different method compared to other group (e.g. one group assessed by self-report survey and other group assessed at clinic/by doctor) = critical

Systematic COVID testing
Vaccinated and unvaccinated systematically tested for COVID and found to be negative at time of PASC assessment = low

Vaccinated and unvaccinated not tested at time of PASC assessment = serious

One group systematically tested for COVID and the other is not, or participants found to be positive with COVID at time of PASC assessment = critical

ROBINS-I: Bias due to missing data

Missing data in vaccinated vs. unvaccinated
Outcome data is available for all/nearly all participants (e.g. 90-95%); or the proportion of missing participants in vaccinated vs. unvaccinated groups is similar, and reasons for missing participants are similar = low

Proportion of missing participants in vaccinated vs. unvaccinated groups differs substantially, or reasons for missing differ substantially; and missing data was not sufficiently addressed through analysis = serious

Missing data was not/could not be addressed through analysis = critical

ROBINS-I: Bias in selection of the reported result

Discrepancies in methods vs. results sections
All measurements for a PASC outcome described in the methods are reported in results; all analyses of the vaccination-PASC relationship (e.g. unadjusted and adjusted models) described in the methods are reported in results; and all subgroups described in the methods are reported in results = low

PASC outcomes are defined in different ways in the methods and results sections; or not all analyses of the vaccination-PASC relationship described in methods are reported in results; or not all subgroups described in methods are reported in results = serious

Analyses of the vaccination-PASC relationship described in methods but not reported in results are likely to produce substantially different estimates from the reported estimates = critical

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