Coronavirus Variants Rapid Response Network | Réseau de réponse rapide aux variants du coronavirus

COVID-END COVID-19 Evidence Network to support Decision-making ... in Canada

COVID-19 Living Evidence Synthesis #6

(Version 21: 06 October 2021)

Question

What is the efficacy and effectiveness of available COVID-19 vaccines for variants of concern?

Findings

For vaccine effectiveness in variants of concern (VOC), we present a visual summary of evidence in Table 1 and detailed statements in Table 2.

Methods are presented in Box 1 and in the following appendices:

1) reference list
2) glossary
3) data-extraction template
4) process for assigning variant of concern to studies
5) research question and critical appraisal process
6) detailed description of the narrative summary statement.

Overall, 221 studies were appraised and 85 used to complete this summary. The reasons for excluding the remaining 136 studies are reported in the second section of Appendix 2.

6 new studies have been added since the previous edition of this living evidence synthesis, all of which are signaled by a last-updated date of 06 October 2021 (highlighted in yellow). The new studies included results for VOC Alpha[1] [B.1.1.7] (2), VOC Beta to VOC Delta [B.1.351] (1); VOC Alpha to VOC Delta (2), and VOC Delta [B.1.617.2] (1).

Box 1: Our approach

We retrieved candidate studies and updates to living evidence syntheses on vaccine effectiveness using the following mechanisms: 1) PubMed via COVID-19+ Evidence Alerts; 2) systematic scanning of pre-print servers; 3) updates to the COVID-END inventory of best evidence syntheses; and 4) cross-check with updates from the VESPa team. We included studies and updates to living evidence syntheses identified up to two days before the version release date. We did not include press releases unless a preprint was available. A full list of included and excluded studies is provided in **Appendix 1**. A glossary is provided in **Appendix 2**.

Prioritized outcome Measures: Infection, severe disease (as defined by the study investigators), death, and transmission.

Data extraction: We prioritized variant-confirmed and vaccine-specific data over total study population data (variant assumed and/or vaccine unspecified). We extracted data from each study in duplicate using the template provided in **Appendix 3**. Relevance to VOC is determined directly, when reported by study authors, or indirectly where reasonable assumptions can be made about the variant prevalent in the jurisdiction at the time of the study as described in **Appendix 4**.

Critical appraisal: We assessed risk of bias, direction of effect, and certainty of evidence. **Risk of bias:** assessed in duplicate for individual studies using an adapted version of ROBINS-I. **Direction of vaccine effect:** "prevented" or "protects" was applied to mean estimates or range of mean estimates of effect that are greater than or equal to 50% (the lowest acceptable limit for vaccine effectiveness as determined by WHO). **Certainty of evidence:** assessed for the collection of studies for each vaccine according to variant of concern using a modified version of GRADE. Details of the research question for this synopsis and the critical appraisal process are provided in **Appendix 5**.

Summaries: We summarized the evidence by presenting narrative evidence profiles across studies, with or without pooling, as appropriate. A template for the summary statements used on page 1 under "Findings" and in Table 1 under each VOC is provided in **Appendix 6**.

We update this document every Wednesday and post it on the COVID-END website.

[1] As of August 9, inclusion of Alpha studies may be temporarily delayed to permit resource allocation to Delta.

Pfizer/Comirnaty [BNT162b2]

We have moderate certainty evidence that 2 doses of BNT162b2 prevented infection (range of mean estimates: 70 to 97%), prevented severe disease (range of mean estimates: 92 to 98%), prevented death (range of mean estimates: 91 to 99%), and reduced transmission of VOC **Alpha** to close contacts (range of mean estimates: 65 to 80%).

We have moderate certainty evidence that 2 doses of BNT162b2 prevented symptomatic infection from VOC **Beta** (range of mean estimates: 84 to 88%).

We have low certainty evidence that 2 doses of BNT162b2 prevented infection from VOC **Delta** (range of mean estimates: 42 to 80%); moderate certainty evidence it prevented symptomatic infection from VOC Delta (range of mean estimates: 62 to 94%); and low certainty evidence it prevented severe, critical, or fatal disease from VOC Delta (range of mean estimates: 93 to 98%).

We have low certainty evidence that BNT162b2 prevented symptomatic disease from VOC **Gamma** (range of mean estimates: 84 to 88% - 2 reports from the same study population).

Moderna/Spikevax [mRNA-1273]

We have moderate certainty evidence that 2 doses of mRNA-1273 prevented infection from VOC **Alpha** (range of mean estimates: 86 to 100%) and low certainty evidence it prevented infection from VOC Beta (96.4% [95% CI, 92 to 99] – 1 Obs). We have low certainty evidence that it prevented severe, critical, or fatal disease from VOC Alpha (combined with Beta) (95.7% [95% CI, 73.4 to 99.9] – 1 Obs).

We have moderate certainty evidence that 2 doses of mRNA-1273 prevented infection from VOC **Delta** (range of mean estimates: 74 to 86%) and low certainty evidence that it prevented severe, critical, or fatal disease (range of mean estimate: 93 to 100%).

We have low certainty evidence that 2 doses of mRNA-1273 prevented symptomatic infection from VOC **Delta** (90.3% [95% CI, 67.2 to 97.1] – 1 Obs).

We have low certainty evidence that 2 doses of mRNA-1273 prevented symptomatic infection from VOC **Gamma** (88% [95% CI, 61 to 96] – 1 Obs).

AstraZeneca/Vaxzevria [ChAdOx1]

We have moderate certainty evidence that 2 doses of ChAdOx1 prevented infection from VOC **Alpha** (range of mean estimates: 62 to 79%) and moderate certainty evidence that it provided limited protection from infection by VOC Beta (10.4% [95% CI, -76.8 to 54.8]- 1 RCT).

We have low certainty evidence that 2 doses of ChAdOx1 prevented infection from VOC **Delta** (range of mean estimates: 60 to 67%) and moderate certainty evidence it prevented symptomatic infection from VOC Delta (range of mean estimates: 61 to 70%). We have low certainty evidence that 2 doses of ChAdOx1 prevented ICU admission (99.2% [95% CI, 97.6 to 99.7] – 1 Obs*) and low certainty evidence it prevented death (range of mean estimates: 97 to 99.6%).

We have low certainty evidence one dose of ChAdOx1 provided limited protection against symptomatic infection against VOC **Gamma** (48% [95% CI, 28 to 63] – 1 Obs). ***combined with Alpha

Other vaccines

We have moderate certainty evidence that **Johnson & Johnson** [**AD26.COV2.S]** prevented severe disease from VOC **Beta** (81.7% [95% CI, 46.2 to 95.4] - 1 RCT). We have low certainty evidence that AD26.COV2.S prevented infection from VOC Delta (51% [95% CI, -2 to 76] – 1 Obs).

We have moderate certainty evidence that 2 doses of **Novavax [NVX-Co2373]** prevented symptomatic infection from VOC **Alpha** (86.3% [95% CI, 71.3 to 93.5] - 1 RCT) and moderate certainty evidence that it prevented symptomatic infection from VOC **Beta** (43% [95% CI, -9.8 to 70.4] - 1 RCT).

We low certainty evidence that 2 doses of **Sinovac** [**CoronaVac]** prevented symptomatic infection due to VOC **Delta** (59% [95% CI, 16 to 81.6] – 1 Obs) and prevented severe infection (range of mean estimates: 89 to 100%) due to VOC **Delta**.

We have low certainty evidence that 2 doses of CoronaVac prevented infection from VOC **Gamma** (65.9% [95% CI, 65.2 to 66.6] – 1 Obs).

We have low certainty evidence that 2 doses of Sinopharm [BBIBP-CorV] prevented ICU admission (95.4% [95% CI, 94.6 to 96.2] – 1 Obs*) from VOC **Delta** and low certainty evidence it prevented death (94.3% [95% CI, 93.1 to 95.4] – 1 Obs*).

We have low certainty evidence that 2 doses of Gamaleya [Sputnik V] prevented ICU admission (100% [95% CI, 99.2 to 100] – 1 Obs*) from VOC **Delta** and low certainty evidence it prevented death (99.5% [95% CI, 98.5 to 99.9] – 1 Obs*).

Combinations of vaccines

We have low certainty evidence that 1 dose of **AstraZeneca [ChAdOx1]** followed by 1 dose of **Pfizer [BNT162b2]** or **Moderna [mRNA-1273]** prevented infection by VOC **Alpha** (88% [95% CI, 83 to 92] – 1 Obs).

Table 1: Visual summary of evidence for COVID-19 vaccines for variants of concern

Percentages indicate level of effectiveness from 0% (no effect) to 100% (full protection): ranges of estimated means are provided when ≥ 1 study is available; estimated mean value is provided for single studies

Colour indicates level of certainty based on the evidence

High certainty evidence = pooling of moderate to high quality RCTs or pooling of observational studies with low risk of bias and with consistent findings

Moderate certainty evidence = single RCT of moderate to high quality or ≥ one observational study with low to moderate risk of bias and with at least partially consistent findings

Low certainty evidence = single RCT of low quality or single observational study of any quality or multiple low or moderate observational studies with inconsistent findings

Outcome (and vaccine)	Vaccine Effectiveness (2 doses unless otherwise stated) for each combination of vaccine, variant, and outcome			
	Alpha	**Beta**	**Gamma**	**Delta**
Any Infection				
Pfizer	70 to 97%			42 to 80%
Moderna	86 to 100%	96%		74 to 86%
AstraZeneca	62 to 79%	10%**		60 to 67%
Johnson & Johnson				51%
Novavax				
CoronaVac			66%	
AZ/PF or MOD	88%			
Symptomatic Infection (reported when data on "any infection" is limited)				
Pfizer		84 to 88%	84 to 88%	62 to 94%
Moderna			88%	90%
AstraZeneca			48%*	61 to 70%
Johnson & Johnson				
Novavax	86%	43%**		
CoronaVac				59%
Transmission				
Pfizer	65 to 80%			
Moderna				
AstraZeneca				
Johnson & Johnson				
Novavax				
CoronaVac				
Severe Disease (may include death for some studies)				
Pfizer	92 to 98%			93 to 98%
Moderna	96%	96%		93 to 100%
AstraZeneca				99% ICU admit
Johnson & Johnson		82%*		
Novavax				
CoronaVac				89 to 100%
Sinopharm				95% ICU admit

Sputnik V				100% ICU admit
Outcome (and vaccine)	**Vaccine Effectiveness (2 doses unless otherwise stated) for each combination of vaccine, variant, and outcome**			
	Alpha	**Beta**	**Gamma**	**Delta**
Death				
Pfizer	91 to 99%			
Moderna				
AstraZeneca				97 to 100%
Johnson & Johnson				
Novavax				
CoronaVac				
Sinopharm				94%
Sputnik V				99%

*single dose

**mean estimate of effect less than the lowest acceptable limit for vaccine effectiveness as determined by WHO

AZ, AstraZeneca; MOD, Moderna; PF, Pfizer

Table 2: Key findings about vaccine effectiveness

Vaccine	Effectiveness	Findings
Pfizer/ BioNTech **Comirnaty** **[BNT162b2]**	From COVID-NMA	Compared to placebo, vaccination with BNT162b2 reduces the incidence of symptomatic cases of COVID-19 and probably reduces severe and critical disease substantially, although there remains uncertainty about the effect on mortality; it may increase the incidence of severe adverse events. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-03;* GRADE evidence profile updated on *2021-09-17*. [BNT162b2 to complete vaccination scheme started with Astra Zeneca vaccine] Synthesis pending. Review of RCTs (AMSTAR 8/9); *last search date 2021-09-17*. [BNT162b2 to complete vaccination scheme started with Astra Zeneca at 28 days vs two doses Astra Zeneca separated by 28 days] Compared to vaccination with Astra Zeneca vaccine, having a second dose of BNT16b2 after a first dose of Astra Zeneca may not increase the risk of any adverse event, while the incidence of serious adverse events is uncertain. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17;* GRADE evidence profile updated on 2021-07-19
	By variant of concern	
	• Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes 14 days after 1st dose: • 46 to 78% from infection (RME) BNT162b2 provided protection against VOC Alpha for the following outcomes 42 to 49 days after at least one dose: • 93% (95% CI, 89 to 96) from death BNT162b2 provided protection against VOC Alpha for the following outcomes at least 7 days after 2nd dose: • 70 to 97% from infection (RME) • 87% (95% CI, 74 to 93) from symptomatic infection • 92 to 98% from severe disease (RME) • 90% (86 to 93) from ICU admission • 91 to 99% from death (RME) (24 Obs) [1][2][3][8][9][10][15][21][22][23][28][31][34][36][41][43][53][60][74][75][79][88][94][99]; *last update 2021-10-06*
	• Alpha, VE over time	BNT162b2 provided protection against symptomatic infection by VOC Alpha when the 2nd dose was given the following number of days after 1st dose: • 77% (95% CI, 66 to 85) at 19-29 days (age 65 to 79) • 86% (95% CI, 70 to 94) at 85+ days (age 65 to 79) BNT162b2 provided protection against hospitalization by VOC Alpha for the following number of days after the 2nd dose:

Vaccine	Effectiveness	Findings
		• 92% (95% CI, 88 to 94) at 28 to 41 days • 86% (95% CI, 74 to 93) at ≥112 days (2 Obs) [79][99]; *last update 2021-10-06*
	• Beta	BNT162b2 provided protection against VOC Beta (or Gamma) for the following outcomes 35-41 days after 1st dose: • 43% (95% CI, 22 to 59) from symptomatic infection BNT162b2 provided protection against VOC Beta (or Gamma) for the following outcome 7 days after 2nd dose: • 84 to 88% from symptomatic infection (RME) • 95% (95% CI, 81 to 99) from hospitalization BNT162b2 provided protection against VOC Beta for the following outcomes ≥ 14 days after 2nd dose: • 75% (95% CI, 70.5 to 78.9) from infection • 100% (95% CI, 73.7 to 100) from severe, critical, or fatal disease (2 Obs – 3 refs)[23][36][47]; *last update 2021-07-14*
	• Beta to Delta	BNT162b2 provided protection against infection by VOC Beta to VOC Delta for the following number of days after the 2nd dose: • 65.8% (95% CI, 63.8 to 67.7) at 5 to 9 weeks • 29.7% (95% CI, 21.7 to 36.9) at 15 to 19 weeks • 0% (95% CI, 0 to 0) 20 to 24 weeks BNT162b2 provided protection against hospitalization or death by VOC Beta to VOC Delta for the following number of days after the 2nd dose: • 94.2% (95% CI, 91.0 to 96.5) at 5 to 9 weeks • 86.4% (95% CI, 69.9 to 94.8) at 15 to 19 weeks • 95.3% (95% CI, 70.5 to 99.9) at 20 to 24 weeks (1 Obs) [98]; *last update* 2021-10-06
	• Alpha to Delta	BNT162b2 or mRNA-1273 provided protection against VOC Alpha to Delta for the following outcomes ≥ 14 days after 2nd dose: • 92% (95% CI, 85 to 96) from severe disease in people with no risk conditions • 72% (95% CI, 51 to 84) from severe disease with very high risk conditions BNT162b2 showed OR 1.61 (95% CI, 1.45 to 1.79) for infection comparing fully vaccinated Jan to Feb (VOC Alpha) vs fully vaccinated Mar to May (VOC Delta). (2 Obs) [95][96]; *last update* 2021-10-06
	• Delta	BNT162b2 provided protection against VOC Delta for the following outcome at least 14 to 21 days after 1st dose: • 30 to 65% from infection (RME) • 33 to 47.5% from symptomatic infection (RME) • 87 to 94% from hospitalization (RME) • 100% (95% CI not reported) from severe, critical or fatal disease

Vaccine	Effectiveness	Findings
		BNT162b2 provided protection against VOC Delta for the following outcome at least 7 days after 2nd dose: • 42 to 80% from infection (RME) • 62 to 93.7% from symptomatic infection (RME) • 96% (95% CI, 86 to 99) from hospitalization • 93 to 98% from severe, critical, or fatal disease (RME) (15 Obs) [29][38][42][47][57][63][64][65][71][74][76][84][88][92][97]; *last update 2021-10-06*
	• Delta, VE over time	BNT162b2 showed a higher risk of infection by VOC Delta in participants fully vaccinated (≥14 days after 2nd dose) longer than or equal to 146 days ago vs fully vaccinated less than 146 days ago [OR 2.06 (95% CI, 1.69 to 2.51)] (1 Obs) [69]; *last update 2021-08-25* BNT162b2 provided protection against infection by VOC Delta for the following number of days after 2nd dose: • 93% (95% CI, 85 to 87) at 7 to 30 days • 53% (95% CI, 39 to 65) at ≥127 days BNT162b2 provided protection against infection by VOC Delta 5 months after 2nd dose: • 50% (95% CI, 45 to 55) - age 16 to 39 • 58% (95% CI, 54 to 62) - age 40 to 59 • 57% (95% CI, 52 to 62) - age 60+ BNT162b2 provided protection against symptomatic infection by VOC Delta for the following number of days after 2nd dose: • 62.7% (95% CI, 61.7 to 63.8) – at 1 week • 47.3% (95% CI, 45 to 49.6) – at 20+ weeks BNT162b2 provided protection against severe, critical, or fatal disease by VOC Delta 5 months after 2nd dose: • 94% (95% CI, 87 to 97) - age 40 to 59 • 86% (95% CI, 82 to 90) - age 60+ (3 Obs) [76][84][92]; *last update 2021-09-22*
	• Delta, prior infection	BNT162b2 (2 doses) provided protection against VOC Delta for the following outcomes: • OR 13.06 (95% CI, 8.08 to 21.11) against infection compared to previously infected (unvaccinated) • OR 27.02 (95% CI, 12.7 to 57.5) against symptomatic infection compared to previously infected (unvaccinated) (1 Obs) [73]; *last update 2021-09-02*
	• Delta, 3 doses	BNT162b2 (3 doses) provided protection against infection by VOC Delta compared to 2 doses: • 3% (95% CI, -5 to 10) – at 0 to 6 days after 3rd dose • 84.0% (95% CI, 79 to 88) – at 14 to 20 days after 3rd dose (1 Obs) [93]; *last update 2021-09-22*
	• Gamma	BNT162b2 provided protection against VOC Gamma (or Beta) for the following outcomes 35-41 days after 1st dose:

Vaccine	Effectiveness	Findings
		• 43% (95% CI, 22 to 59) from symptomatic infection BNT162b2 provided protection against VOC Gamma (or Beta) for the following outcome 7 days after 2nd dose: • 84 to 88% from symptomatic infection (RME) • 95% (95% CI, 81 to 99) from hospitalization (1 Obs – 2 refs)[23][47]; *last update 2021-07-14*
	• Epsilon	BNT162b2 provided protection against VOC Epsilon for the following outcome 15 days after 1st dose: • 58.9% (95% CI, −9.7 to 84.5) from infection BNT162b2 provided protection against VOC Epsilon for the following outcome 15 days after 2nddose: • 85.7% (67.2 to 93.9) from infection (2 Obs) [8][31]; *last update 2021-06-08*
	By special population	
	• HCW, Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes 14 to 21 days after 1st dose: • 64 to 84% from infection (RME) BNT162b2 provided protection against VOC Alpha for the following outcomes at least 7 days after 2nd dose: • 80 to 96% from infection (RME) BNT162b2 provided protection against VOC Alpha for the following outcome 7 days after 2nd dose: • 86% (95% CI, 69 to 93) from asymptomatic infection [25] BNT162b2 provided protection against infection by VOC Alpha for the following number of days after 2nd dose: • 85% (95% CI, 68 to 93) at 14 to 119 days • 73% (95% CI, 49 to 86) ≥150 days (7 Obs)[11][26][32][45][46][56][81]; *last update 2021-09-22*
	• Over 65 years, requiring support at home, Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes 7 days after 2nd dose: • 86% (95% CI, 78 to 91) from infection • 97% (95% CI, 88 to 99) from death (1 Obs)[32]; *last update 2021-07-07*
	• Over 70 years, Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes at least 21 days after 1st dose: • 41 to 67% from infection (RME) BNT162b2 provided protection against VOC Alpha for the following outcomes at least 7 days after 2nd dose: • 75 to 90% from infection (RME) (3 Obs)[28][35][51]; *last update 2021-10-06*
	• Over 80 years, Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes at least 14 days after 1st dose: • 42 to 55.2% from infection (RME) • 71 to 81% from hospitalization (RME) BNT162b2 provided protection against VOC Alpha for the following outcomes >14 days after 2nd dose: • 94% (95% CI, 73 to 99) from symptomatic infection

Vaccine	Effectiveness	Findings
		• 93% (95% CI, 89 to 95) from hospitalization • 81% (95% CI, 74 to 87) from death BNT162b2 provided protection against death by VOC Alpha for the following number of days after 2nd dose: • 86% (95% CI, 68 to 93) at 14 to 41 days • 74% (95% CI, 60 to 83) ≥98 days (5 Obs)[13][20][55][79][83]; *last update 2021-09-22*
	• LTC, Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes 7 days after 2nd dose: • 53% (95% CI, 29 to 69) from infection • 89% (95% CI, 81 to 93) from death (1 Obs)[32]; *last update 2021-10-06*
	• Pregnant, Alpha	BNT162b2 provided protection against VOC Alpha for the following outcomes at least 28 days after 1st dose: • 78% (95% CI, 57 to 89) from infection BNT162b2 provided protection against VOC Alpha for the following outcomes 7 to 56 days after 2nd dose: • 86.1% (95% CI, 82.4 to 89.1) from infection • 89% (95% CI, 43 to 100) from hospitalization (2 Obs) [52][54]; *last update 2021-07-28*
	• Previously infected, Alpha or Beta	BNT162b2 (2 doses) after prior infection provided protection against VOC Alpha (or Beta) for the following outcomes: • 85% (95% CI, 80 to 89) against re-infection compared to BNT162b2 without prior infection (1 Obs) [72]; *last update 2021-08-25*
	• Immunosuppressed, renal transplant, Alpha or Beta	BNT162b2 or mRNA-1273 provided protection against infection by VOC Alpha or Beta at the following number of days after 2nd dose: • 46.6% (95% CI, 0.0 to 73.7) ≥14 days • 66.0% (95% CI, 21.3 to 85.3) ≥42 days • 73.9% (95% CI, 33 to 98.9) ≥56 days BNT162b2 or mRNA-1273 provided protection against severe, critical, or fatal disease by VOC Alpha or Beta at the following number of days after 2nd dose: • 72.3% (95% CI, 0.0 to 90.9) ≥14 days • 85% (95% CI, 35.7 to 96.5) ≥42 days • 83.8% (95% CI, 31.3 to 96.2) ≥56 days (1 Obs) [90]; *last update 2021-09-22*
	• Over 70 years, Gamma	BNT162b2 provided protection against VOC Gamma for the following outcomes ≥ 21 days after 1st dose: • 61% (95% CI, 45 to 72) from infection (1 Obs)[35]; *last update 2021-07-07*
	• HCW, Delta	BNT162b2 provided protection against VOC Delta for the following outcomes ≥ 14 days after 2nd dose: • 66% (95% CI, 26 to 84) (1 Obs) [81]; *last update 2021-09-22*

Vaccine	Effectiveness	Findings
	• HCW, Beta or Gamma	BNT162b2 provided protection against VOC Beta or Gamma for the following outcomes 14 to 42 days after 1st dose: • 37.2% (95% CI, 16.6 to 52.7) from infection BNT162b2 provided protection against VOC Beta or Gamma for the following outcome 7 days after 2nd dose: • 79.2% (95% CI, 64.6 to 87.8) from infection (1 Obs)[27]; *last update 2021-06-01*
	• LTC, Gamma (residents)	BNT162b2 (or mRNA-1273) provided protection against VOC Gamma 14 days after 2nd dose: • 52.5% (95% CI, 26.9 to 69.1) against infection • 78.6% (95% CI, 47.9 to 91.2) against severe disease (1 Obs) [61]; *last update 2021-08-11*
	Transmission	
	• Household of vaccinated individual, Alpha	BNT162b2 reduced transmission of VOC Alpha from a vaccinated index case (14 to 21 days after 1st dose) to household contacts compared to households of unvaccinated index cases: • 30 to 49% from infection (RME) BNT162b2 reduced transmission of VOC Alpha from a vaccinated HCW (10 weeks after 1st dose) to household spouse: • 42.9% (95% CI, 22.3 to 58.1) from infection (3 Obs) [6][14][33]; *last update 2021-07-07*
	• Vaccinated close contacts of COVID+, Alpha	BNT162b2 reduced transmission to close contacts COVID+ index cases at least 7 to 14 days after 2nd dose: • 65 to 80% from infection (RME) • 94% (95% CI, 60 to 99) from hospitalization (2 Obs)[40][48]; *last update 2021-07-14*
	• Vaccinated HCW vs unvaccinated community, Beta and Gamma	BNT162b2 reduced transmission of VOC Beta or Gamma from vaccinated HCW compared to unvaccinated community ≥14 days after 1st dose: • 54.7% (95% CI, 44.8 to 62.9) from infection BNT162b2 reduced transmission of VOC Beta or Gamma from vaccinated HCW compared to unvaccinated community ≥7 days after 2nd dose: • 84.8% (95% CI, 75.2 to 90.7) from infection (1 Obs) [27]; *last update 2021-06-08*
Moderna **Spikevax** **[mRNA-1723]**	From COVID-NMA	Compared to placebo, vaccination with mRNA-1723 probably reduces the incidence of symptomatic cases of COVID-19 substantially and it may reduce severe disease, while the incidence of serious adverse events is probably not increased. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17;* GRADE evidence profile updated on 2021-01-25
	By variant of concern	
	• Alpha	mRNA-1273 provided protection against VOC Alpha for the following outcomes 14-41 days after 1st dose:

Vaccine	Effectiveness	Findings
		• 58.9 to 88.1% from infection (RME) • 60 to 61% from symptomatic infection (RME) • 81.6% (95% CI, 71.0 to 88.8) from severe, critical, or fatal disease (combined with Beta) mRNA-1273 provided protection against VOC Alpha for the following outcomes at least 7 to 15 days after 2nd dose: • 86 to 100% from infection (RME) • 90 to 95.7% from symptomatic infection (RME) • 95.7% (95% CI, 73.4 to 99.9) from severe, critical, or fatal disease (combined with Beta) (8 Obs – 9 refs) [8][23][31][34][37][47][50][60][74]; *last update 2021-10-06*
	• Beta	mRNA-1273 provided protection against VOC Beta for the following outcomes 14 days after 1st dose: • 61.3% (95% CI, 56.5 to 65.5) from infection • 77% (95% CI, 63 to 86) from symptomatic infection • 89% (95% CI, 73 to 95) from hospitalization • 81.6% (95% CI, 71.0 to 88.8) from severe, critical, or fatal disease (combined with Alpha) mRNA-1273 provided protection against VOC Beta for the following outcomes 35-41 days after 1st dose: • 43% (95 CI, 22 to 59) from symptomatic infection mRNA-1273 provided protection against VOC Beta for the following outcome 7 days after 2nd dose: • 96.4% (95% CI, 91.9 to 98.7) from infection • 88% (95% CI, 61 to 96) from symptomatic infection • 95.7% (95% CI, 73.4 to 99.9) from severe, critical, or fatal disease (combined with Alpha) (2 Obs – 3 refs) [23][47][50]; *last update 2021-07-14*
	• Alpha to Delta	mRNA-1273 or BNT162b2 provided protection against VOC Alpha to Delta for the following outcomes ≥ 14 days after 2nd dose: • 92% (95% CI, 85 to 96) from severe disease in people with no risk conditions • 72% (95% CI, 51 to 84) from severe disease with very high risk conditions (1 Obs) [95]; *last update* 2021-10-06
	• Delta	mRNA-1273 provided protection against VOC Delta for the following outcomes at least 14 days after 1st dose: • 75 to 80% from infection (RME) • 72% (95% CI, 57 to 82) from symptomatic infection • 96% (95% CI, 72 to 99) from hospitalization • 93 to 100% from severe, critical, or fatal disease (RME) mRNA-1273 provided protection against VOC Delta for the following outcomes 14 days after 2nd dose: • 74 to 86% from infection (RME) • 93 to 100% from severe, critical or fatal disease (RME) (7 Obs) [47][57][63][64][71][74][97]; *last update 2021-10-06*

Vaccine	Effectiveness	Findings
	• Delta, VE over time	mRNA-1273 provided protection against symptomatic infection by VOC Delta the following number of days after 2nd dose: • 95.2% (95% CI, 94.4 to 95.9) – at 1 week • 90.3% (95% CI, 67.2 to 97.1) – at 10 to 14 weeks (1 Obs) [92]; *last update 2021-09-22*
	• Gamma	mRNA-1273 provided protection against VOC Gamma for the following outcomes 14 days after 1st dose: • 77% (95% CI, 63 to 86) from symptomatic infection • 89% (95% CI, 73 to 95) from hospitalization mRNA-1273 provided protection against VOC Gamma (or Beta) for the following outcomes 35-41 days after 1st dose: • 43% (95% CI, 22 to 59) from symptomatic infection mRNA-1273 provided protection against VOC Gamma (or Beta) for the following outcome 7 days after 2nd dose: • 88% (95% CI, 61 to 96) from symptomatic infection (1 Obs – 2 refs) [23][47]; *last update 2021-07-07*
	• Epsilon	mRNA-1273 provided protection against VOC Epsilon for the following outcome 15 days after 1st dose: • 58.9% (95% CI, −9.7 to 84.5) from infection mRNA-1273 provided protection against VOC Epsilon for the following outcome 15 days after 2nddose: • 85.7% (67.2 to 93.9) from infection (2 Obs) [8][31]; *last update 2021-06-08*
	Special population	
	• Over 70 years, Alpha	mRNA-1273 provided protection against VOC Alpha for the following outcome ≥21 days after 1st dose: • 67% (95% CI, 57 to 75) from infection (1 Obs) [35]; *last update 2021-06-23*
	• Previously infected, Alpha or Beta	mRNA-1273 (2 doses) after prior infection did not offer additional protection against VOC Alpha (or Beta) for the following outcomes: • 15% (95% CI, -105 to 66) against re-infection compared to mRNA-1273 without prior infection (1 Obs) [72]; *last update 2021-08-25*
	• Immunosuppressed, renal transplant, Alpha or Beta	mRNA-1273 or BNT162b2 provided protection against infection by VOC Alpha or Beta at the following number of days after 2nd dose: • 46.6% (95% CI, 0.0 to 73.7) ≥14 days • 66.0% (95% CI, 21.3 to 85.3) ≥42 days • 73.9% (95% CI, 33 to 98.9) ≥56 days mRNA-1273 or BNT162b2 provided protection against severe, critical, or fatal disease by VOC Alpha or Beta at the following number of days after 2nd dose: • 72.3% (95% CI, 0.0 to 90.9) ≥14 days • 85% (95% CI, 35.7 to 96.5) ≥42 days • 83.8% (95% CI, 31.3 to 96.2) ≥56 days (1 Obs) [90]; *last update 2021-09-22*

Vaccine	Effectiveness	Findings
	• Over 70 years, Gamma	mRNA-1273 provided protection against VOC Gamma for the following outcome ≥21 days after 1st dose: • 61% (95% CI, 45 to 72) from infection (1 Obs) [35]; *last update 2021-06-23*
	• LTC, Gamma (residents)	mRNA-1273 (or BNT162b2) provided protection against VOC Gamma for the following outcomes 14 days after 2nd dose: • 52.5% (95% CI, 26.9 to 69.1) against infection • 78.6% (95% CI, 47.9 to 91.2) against severe disease (1 Obs) [61]; *last update 2021-08-11*
	Transmission	
	• Household of vaccinated individual, Alpha	mRNA-1273 reduced transmission of VOC Alpha from a vaccinated HCW (10 weeks after 1st dose) to household spouse: • 42.9% (95% CI, 22.3 to 58.1) from infection (1 Obs)[33]; *last update 2021-07-07*
AstraZeneca [ChAd0x1] **Vaxzevria** **Serum Institute of India [Covishield]**	From COVID-NMA	Compared to vaccinating with MedACWY (meningitis vaccine), vaccination with ChAd0x1 probably reduces the cases of symptomatic COVID-19 infection. The effects on severe or critical disease and mortality are uncertain. (*)Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17;* GRADE evidence profile updated on 2021-01-25 . (*) Rare cases of serious blood clots associated with a low platelet count known as vaccine-induced thrombotic thrombocytopenia (VITT or VIPIT) have been reported. The frequency of VITT varies by age and country. [AstraZeneca to complete vaccination scheme started with BNT16b2 at 28 days vs two doses of BNT16b2 separated by 28 days] Compared to vaccination with BNT16b2 vaccine, having a second dose of AstraZeneca after a first dose of BNT 16b2 may increase the risk of any adverse event, while the incidence of serious adverse events is uncertain. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17;* GRADE evidence profile updated on 2021-07-19
	By variant of concern	
	• Alpha	ChAdOx1 provided protection against VOC Alpha for the following outcome 14 days after 1st dose: • 64% (95% CI, 60 to 68) from symptomatic infection • 85% (95% CI, 81 to 88) from hospitalization ChAdOx1nCoV-19 provided protection against VOC Alpha for the following outcome 21 to 28 days after 1st dose: • 44 to 74% from infection (RME) ChAdOx1provided protection against confirmed VOC Alpha for the following outcome at least 14 days after 2 doses: • 62 to 79% from infection (RME)

Vaccine	Effectiveness	Findings
		(1 RCT, moderate quality; 5 Obs)[9][10][5][47][70][71][]; *last update 2021-08-25*
	• Alpha, VE over time	ChAdOx1 provided protection against symptomatic infection by VOC Alpha when the 2nd dose was given the following number of days after 1st dose: • 66% (95% CI, 47 to 77) at 19-29 days (age 65 to 79) • 73% (95% CI, 56 to 83) at 85+ days (age 65 to 79) (1 Obs) [79]; *last update 2021-09-22*
	• Beta	ChAdOx1 provided protection against VOC Beta for the following outcome 14 days after 1st dose: • 48% (95% CI, 28 to 63) from symptomatic infection • 83% (95% CI, 66 to 92) from hospitalization ChAdOx1 provided protection against VOC Beta for the following outcome after 2 doses: • 10.4% (95% CI, -76.8 to 54.8) from mild to moderate disease (1 RCT, moderate quality; 1 Obs) [4][47]; *last update 2021-07-07*
	• Alpha to Delta	ChAdOx1 provided protection against VOC Alpha to Delta for the following outcomes ≥ 14 days after 2nd dose: • 94% (95% CI, 90 to 96) from severe disease in people with no risk conditions • 63% (95% CI, 46 to 75) from severe disease with very high risk conditions (1 Obs) [95]; *last update* 2021-10-06
	• Delta	ChAdOx1 provided protection against VOC Delta for the following outcome at least 21 days after 1st dose: • 18 to 49% from infection (RME) • 33 to 58% from symptomatic infection (RME) • 71% (95% CI, 51 to 83) from hospitalization • 69% (95% CI, -160 to 97) from death ChAdOx1 provided protection against VOC Delta for the following outcome 14 to 21 days after 2nd dose: • 60 to 67% from infection (RME) • 28 to 67% from symptomatic infection (RME) • 99.2% (95% CI, 97.6 to 99.7) from ICU admission* • 92% (95% CI, 75 to 97) from hospitalization • 97 to 99.6% from death (RME) (8 Obs) [29][38][42][47][65][71][75][87]; *last update 2021-10-06* *combined with VOC Alpha
	• Delta, VE over time	ChAdOx1 provided protection against symptomatic infection by VOC Delta the following number of days after 2nd dose: • 92.4% (95% CI, 92.1 to 92.7) – at 1 week • 69.7% (95% CI, 68.7 to 70.5) – at 20 weeks (1 Obs) [92]; *last update 2021-09-22*

Vaccine	Effectiveness	Findings
	• Gamma	ChAdOx1nCoV-19 provided protection against VOC Gamma for the following outcome 14 days after 1st dose: • 48% (95% CI, 28 to 63) from symptomatic infection • 83% (95% CI, 66 to 92) from hospitalization (1 Obs)[47]; *last update 2021-07-07*
	• Epsilon	no data
	Special populations	
	• HCW, Alpha	ChAdOx1provided protection against VOC Alpha for the following outcomes at least 14 days after 1st dose: • 64% (95% CI, 50 to 74) from infection ChAdOx1provided protection against VOC Alpha for the following outcomes at least 14 days after 2nd dose: • 90% (95% CI, 62 to 98) from infection (1 Obs) [46]; *last update 2021-07-07*
	• Over 80 years, Alpha	ChAdOx1 provided protection against VOC Alpha for the following outcomes at least 14 days after 1st dose: • 73 to 80% from hospitalization (RME) • 42% (95% CI, 29 to 53) from infection ChAdOx1provided protection against VOC Alpha for the following outcomes at least 14 days after 2nd dose: • 88% (95% CI, 48 to 97) from symptomatic infection (3 Obs) [13][20][79]; *last update 2021-09-22*
	• HCW, Delta	ChAdOx1 provided protection against VOC Delta for the following outcomes at least 14 days after 2nd dose: • 54 to 85% from infection (RME) • 64% (95% CI, 38 to 78) from symptomatic infection (2 Obs) [59][66]; *last update* 2021-10-06
	Transmission	
	• Household of vaccinated individual, Alpha	ChAdOx1nCoV-19 reduced transmission of VOC Alpha from a vaccinated index case (14 to 21 days after 1st dose) to household contacts compared to households of unvaccinated index cases: • 30 to 47% from infection (RME) (2 Obs) [6][14]; *last update 2021-06-08*
	• Vaccinated close contacts of COVID+, Alpha	ChAdOx1nCoV-19 reduced transmission to close contacts COVID+ index cases at least 14 days after 2nd dose: • 44% (95% CI, 31 to 54) from infection • 92% (95% CI, 46 to 99) from hospitalization (1 Obs)[40]; *last update 2021-06-23*
Johnson & Johnson [AD26.COV2.S]	From COVID-NMA	[Johnson & Johnson's Janssen vaccine] Vaccination with AD26.COV2.S probably reduces the incidence of symptomatic cases of COVID-19 by around 67%, and it probably reduces severe disease and mortality, while the incidence of serious adverse events may not increase. Review of RCTs (AMSTAR 10/11); *last search update 2021-09-17*. GRADE evidence profile updated on 2021-05-28

Vaccine	Effectiveness	Findings
		Interim summary, provided by VOC-study group: Ad26.COV2.S VE in ~40,000 randomized subjects was 66.9%; adjusted (95% CI, 59.0 to 73.4) at 14 days and 66.1% (95% CI, 55.0 to 74.8) at 28 days. For severe cases VE was 76.7% (95% CI, 54.6 to 89.1) at ≥14 days and 85.4% (95% CI, 54.2 to 96.9) at ≥28 days). (1 RCT, moderate quality of evidence) [7] Rare cases of serious blood clots associated with a low platelet count known as vaccine-induced thrombotic thrombocytopenia (VITT, VIPIT) have been reported. The frequency of VITT varies by age and country. (data not systematically reviewed); *last update 2021-05-17*
	By variant of concern	
	• Alpha	no data
	• Beta	VE against VOC 20H/501Y.V2 variant (Beta) was 52.0% and 64.0% at 14 days and 28 days for moderate, and 73.1% and 81.7% for severe cases. (1 RCT) [7]; *last update 2021-04-22*
	• Delta	Ad26.COV2.S provided protection against VOC Delta for the following outcomes ≥ 14 days after 2nd dose: • 51% (95% CI, -2 to 76) against infection (1 Obs) [97]; *last update* 2021-10-06
	• Gamma	no data
	• Epsilon	no data
Sinovac [CoronaVac]	• Overall	[Coronavac vaccine] Compared to placebo, vaccination with CoronaVac may reduce the incidence of symptomatic cases of COVID-19 by 50%, close to the lowest level deemed effective by the WHO and it may substantially reduce the incidence of severe disease due to COVID-19; the evidence for any difference in serious adverse events is uncertain, although the vaccination probably increases the incidence of any adverse event. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17*; GRADE evidence profile updated 2021-06-25
	By variant of concern	
	• Delta	CoronaVac provided protection against VOC Delta for the following outcome ≥ 14 days after 2nd dose: • 59% (95% CI, 16 to 81.6) from symptomatic infection • 89 to 100% from severe infection (RME) (2 Obs) [85][91]; *last update 2021-09-22*
	• Gamma	CoronaVac provided protection against VOC Gamma for the following outcome ≥ 14 days after 2nd dose: • 65.9% (95% CI, 65.2 to 66.6) from infection CoronaVac provided protection against VOC Gamma for the following outcome ≥ 14 days after 2nd dose for people over age 70: • 41.6% (95% CI, 26.9 to 63.3) from symptomatic infection

Vaccine	Effectiveness	Findings
		(2 Obs) [30][49]; *last update 2021-07-14*
	• Epsilon	no data
	By special population	
	• HCW, Gamma	CoronaVac provided protection against VOC Gamma for the following outcomes ≥14 days after 1st dose: • 35.1% (95% CI, -6.6 to 60.5) from infection • 49.6% (95% CI, 11.3 to 71.4) from symptomatic infection (1 Obs)[18]; last update 2021-05-07
Sinopharm (Wuhan) [WIV04] **Sinopharm (Beijing) [HBO2] [BBIBP-CorV]**	• From COVID-NMA	[Sinopharm - strain HBO2] Vaccination with Sinopharm HBO2 probably reduces the incidence of symptomatic cases of COVID-19, and it may reduce severe disease, while the incidence of adverse events is probably not increased. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17*. GRADE evidence profile updated on 2021-06-11 [Sinopharm - strain WIV04] Vaccination with Sinopharm WIV04 probably reduces the incidence of symptomatic cases of COVID-19, and it may reduce severe disease, while the incidence of adverse events is probably not increased. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17*. GRADE evidence profile updated on 2021-06-11
	• Delta	BBIBP-CorV provided protection against VOC Delta for the following outcomes ≥14 days after 2nd dose: • 95.4% (95% CI, 94.6 to 96.2) against ICU admission* • 94.3% (95% CI, 93.1 to 95.4) against death* (1 Obs) [75]; *last update* 2021-09-02 *combined with VOC Alpha
Novavax [NVX-CoV2373]	• From COVID-NMA	[Novavax vaccine] The effects of vaccination against COVID-19 with the Novavax vaccine are currently uncertain; it probably slightly increase the risk of any adverse events Review of RCTs (AMSTAR 10/11); last search date *2021-09-17*; GRADE evidence profile updated on 2021-07-01
	By variant of concern	
	• Alpha	NVX-CoV2373 provided protection against VOC Alpha for the following outcome after 2 doses: • 89.7% (95% CI, 80.2 to 94.6) from infection. • No hospitalizations or deaths in vaccinated group • Post hoc: 86.3% (95% CI, 71.3 to 93.5) from confirmed Alpha symptomatic infection (1 RCT, moderate quality), [19]; *last update 2021-06-16*
	• Beta	NVX-CoV2373 provided protection against VOC Beta for the following outcome after 7 days after 2nd dose: • Post-hoc: 43% (95% CI, -9.8 to 70.4) from symptomatic infection (1 RCT, moderate quality), [17]; *last update 2021-07-14*

Vaccine	Effectiveness	Findings
FBRI [EpiVacCorona]	• From COVID-NMA	[EpiVacCorona] The effects of using vaccination with EpiVacCorona are uncertain. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17*; GRADE evidence profile updated on 2021-06-11
Bharat Biotech [Covaxin]	• From COVID-NMA	[COVAXIN] Vaccination with BBV152 probably reduces the incidence of symptomatic cases of COVID-19, and it may reduce severe disease, while the incidence of serious adverse events is probably not increased. Review of RCTs (AMSTAR 10/11); *last search date 2021-09-17*. GRADE evidence profile updated on 2021-07-29.
	By special population	
	• HCW, Delta	Covaxin provided protection against VOC Delta for the following outcomes ≥14 days after 2nd dose: • 83% (95% CI, 73 to 89) from symptomatic infection • 93% (95% CI, 64 to 99) from ICU admission or death (1 Obs); [82]; *last update 2021-09-22*
Gamaleya [Sputnik V] [Gam-COVID-Vac]		
	• Delta	Gam-COVID-Vac provided protection against VOC Delta for the following outcomes ≥14 days after 2nd dose: • 100% (95% CI, 99.2 to 100) against ICU admission* • 99.5% (95% CI, 98.5 to 99.9) against death* (1 Obs) [75]; *last update* 2021-09-02 *combined with VOC Alpha
Combinations of Vaccines		
AstraZeneca followed by Pfizer or Moderna	• Alpha	First dose ChAdOx1 followed by second dose BNT162b2 or mRNA-1273 (≥ 14 days) provided protection against VOC Alpha for the following outcomes: • 88% (95% CI, 83 to 92) against infection (1 Obs) [70]; *last search date* 2021-08-25

*delayed exclusion (see Section 2: excluded studies for reason)

Links to references are provided in Appendix 1

Pan American Health Organization/World Health Organization. Pharmacovigilance for COVID-19 Vaccines. https://covid-19pharmacovigilance.paho.org

Iorio A, Little J, Linkins L, Abdelkader W, Bennett D, Lavis JN. COVID-19 living evidence synthesis #6 (version 6.21): What is the efficacy and effectiveness of available COVID-19 vaccines in general and specifically for variants of concern? Hamilton: Health Information Research Unit, 6 October 2021.

The COVID-19 Evidence Network to support Decision-making (COVID-END) is supported by an investment from the Government of Canada through the Canadian Institutes of Health Research (CIHR). To help Canadian decision-makers as they respond to unprecedented challenges related to the COVID-19 pandemic, COVID-END in Canada is preparing rapid evidence responses like this one. The opinions, results, and conclusions are those of the evidence-synthesis team that prepared the rapid response, and are independent of the Government of Canada and CIHR. No endorsement by the Government of Canada or CIHR is intended or should be inferred.

Appendix 1: Reference list

Section 1: included studies				
Ref	**Author**	**Bottom line**	**ROBINS-I***	**Design, Notes**
*Note: ROBINS-I score risk of bias: Low risk of bias indicates high quality				
1	Dagan	BNT162b2 showed VE 46% (95% CI, 40 to 51) against infection 14 to 20 days after 1st dose and VE 92% (95% CI, 88 to 95) 7 days after 2nd dose.	Moderate	Data-linkage study in Israel; .5 M matched participants (2 M excluded – also (possible overlap with Haas); time and setting for VOC Alpha (estimated 80%).
2	Haas	BNT162b2 showed VE 95.3% (95% CI, 94.9 to 95.7) against infection; VE 97.5% (95% CI, 97.1 to 97.8) against severe or critical COVID-19-related hospitalization; VE 96.7% (95% CI, 96.0 to 97.3) against death 7 days after 2nd dose.	Serious	Data-linkage study in Israel; >6.5 M matched participants (possible overlap with Dagan) Updated May 14 due to final publication; sample confirmed VOC Alpha (estimated 94%).
3	Kustin	BNT162b2 showed lower relative VE (2.4:1) against Alpha. after 1st dose; and lower VE (8:1) against Beta after 2nd dose in a population with >90% of Alpha and <1% Beta	Moderate	Case-control study in Israel; small sample for Beta (no overlap CHS cohort); confirmed VOC Alpha and Beta.
4	Madhi	ChAdOx1 nCoV-19 showed VE 10.4% (95% CI, -76.8 to 54.8) against mild to moderate disease 14 days after 2nd dose.	Moderate quality (RCT)	RCT in South Africa; Underpowered for 20% efficacy (42 cases); VOC Beta.
5	Emary	ChAdOx1nCoV-19 showed VE 61.7% (95% CI, 36.7 to 76.9) against infection by VOC Alpha ≥ 15 days after 2nd dose.	Moderate quality (RCT)	RCT in UK; neutralization of Alpha 9 times lower; no sequencing for 45% of cases; 52 cases (19%) had VOC Alpha.
6	Shah	ChAdOx1nCoV-19 or BNT162b2 reduced infection in unvaccinated household contacts of vaccinated HCW by about 30% (HR, 0.70, 95% CI, 0.63 to 0.78) ≥ 14 days after 1st dose; ChAdOx1nCoV-19 or BNT162b2 reduced infection in HCW by about 55% (HR 0.45, 95% CI, 0.42 to 0.49) and hospitalization by 84% (HR 0.16, 95% CI, 0.09 to 0.27) ≥ 14 days after 1st dose.	Moderate	Data-linkage study in Scotland - (25% of cases had received 2 doses); time and setting for VOC Alpha.
7	Sadoff	Single dose Ad26.COV2.S showed VE 52.0% (95% CI, 30.3 to 67.4) at 14 days and VE 64.0% (95% CI, 41.2 to 78.7) at 28 days against moderate to severe disease and VE 81.7% (95% CI, 46.2 to 95.4) at 28 days against severe disease (VOC Beta in South Africa).	Moderate quality (RCT)	RCT; over 40,000 participants; Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States; 86 of 91 cases sequenced for VOC Beta.

8	Andrejko	BNT162b2 or mRNA-1273 showed VE 58.9% (95% CI, −9.7 to 84.5) at 15 days after 1st dose, and VE 85.7% (95% CI, 67.2 to 93.9) 15 days after 2nd dose against infection.	Moderate	Test-negativease-positive random sampling matched control study in California; 645 participants; 69% of population at time had VOC Alpha or Epsilon.
9	Glampson	ChAdOx1nCoV-19 showed VE 74% (95% CI, 65 to 81) against infection 28 days after 1st dose. BNT162b2 showed VE 78% (95% CI, 73 to 82) against infection 28 days after 1st dose.	Moderate	Retrospective cohort in UK; 2M participants; 389,587 vaccinated (58% Pfizer, 42 AZ); time and setting for VOC Alpha.
10	Pritchard	ChAdOx1nCoV-19 or BNT162b2 showed VE 66% (95% CI, 59 to 72%) 21 days after 1st dose and 78% (95% CI, 68 to 85%) after 2nd dose against infection.	Moderate	Prospective cohort in UK; 370,000 participants; sample confirmed VOC Alpha.
11	Hall (SIREN)	BNT162b2 vaccine showed VE of 70% (95% CI, 55 to 85) 21 days after 1st dose and 85% (95% CI, 74 to 96) 7 days after 2nd dose against infection in HCW.	Moderate	Prospective cohort with standardized testing for HCW over all of England; 23,000 participants; time and setting for VOC Alpha
12	Shrotri *Delayed exclusion – critical ROB	Similar effect sizes were seen for ChAdOx1 (aHR 0.32, 95% CI, 0.15 to 0.66) and BNT162b2 (aHR 0.35, 95% CI, 0.17 to 0.71) at 35-48 days after 1st dose.	Critical	Prospective cohort in England: 9160 of 10412 frail LTC residents, 66% Pfizer, 33% AZ; routine screening; time and setting for VOC Alpha
13	Hyams	1st BNT162b2 showed VE 71.4% (95% CI, 43.1 to 86.2) against hospitalization 14 days after 1st dose; ChAdOx1nCoV-19 showed VE 80.4% (95% CI, 36.4 to 94.5) against hospitalization 14 days after 1st dose for 80+. When effectiveness analysis for BNT162b2 was restricted to the period covered by ChAdOx1nCoV-19, the estimate was 79.3% (95% CI, 47.0 to 92.5).	Moderate	Test negative case-control study in Scotland. Single center; 466 participants, 80+; time and setting for VOC Alpha
14	Harris	BNT162b2 or ChAdOx1 reduced likelihood of transmission by 40-50% for household contacts of HCW 21 days after 1st dose.	Moderate	Data-linkage and case-control study in England; 338,887 participants; time and setting for VOC Alpha
15	Goldberg	Prior infection (in unvaccinated) has similar VE against infection [94.8%], and severe illness [96.4%] as two doses of BNT162b2.	Serious	Data-linkage study in Israel; 6,351,903 participants; likely overlaps with Dagan and Haas; time and setting for VOC Alpha

16	Cavanaugh *Delayed exclusion – VOI instead of VOC	VE 66.2% (95% CI, 40.5% to 80.8%) against infection among LTC residents and 75.9% (95% CI, 32.5% to 91.4%) among HCW. VE 94.4% (95% CI, 73.9% to 98.8%) against hospitalization among residents; no HCW were hospitalized. Three residents died, two of whom were unvaccinated (VE 94.4%; 95% CI, 44.6% to 99.4%).	Critical	Outbreak analysis in LTC in Kentucky; small number of events; VOI R.1
17	Shinde	NVX-CoV2372 VE showed VE 50.4% (95% CI, 16.6 to 70.5) against symptomatic infection 7 days after 2nd dose.	Moderate quality (RCT)	RCT in South Africa; 4387 participants; 38/41 cases VOC Beta
18	Hitchings	CoronaVac showed VE of 35.1% (95% CI, -6.6 to 60.5) against infection in HCW after 1st dose.	Moderate	Case-control study in HCWs in Manaus; 53,176 participants; 75% prevalence of Gamma; 776 (28%) of 2797 PCR were used for the case-controls; rate of previous infection high in the population
19	Heath	NVX-CoV2373 showed VE 89.7% (95% CI, 80.2 to 94.6) against infection after 2nd dose. No hospitalizations or deaths in vaccinated group.	Moderate quality (RCT)	RCT; 15,187 participants in UK Post hoc: VE 86.3% (95% CI, 71.3 to 93.5) against Alpha variant; 10 cases in vaccinated participants; 66 infections confirmed Alpha; 11 infections no sequencing available
20	Ismail	BNT162b2 showed VE 81% (95% CI, 76 to 85) against hospitalization 28 days after 1st dose and 93% (95% CI,89 to 95) 14 days after the 2nd dose for people 80+. ChAdOx1 showed VE 73% (95% CI, 60 to 81) against hospitalization 28 days after 1st dose; sample size too small to report VE after 2nd dose for people 80+.	Moderate	Screening study in UK; 13,907 hospitalized patients; results for age 80+; time and setting for VOC Alpha
21	Bernal (2) *Delayed exclusion – critical ROB	BNT162b2 showed VE 44% (95% CI, 32 to 53) after 1st dose and 69% (95% CI, 31 to 86) after 2nd dose against symptomatic infection in 70+. Single dose ChAdOx1 showed VE 55% (95% CI, 41 to 66) against death.	Critical	Data-linkage study in England; 48,096 cases above age 70+; 12.7% BNT162b2 and 8.2% ChAdOx1; VE also reported for 80+ and LTC; time and setting for VOC Alpha
22	Chodick	BNT162b2 showed VE 90% (95% CI, 79 to 95) against infection and VE 94% (95% CI, 88 to 97) against death 7-27 days after 2nd dose; 71% (95% CI, 37 to 87) in immunosuppressed.	Moderate	Data-linkage study in Israel (Maccabi Health Care Organization); 1,178,597 participants; compared time

				frames to estimate effectiveness against Alpha
23	Chung	BNT162b2 or mRNA-1273 showed VE 61% (95% CI, 56 to 66) against symptomatic infection by VOC Alpha 14 days after 1st dose and 90% (95% CI, 85 to 94) 7 days after 2nd dose; 43% (95% CI, 22 to 59) against symptomatic infection by VOC Beta or Gamma 14 days after 1st dose and 88% (95% CI, 61 to 96) 7 days after 2nd dose.	Moderate	Test-negative study in Ontario 324,033 participants; limitations in symptom collection; screening for variants started 2 months into study period; results also reported for age>70 and according to vaccine (but not according to confirmed variant)
24	Bailly *Delayed exclusion – critical ROB	BNT162b2 showed VE 50% (95% CI, 34 to 73) against infection with VOC Beta >28 days after 2 doses.	Critical	Outbreak in a single LTC in France; 90 participants; all samples genome sequenced for VOC Beta; 2 deaths in vaccinated group
25	Angel	BNT162b2 showed VE 97% (95% CI, 94 to 99) against symptomatic infection and 86% (95% CI, 69 to 93) against asymptomatic infection ≥ 7 days after 2 doses in HCW.	Moderate	Retrospective cohort at a single centre tertiary medical centre in Israel, 6,710 participants; testing strategy was different between vaccinated and unvaccinated; time and setting for VOC Alpha
26	Bianchi	BNT162b2 showed VE 61.9% (95% CI, 19.2 to 82) against infection 14 to 20 days after 1st dose; 96% (95% CI, 82.2 to 99.1) ≥ 7 days after 2nd dose in HCW.	Moderate	Data-linkage, single centre medical centre in Italy, 2,034 participants; time and setting for VOC Alpha
27	Yassi	BNT162b2 (93%) or mRNA-1273 showed VE 37.2% (95% CI, 16.6 to 52.70) against infection by VOC Beta or Gamma 14 to 42 days after 1st dose and 79.2% (95% CI, 64.6 to 87.8) 7 days after 2nd dose in HCW.	Moderate	Data-linkage, 25,558 Canadian HCW; evenly split between VOC Gamma and VOC Beta by end of study period
28	Bernal (1)	BNT162b2 showed VE 60% (95% CI, 40 to 73) against confirmed symptomatic infection by VOC Alpha at least 28 days after 1st dose and 90% (95% CI, 84 to 94) at least 14 days after 2nd dose for people 70+.	Serious	Test-negative in England, 156,930 participants; spike gene target failure as proxy for confirmed VOC Alpha
29	Bernal (3)	BNT162b2 showed VE 47.5% (95% CI, 41.6 to 52.8) at least 21 days after 1st dose and VE 93.7% (95% CI, 91.6 to 95.3) at least 14 days after 2nd dose against symptomatic infection by confirmed VOC Alpha. ChadOx1showed VE 48.7% (95% CI, 45.2 to 51.9) at least 21 days after 1st dose and VE 74.5% (95% CI, 68.4 to 79.4) at least 14 days after 2nd dose	Serious	Test-negative in England; 19,109 sequenced cases: 14,837 Alpha and 4,272 Delta.

		against symptomatic infection by confirmed VOC Alpha. BNT162b2 showed VE 35.6% (95% CI, 22.7 to 46.4) at least 21 days after 1st dose and VE 88% (95% CI, 85.3 to 90.1) at least 14 days after 2nd dose against symptomatic infection by confirmed VOC Delta. ChAdOx1 showed VE 30% (95% CI, 24.3 to 35.3) at least 21 days after 1st dose and VE 67% (95% CI, 61.3 to 71.8) at least 14 days after 2nd dose against symptomatic infection by confirmed VOC Delta.		
30	Ranzani	CoronaVac reduced risk of symptomatic infection by VOC Gamma VE 41.6% (95% CI, 26.9 to 63.3) ≥ 14 days after 2nd dose for people 70+.	Moderate	Test-negative in Brazil; 44,055 participants; sequencing not performed; effectiveness declined with age; time and setting for VOC Gamma
31	Andrejko (2)	BNT162b2 and mRNA-1273 showed VE 86.8% (95% CI, 68.6 to 94.7) and VE 86.10% (95% CI, 69.1 to 93.9), respectively, against infection 15 days after 2nd dose.	Moderate	Test-negative in California; 1,023 participants; expansion of sample size and timeline since previous study by same authors; self-reported vaccine receipt; VOC Alpha, Epsilon
32	Emborg	BNT162b2 showed VE 53-86% against infection across high-risk groups, VE 75-87% against hospitalization across high-risk groups, VE 89% (95% CI, 81 to 93) against death in LTCF residents and VE 97% (95% CI, 88 to 99) against death in 65+ requiring personal care 7 days after 2nd dose.	Serious	Data-linkage population study of high-risk groups in Denmark; 864,096 participants; sample confirmed VOC Alpha
33	Salo	BNT162b2 showed VE 42.9% (95% CI, 22.3 to 58.1) against infection in unvaccinated household members of vaccinated HCW 10 weeks after 1st dose.	Moderate	Data-linkage for household contacts of HCW in Finland; 52,766 spouses of vaccinated HCW; time and setting for VOC Alpha
34	Shrestha	BNT162b2 or mRNA-1273 showed VE 97.1% (95% CI, 94.3 to 98.5) against infection ≥14 days after 2nd dose (based on multivariable model).	Moderate	Retrospective cohort of employees of a health care system in Ohio; 46,866 participants (60%) vaccinated by end of study; time and setting for VOC Alpha
35	Skowronski	BNT162b2 (85%) or mRNA-1273 showed VE 67% (95% CI, 57 to 75) against infection by confirmed VOC Alpha ≥21 days after 1st dose for 70+.	Serious	Test-negative in Canada; 16,993 specimens; out of 1,131 genetically sequenced: 45% VOC Alpha and 28% Gamma;

		BNT162b2 (85%) or mRNA-1273 showed VE 61% (95% CI, 45 to 72) against infection by confirmed VOC Gamma ≥21 days after 1st dose for 70+.		limitations in symptom collection and assessment for covariates; results reported by vaccine but not according to confirmed variant
36	Abu-Raddad	BNT162b2 showed VE 89.5% (95% CI, 85.9 to 92.3) against infection, VE 100% (95% CI, 81.7 to 100) against any severe, critical, or fatal disease by VOC Alpha ≥ 14 days after 2nd dose. BNT162b2 showed VE 75% (95% CI, 70.5 to 78.9) against infection, VE 100% (95% CI, 73.7 to 100) against severe, critical, or fatal disease by VOC Beta ≥ 14 days after 1st dose.	Serious	Test-negative in Qatar; 17,293 cases; sequencing showed 50% VOC Beta and 45% VOC Alpha between February-March 2021
37	Akhrass *Delayed exclusion - failure to report outcomes of interest for this LES	BNT162b2 or mRNA-1273 showed overall VE 60.4% (95% CI, 30 to 77.6) against symptomatic infection ≥ 14 days after 1st dose; BNT162b2 or mRNA-1273 showed overall VE 95.7% (95% CI, 90 to 98.2) against symptomatic infection ≥ 14 days after 2nd dose.	Critical	Retrospective cohort of HCW at a single centre in Kentucky, USA; 2,134 participants; time and setting for VOC Alpha
38	Sheikh	BNT162b2 showed VE 30% (95% CI, 17 to 41) against confirmed VOC Delta infection and VE 33% (95% CI, 15 to 47) against symptomatic infection at least 28 days after 1st dose; VE 79% (95% CI, 75 to 82) against infection and VE 83% (95% CI, 78 to 87) against symptomatic infection at least 14 days after 2nd dose. ChAdOx1 showed VE 18% (95% CI, 9 to 25) against confirmed VOC Delta infection and VE 33% (95% CI, 23 to 41) against symptomatic infection at least 28 days after 1st dose; VE 60% (95% CI, 53 to 66) against infection and VE 61% (95% CI, 51 to 70%) against symptomatic infection at least 14 days after 2nd dose.	Moderate	Test-negative in Scotland; 626,900 specimens; also compared hospitalization rates between S gene positive (VOC Delta) and S gene negative specimens within 14 days of positive test result (not summarized here)
39	Furer *Delayed exclusion – critical risk of bias	BNT162b2 reported no symptomatic infections in the vaccinated group (0/686) compared to 0.83% infections in the vaccinated general population control group.	Critical	Prospective cohort of adults with autoimmune inflammatory rheumatic diseases in Israel; 686 participants; time and setting for VOC Alpha

40	Martinez-Baz	BNT162b2 showed VE 65% (95% CI, 56 to 73) against infection and VE 94% (95% CI, 60 to 99) against hospitalization at least 14 days after 2nd dose in close contacts of COVID+ index cases. ChAdOx1 showed VE 44% (95% CI, 31 to 54) against infection and VE 92% (95% CI, 46 to 99) against hospitalization at least 14 days after 1st dose in close contacts of index cases. Second dose results not reported.	Serious	Prospective cohort of close contacts of COVID+ people in Spain; 20,961 participants; VOC Alpha confirmed for small sample; sample size for Moderna too small to report results separately
41	Chodick (2)	BNT162b2 showed VE 51.4% (95% CI, 16.3 to 71.8) against infection 13 to 24 days after 1st dose.	Serious	Data-linkage study in Israel (Maccabi Health Care Services); 351,897 participants; time and setting for VOC Alpha
42	Stowe	BNT162b2 showed VE 94% (95% CI, 46 to 99) at least 21 days after 1st dose and VE 96% (95% CI, 86 to 99) at least 14 days after 2nd dose against hospitalization by confirmed VOC Delta. ChAdOx1 showed VE 71% (95% CI, 51 to 83) at least 21 days after 1st dose and VE 92% (95% CI, 75 to 97) 14 days after 2nd dose against hospitalization by confirmed VOC Delta.	Serious	Same cohort as Bernal (3) with extended time frame for symptomatic infection and adding in data-linkage to hospitalization; 14,019 participants; sample confirmed VOC Delta
43	Saciuk	BNT162b2 showed VE 93% (95% CI, 92.6 to 93.4) against infection, VE 93.4% (95% CI, 91.9 to 94.7) against hospitalization and VE 91.1% (95% CI, 86.5 to 94.1) against death at least 7 days after 2nd dose	Serious	Retrospective cohort of members of a health management organization in Israel; 1,650,885 participants; time and setting for VOC Alpha
44	Zacay *Delayed exclusion – critical risk of bias	BNT162b2 showed VE 61% (95% CI, 49 to 71) at least 14 days after 1st dose and VE 89% (95% CI, 82 to 94) at least 7 days after 2nd dose against infection	Serious	Retrospective cohort of a subpopulation of members of a health management organization in Israel who had undergone repeated PCR testing; 6,286 participants; time and setting for VOC Alpha
45	Azamgarhi	BNT162b2 showed VE 70% (95% CI, 6 to 91) against infection at least 14 days after 1st dose	Serious	Single centre cohort study of HCW in UK; 2,260 participants; time and setting for VOC Alpha
46	Lumley	BNT162b2 (63%) or ChAdOx1showed VE 64% (95% CI, 50 to 74) 14 days after 1st dose and VE 90% (95% CI, 62 to 98) 14 days after 2nd dose against infection	Serious	Prospective cohort of HCWs in Oxfordshire, UK; 13,109 participants; confirmed VOC Alpha

47	Nasreen	BNT162b2 showed VE 89% (95% CI, 86 to 91) against symptomatic infection and VE 95% (95% CI, 92 to 97) against hospitalization at least 7 days after 2nd dose (VOC Alpha); VE 84% (95% CI, 69 to 92) against symptomatic infection and VE 95% (95% CI, 81 to 99) against hospitalization at least 7 days after 2nd dose (VOC Beta/Gamma); VE 87% (95% CI, 64 to 95) against symptomatic infection at least 7 days after 2nd dose (VOC Delta). BNT162b2 showed VE 78% (95% CI, 65 to 86) against hospitalization at least 7 days after 2nd dose (VOC Delta). mRNA-1273 showed VE 92% (95% CI, 86 to 96) against symptomatic infection and VE 94% (95% CI, 89 to 97) against hospitalization at least 7 days after 2nd dose (VOC Alpha). mRNA-1273 showed VE 77% (95% CI, 63 to 86) against symptomatic infection and VE 89% (95% CI, 73 to 95) against hospitalization at least 14 days after 1st dose (VOC Beta/Gamma); VE 72% (95% CI, 57 to 82) against symptomatic infection and VE 96% (95% CI, 72 to 99) against hospitalization at least 14 days after 1st dose (VOC Delta). ChAdOx1 showed VE 64% (95% CI, 60 to 68) against symptomatic infection and VE 85% (95% CI, 81 to 88) against hospitalization at least 14 days after 1st dose (VOC Alpha); VE 48% (95% CI, 28 to 63) against symptomatic infection and VE 83% (95% CI, 66 to 92) against hospitalization at least 14 days after 1st dose (VOC Beta/Gamma); VE 67% (95% CI, 44 to 80) against symptomatic infection and VE 88% (95% CI, 60 to 96) against hospitalization at least 14 days after 1st dose (VOC Delta).	Moderate	Test-negative study in Ontario 421,073 participants (same population as for Chung but extended to May 2021 and more detailed with respect to reporting of VOC); limitations in symptom collection; screening for VOC Alpha, Beta/Gamma and Delta varied during study period
48	Gazit	BNT162b2 showed VE 80% (95% CI, 73 to 85) at least 7 days after 2nd dose against infection in vaccinated	Serious	Retrospective cohort of household members (household = 2 adults with no children) of a health management organization

		household members of a confirmed COVID+ case.		in Israel; 173,569 households; time and setting for VOC Alpha
49	Jara	CoronaVac showed VE 65.9% (95% CI, 65.2 to 66.6) against infection and VE 86.3% (95% CI, 84.5 to 87.9) against death at least 14 days after 2nd dose.	Moderate	Prospective cohort in Chile; 10.2 million participants; time and setting for VOC Gamma
50	Chemaitelly	mRNA-1273 showed VE 88.1% (95% CI, 83.7 to 91.5) and VE 100% (95% CI, 91.8 to 100) against infection by confirmed VOC Alpha at least 14 days after 1st and 2nd dose, respectively. mRNA-1273 showed VE 61.3% (95% CI, 56.5 to 65.5) and VE 96.4% (95% CI, 91.9 to 98.7) against infection by confirmed VOC Beta at least 14 days after 1st and 2nd dose, respectively. mRNA-1273 showed VE 81.6% (95% CI, 71.0 to 88.8) and VE 95.7% (95% CI, 73.4 to 99.9) against severe, critical, or fatal disease at least 14 days after 1st and 2nd dose, respectively (combined VOC Alpha and Beta).	Serious	Test-negative in Qatar; >75,000 participants; sample genome sequenced for VOC Alpha and VOC Beta
51	Baum	BNT162b2 or mRNA-1273 showed VE 41% (95% CI, 25 to 54) against infection ≥ 21 days after 1st dose; BNT162b2 or mRNA-1273 showed VE 75% (95% CI, 65 to 82) against infection ≥ 7 days after 2nd dose in age 70+. BNT162b2 or mRNA-1273 showed VE 41% (95% CI, 17 to 58) against infection ≥ 21 days after 1st dose; BNT162b2 or mRNA-1273 showed VE 77% (95% CI, 65 to 85) against infection ≥ 7 days after 2nd dose in chronically ill (age 16-69). ChAdOx1 showed VE 24% (95% CI, -1 to 43) against infection ≥ 21 days after 1st dose in chronically ill (age 16-69).	Serious	Data-linkage study in Finland; 901,092 participants age 70+ and 774,526 participants age 16 to 69 years with chronic illness; time and setting for VOC Alpha; results for mRNA vaccines not reported separately
52	Balicer	BNT162b2 showed VE 86.1% (95% CI, 82.4 to 89.1) against infection; VE 89% (95% CI, 43 to 100) against hospitalization 7 to 56 days after 2nd dose.	Serious	Data-linkage study of pregnant women over age 16 in Israel (same database as Dagan); 21,722 participants; time and setting for Alpha.

		Too few events to report VE for severe disease or death.		
53	Mateo-Urdiales	BNT162b2 (61%) or ChAdOx1 (31%) or mRNA-1273 (7%) or Ad26.COV$_2$-S (0.6%) showed VE 78% (95% CI, 76 to 79) against infection 42 to 49 days after at least 1st dose; VE 93% (95% CI, 89 to 96) against death 35 to 42 days after at least 1st dose.	Serious	Data-linkage study in Italy; 13,721,506 participants; time and setting for VOC Alpha. Results not reported by vaccine and some participants (42%) who also received 2nd dose were included in estimates.
54	Goldshtein	BNT162b2 showed VE 78% (95% CI, 57 to 89) against infection at least 28 days after 1st dose.	Serious	Data-linkage study of pregnant women in Israel (same database as Gazit); 15,060 participants; time and setting for VOC Alpha.
55	Mason	BNT162b2 showed VE 55.2% (95% CI, 40.8 to 66.8) and VE 70.1% (95% CI, 55.1 to 80.1) against infection 21 to 27 days and 35 to 41 days after 1st dose, respectively.	Moderate	Case-control study of age 80-83 vs 76-79 community-dwelling unvaccinated residents in England; time and setting for VOC Alpha
56	Fabiani	BNT162b2 showed VE 84.1% (95% CI, 39.7 to 95.8) and VE 85.4% (95% CI, -35.3 to 98.4) against infection 14 to 21 days and ≥21 days after 1st dose, respectively in HCW. BNT162b2 showed VE 95.1% (95% CI, 62.4 to 99.4) against infection ≥7 days after 2nd dose in HCW.	Serious	Retrospective cohort of HCW in Italy; 6,423 participants; time and setting for VOC Alpha
57	Chia	BNT162b2 or mRNA-1273 showed VE 92.7% (95% CI, 65.7 to 98.4) against severe disease (defined as requiring supplemental oxygen) > 14 days after 2nd dose.	Serious	Retrospective cohort of confirmed VOC Delta admitted to hospital (including asymptomatic) in Singapore; 218 participants; not reported by vaccine and non-m-RNA vaccine outcomes excluded
58	Kaur *Delayed exclusion – critical ROB	Two doses of Covishield showed VE 87% (95% CI, 33 to 97) against severe disease when compared with one dose (timing of doses not reported).	Critical	Preliminary report of prospective cohort in India; 1500 participants; time and setting for VOC Delta
59	Pramod	Covishield showed VE 49% (95% CI, 17 to 68) against infection 21 days after 1st dose and VE 54% (95% CI, 27 to 71) against infection 14 days after 2nd dose. Covishield showed VE 58% (95% CI, 28 to 75) against symptomatic infection 21 days after 1st dose and VE 64% (95%	Serious	Test-negative study in a single hospital site in India; 360 matched pairs (203 symptomatic pairs); time and setting for VOC Delta

		CI, 38 to 78) against symptomatic infection 14 days after 2nd dose.		
60	Carazo	BNT162b2 or mRNA-1273 showed VE 60% (95% CI, 53.6 to 65.5) against infection by confirmed VOC Alpha 14 days after 1st dose. BNT162b2 or mRNA-1273 showed VE 92.6% (95% CI, 87.1 to 95.8) against infection by confirmed VOC Alpha 7 days after 2nd dose.	Serious	Test-negative study in Quebec, Canada; 58,476 participants; sample confirmed VOC Alpha; reported according to vaccine but not for Alpha at same time
61	Williams	BNT162b2 or mRNA-1273 showed VE 52.5% (95% CI, 26.9 to 69.1) against infection and VE 78.6% (95% CI, 47.9 to 91.2) against severe disease 14 days after 2nd dose in residents at LTCF. Two deaths in vaccinated residents but were palliative prior to infection. BNT162b2 or mRNA-1273 showed VE 66.2% (95% CI, 2.3 to 88.3) against infection 14 days after 2nd dose in staff at LTCF. None of the staff developed severe disease.	Serious	Outbreak in a single LTCF in Ontario; 60 residents and 83 staff; sample confirmed VOC Gamma
62	Hitchings(2) *Delayed exclusion – critical ROB	ChAdOx1 showed VE 33.4% (95% CI, 26.4 to 39.7) against symptomatic infection and VE 50.9% (95% CI, 33.6 to 63.8) against ICU admission and VE 61.8% (95% CI, 48.9 to 71.4) against death at least 28 days after 1st dose for 60+. ChAdOx1 showed VE 77.9% (95% CI, 69.2 to 84.2) against symptomatic infection and VE 89.9% (95% CI, 70.9 to 96.5) against ICU admission and VE 93.6% (95% CI, 81.9 to 97.7) against death at least 14 days after 2nd dose.	Critical	Test-negative study in Sao Paulo, Brazil; 61,164 participants over age 60; time and setting for VOC Gamma
63	Tang	BNT162b2 showed VE 65.5% (95% CI, 40.9 to 79.9) against infection ≥ 14 days after 1st dose; BNT162b2 showed VE 59.6% (95% CI, 50.7 to 66.9) against infection ≥ 14 days after 2nd dose. BNT162b2 showed VE 100% (95% CI, not reported) against severe, critical or fatal disease ≥ 14 days after 1st dose; BNT162b2 showed VE 97.3% (95%	Serious	Test-negative study in Qatar; 1,140,337 participants; weekly random sequencing of positive samples for VOC Delta

		CI, 84.4 to 99.5) against severe, critical or fatal disease ≥ 14 days after 2nd dose. mRNA-1273 showed VE 79.7% (95% CI, 60.8 to 89.5) against infection ≥ 14 days after 1st dose; mRNA-1273 showed VE 86.1% (95% CI, 78.0 to 91.3) against infection ≥ 14 days after 2nd dose. mRNA-1273 showed VE 100% (95% CI, not reported) against severe, critical or fatal disease ≥ 14 days after 1st dose; mRNA-1273 showed VE 100% (95% CI, not reported) against severe, critical or fatal disease ≥ 14 days after 2nd dose.		
64	Puranik	BNT162b2 showed VE 42% (95% CI, 13 to 62) against infection 14 days after 2nd dose. mRNA-1273 showed VE 76% (95% CI, 58 to 87) against infection 14 days after 2nd dose.	Serious	Data-linkage study involving Mayo Clinic Health in USA; 25,859 matched triples from Minnesota only; time and setting for Delta at end of study time frame so only last month of data (July 2021) reported here
65	Elliot	BNT162b2 or ChAdOx1 showed VE 64% (95% CI, 11 to 85) against infection unreported number of days after 2nd dose (Round 12: 2021-05-20 to 2021-06-07). BNT162b2 or ChAdOx1 showed VE 49% (95% CI, 22 to 67) against infection unreported number of days after 2nd dose (Round 13: 2021-06-24 to 2021-07-12).	Serious	Surveillance study in England; 121,872 participants; time and setting for VOC Delta; only included data from aged 18 to 64 years due to lowest risk for misclassification bias due to self-reported vaccination status
66	Issac	ChAdOx1 showed VE 85% (95% CI, 71 to 92) against infection 14 days after 2nd dose.	Serious	Prospective cohort of HCW at a single hospital in India; 342 participants; time and setting for VOC Delta.
67	Marco *Delayed exclusion – critical ROB	ChAdOx1 showed VE 23% (95% CI, not reported) against infection at least 21 days after 1st dose.	Critical	Outbreak study of prison inmates in Barcelona; 217 participants (184 inmates); sequenced for VOC Alpha
68	Kale *Delayed exclusion – critical ROB	ChAdOx1 showed VE 60% (95% CI, 45 to 70) against infection at least 14 days after 2nd dose.	Critical	Prospective cohort of HCW at a single hospital in India; 1858 participants; sample sequenced for VOC Delta
69	Israel	BNT162b2 showed OR 2.06 (95% CI, 1.69 to 2.51) for infection comparing	Moderate	Retrospective cohort of fully vaccinated (>14 days after 2nd

		fully vaccinated longer than or equal to 146 days vs fully vaccinated less than 146 days.		dose) members of a health management organization in Israel who underwent testing; 33,993 participants; time and setting for VOC Delta
70	Gram	ChAdOx1 showed VE 44% (95% CI, 29 to 56) against infection 21 to 27 days after 1st dose. No deaths in vaccinated participants. First dose ChAdOx1 followed by second dose BNT162b2 or mRNA-1273 showed VE 88% (95% CI, 83 to 92) against infection ≥ 14 days after 2nd dose.	Serious	Data-linkage study in Denmark; 5,542,079 participants; time and setting for VOC Alpha
71	Pouwels	BNT162b2 showed VE 59% (95% CI, 52 to 65%) against infection ≥21 days after 1st dose and VE 78% (95% CI, 68 to 84) against infection ≥ 14 days after 2nd dose (VOC Alpha age 18+). BNT162b2 showed VE 57% (95% CI, 50 to 63) against infection ≥21 days after 1st dose and VE 80% (95% CI, 77 to 83) against infection ≥ 14 days after 2nd dose (VOC Delta age 18+). ChAdOx1 showed VE 63% (95% CI, 55 to 69) against infection ≥21 days after 1st dose and VE 79% (95% CI, 56 to 90) against infection ≥ 14 days after 2nd dose (VOC Alpha age 18+). ChAdOx1 showed VE 46% (95% CI, 35 to 55) against infection ≥21 days after 1st dose and VE 67% (95% CI, 62 to 71) against infection ≥ 14 days after 2nd dose (VOC Delta age 18+). mRNA-1273 showed VE 75% (95% CI: 64 to 83) against infection ≥21 days after 1st dose (VOC Delta age 18 to 64).	Serious	Survey of randomly selected private households with longitudinal follow-up in UK; 743,526 participants; also reported for 18-64 years; sample sequenced for VOC Alpha and VOC Delta
72	Abu-Raddad (2)	BNT162b2 after prior infection showed VE 85% (95% CI, 80 to 89) against re-infection compared to BNT162b2 without prior infection. mRNA-1273 after prior infection showed VE 15% (95% CI, -105 to 66)	Serious	Retrospective matched cohorts (2) of fully vaccinated (>14 days after 2nd dose) in Qatar; 151,076 participants; sample sequenced for VOC Alpha and VOC Beta

		against re-infection compared to mRNA-1273 without prior infection.		
73	Gazit (2)	BNT162b2 showed OR 13.06 (95% CI, 8.08 to 21.11) against infection and OR 27.02 (95% CI, 12.7 to 57.5) against symptomatic disease compared to prior infection.	Moderate	Retrospective matched cohorts of fully vaccinated (>14 days after 2nd dose) in Israel; 778,658 participants; time and setting for VOC Delta
74	Rosenberg	BNT162b2 (51%), mRNA-1273 (40%) or Ad26.COV2.S (9%) showed VE 91.7% against infection ≥14 days after 2nd dose (Week of May 3, 2021: VOC Alpha). BNT162b2 (51%), mRNA-1273 (40%) or Ad26.COV2.S (9%) showed VE 79.8% against infection ≥14 days after 2nd dose (Week of July 19, 2021: VOC Delta).	Serious	Surveillance report in New York, USA; >13 million participants; time and setting for VOC Delta (from 2% to 80% during study period)
75	Al-Qahtani	BNT162b2 ≥14 days after 2nd dose, showed VE 99.9% (95% CI, 99.2 to 100) against ICU admission, and VE 99.5% (95% CI, 98.4 to 99.8) against death (VOC Alpha and Delta). ChAdOx1 ≥14 days after 2nd dose, showed VE 99.2% (95% CI, 97.6 to 99.7) against ICU admission, and VE 99.6% (95% CI, 97.2 to 100) against death (VOC Alpha and Delta). BBIBP-CorV ≥14 days after 2nd dose, showed VE 95.4% (95% CI, 94.6 to 96.2) against ICU admission, and VE 94.3% (95% CI, 93.1 to 95.4) against death (VOC Alpha and Delta). Sputnik V ≥14 days after 2nd dose, showed VE 100% (95% CI, 99.2 to 100) against ICU admission, and VE 99.5% (95% CI, 98.5 to 99.9) against death (VOC Alpha and Delta).	Serious	Retrospective cohort of fully vaccinated (>14 days after 2nd dose) in Bahrain; 1,242,279 participants; time and setting for VOC Alpha (dominant before May 2021) and Delta (dominant after May 2021).
76	Goldberg (2)	BNT162b2 showed VE 50% (95% CI, 45 to 55) for those vaccinated in January 2021, and VE 73% (95% CI, 67 to 78) for those vaccinated in May 2021 against infection after the 2nd dose (VOC Delta age 16 to 39). BNT162b2 showed VE 58% (95% CI, 54 to 62) for those vaccinated in	Serious	Data-linkage study of fully vaccinated in Israel; 4,785,245 fully vaccinated participants; time and setting for VOC Delta (dominant after May 2021).

		January 2021, and VE 80% (95% CI, 71 to 86) for those vaccinated in May 2021 against infection after the 2nd dose (VOC Delta age 40 to 59). BNT162b2 showed VE 57% (95% CI, 52 to 62) for those vaccinated in January 2021, and VE 75% (95% CI, 58 to 85) for those vaccinated in May 2021 against infection after the 2nd dose (VOC Delta age 60+). BNT162b2 showed VE 94% (95% CI, 87 to 97) for those vaccinated in January 2021, and VE 98% (95% CI, 94 to 99) for those vaccinated in March 2021 against severe, critical, or fatal disease after the 2nd dose (VOC Delta age 40 to 59). BNT162b2 showed VE 86% (95% CI, 82 to 90) for those vaccinated in January 2021, and VE 91% (95% CI, 85 to 95) for those vaccinated in March 2021 against severe, critical, or fatal disease after the 2nd dose (VOC Delta age 60+).		
77	Herlihy *Delayed exclusion – critical risk of bias	BNT162b2, mRNA-1273, or Ad26.COV2.S showed VE 78% (95% CI, 71 to 84) in Mesa County and VE 89% (95% CI, 88 to 91) in other Colorado counties against symptomatic infection an unreported number of days after 2nd dose (VOC Delta).	Critical	Surveillance report in Mesa County-Colorado, USA; 37,439 cases participants; sample sequenced for VOC Delta (43% to 88% during study period)
78	Ghosh *Delayed exclusion – critical risk of bias	ChAdOx1 showed unadjusted VE 75.2% (95% CI, 73.8 to 76.8) against infection ≥14 days after 1st dose, and unadjusted VE 54.6% (95% CI, 52.6 to 56.6) ≥14 days after 2nd dose against infection in HCW (VOC Alpha to Delta).	Critical	Retrospective cohort of Armed Forces HCW and frontline workers in India; 1,595,630 participants; time and setting for VOC Delta at end of study only.
79	Amirthalingam	BNT162b2 showed VE 77% (95% CI, 56 to 88) against symptomatic infection when 2nd dose given 19-29 days after 1st dose, and VE 94% (95% CI, 73 to 99) against symptomatic infection when 2nd dose given 85+ days after 1st dose (VOC Alpha age 80+).	Moderate	Test-negative study in England; time and setting for VOC Alpha (dominant before May 2021) and Delta (dominant after May 2021).

		BNT162b2 showed VE 77% (95% CI, 66 to 85) against symptomatic infection when 2nd dose given 19-29 days after 1st dose, and VE 86% (95% CI, 70 to 94) against symptomatic infection when 2nd dose given 85+ days after 1st dose (VOC Alpha age 65 to 79). ChAdOx1 showed VE 96%(95% CI, 72 to 100) against infection when 2nd dose given 19-29 days after 1st dose, and VE 88% (95% CI, 48 to 97) against infection when 2nd dose given 85+ days after 1st dose after 2nd dose (VOC Alpha age 80+). ChAdOx1 showed VE 66% (95% CI, 47 to 77) against infection when 2nd dose given 19-29 days after 1st dose, and VE 73% (95% CI, 56 to 83) against infection when 2nd dose given 85+ days after 1st dose after 2nd dose (VOC Alpha age 65 to 79).		
80	Butt (2) *Delayed exclusion – critical ROB	Unvaccinated participants had HR 2.84 (95% CI, 1.80 to 4.47) of severe disease compared to BNT162b2 ≥14 days after 2nd dose.	Critical	Case-control study in Qatar; 456 matched cases; time and setting for VOC Alpha
81	Fowlkes	BNT162b2 (65%), mRNA-1273 (33%), or Ad26.COV2.S (2%) showed VE 91% (95% CI, 81 to 96) against infection ≥ 14 days after 2nd dose (during time of VOC Alpha). BNT162b2 (65%), mRNA-1273 (33%), or Ad26.COV2.S (2%) showed VE 66% (95% CI, 26 to 84) against infection ≥ 14 days after 2nd dose (during time of VOC Delta). BNT162b2 (65%), mRNA-1273 (33%), or Ad26.COV2.S (2%) showed VE 85% (95% CI, 68 to 93) against infection 14-119 days after full vaccination) and VE 73% (95% CI, 49 to 86) against infection ≥150 days after full vaccination (during time of VOC Alpha to Delta).	Moderate	Prospective cohort of HCW and other essential frontline workers in 6 states in the USA; 7,112 participants; updated report to cover VOC Delta period
82	Bhattacharya	Covaxin (94%) and Covishield showed VE 83% (95% CI, 73 to 89) against	Serious	Prospective cross-sectional cohort of HCW and their

		symptomatic infection ≥ 14 days after 2nd dose. Covaxin (94%) and Covishield showed VE 93% (95% CI, 64 to 99) against ICU admission or death ≥ 14 days after 2nd dose.		families at a single site in India; 638 participants (55 inpatients); time and setting of VOC Delta
83	Nunes	BNT162b2 (45%) or mRNA-1273 (8%) showed VE 96% (95% CI, 92 to 98) against COVID-related death ≥14 days after 2nd dose (age 65 to 79). BNT162b2 (80%) or mRNA-1273 (2%) showed VE 81% (95% CI, 74 to 87) against COVID-related death ≥14 days after 2nd dose (age ≥80). BNT162b2 (80%) or mRNA-1273 (2%) showed VE 86% (95% CI, 68 to 93) against COVID-related death 14 to 41 days after 2nd dose and VE 74% (95% CI, 60 to 83) against COVID-related death ≥ 98 days after 2nd dose for HR 1.80 (0.77 to 4.25) (age ≥80).	Moderate	Data-linkage study of community-dwelling adults≥65 in Portugal; 2,050,950 participants; time and setting for VOC Alpha to Delta
84	Tartof	BNT162b2 showed VE 75% (95% CI, 71 to 78) against infection 7 days after 2nd dose (confirmed VOC Delta). BNT162b2 showed VE 91% (95% CI, 88 to 92) against infection 7 days after 2nd dose (confirmed non-VOC Delta). BNT162b2 showed VE 93% (95% CI, 85 to 87) against infection 7 to 30 days after 2nd dose and VE 53% (95% CI, 39 to 65) against infection ≥ 127+ days after 2nd dose (confirmed VOC Delta). BNT162b2 showed VE 97% (95% CI, 95 to 99) against infection 7 to 30 days after 2nd dose and VE 67% (95% CI, 45 to 80) against infection ≥ 127+ days after 2nd dose (confirmed non-VOC Delta).	Moderate	Retrospective cohort of members of a health management organization in California; 3,436,957 participants; VOC Alpha to VOC Delta (only 28% confirmed Delta)
85	Li (3)	CoronaVac (combined with other inactivated vaccines) showed VE 59% (95% CI, 16 to 81.6) against symptomatic infection and VE 100% against severe infection ≥14 days after 2nd dose.	Serious	Test-negative study in Guangzhou, China; 366 participants; sample sequenced for VOC Delta

86	Scobie *Delayed exclusion – critical ROB	BNT162b2 or mRNA-1273 (92%), or Ad26.COV2.S showed VE 90% (95% CI not reported) against infection and VE 93% (95% CI not reported) against death ≥ 14 days after 2nd dose (April to June: VOC Alpha). BNT162b2, mRNA-1273, or Ad26.COV2.S showed VE 76% (95% CI not reported) against infection and VE 90% (95% CI not reported) against death ≥ 14 days after 2nd dose (June to July: VOC Delta>50%).	Critical	Surveillance study in 13 states in the USA; 615,454; time and setting for VOC Alpha to VOC Delta
87	Satwik	ChAdOx1 showed VE 18% (95% CI, -10 to 38) against symptomatic infection; VE 37% (-24 to 68) against moderate to severe disease and VE 69% (95% CI, -160 to 97) against death ≥21 days after 1st dose. ChAdOx1 showed VE 28% (95% CI, 10 to 41) against symptomatic infection; VE 67% (44 to 81) against moderate to severe disease and VE 97% (95% CI, 43 to 99.8) against death ≥14 days after 2nd dose.	Serious	Retrospective cohort study of HCW at a single hospital in New Delhi, India; 4276 participants; sample sequenced for VOC Delta
88	Seppala	BNT162b2 (74%) or ChAdOx1 (22%) or mRNA-1273 (10%) showed VE 84.4% (95% CI, 81.8 to 86.5) against infection ≥7 days after 2nd dose (VOC Alpha). BNT162b2 (74%) or ChAdOx1 (22%) or mRNA-1273 (10%) showed VE 64.6% (95% CI, 60.6 to 68.2) against infection ≥7 days after 2nd dose (VOC Delta).	Serious	Population cohort in Norway; 4,204,859 participants; sequenced for VOC Alpha and VOC Delta
89	Polinski *Delayed exclusion – critical ROB	Ad26.COV2.S showed VE* 67% (95% 60 to 73) against infection unknown number of days after dose (June to July: VOC Delta in high prevalence states). *unadjusted for substantial under-reporting of vaccination status	Critical	Data-linkage of members of a medical insurance group in USA; 1,914,670 participants; time and setting for VOC Alpha to Delta (only data for VOC Delta reported here)
90	Chemaitelly (2)	BNT162b2 or mRNA-1273 showed VE 46.6% (95% CI, 0.0 to 73.7) against infection ≥14 days after 2nd dose, VE 66.0% (95% CI, 21.3 to 85.3) ≥42 days after 2nd dose, and VE 73.9% (95% CI,	Serious	Retrospective cohort of immunosuppressed kidney transplant recipients in Qatar; 782 participants; time and setting for VOC Alpha and VOC Beta.

		33 to 98.9) ≥56 days after 2nd dose (VOC Alpha and Beta). BNT162b2 or mRNA-1273 showed VE 72.3% (95% CI, 0.0 to 90.9) against severe, critical, or fatal disease ≥14 days after 2nd dose, VE 85% (95% CI, 35.7 to 96.5) ≥42 days after 2nd dose, and VE 83.8% (95% CI, 31.3 to 96.2) ≥56 days after 2nd dose (VOC Alpha and Beta).		
91	Hu	Inactivated vaccines showed VE 89% (95% CI, 55 to 98) against severe, critical, or fatal disease ≥14 days after 2nd dose (VOC Delta).	Serious	Outbreak report of hospitalized cases in China; 476 participants; PCR population for VOC Delta.
92	Andrews	BNT162b2 showed VE 62.7% (61.7 to 63.8) against symptomatic infection 1 week after 2nd dose and VE 47.3% (45.0 to 49.6) 20+ weeks after 2nd dose (VOC Delta). ChAdOx1showed VE 92.4% (92.1 to 92.7) against symptomatic infection 1 week after 2nd dose and VE 69.7% (68.7 to 70.5) 20+ weeks after 2nd dose (VOC Delta). mRNA-1273 showed VE 95.2% (94.4 to 95.9) against symptomatic infection 1 week after 2nd dose and VE 90.3% (67.2 to 97.1) 10 to 14 weeks after 2nd dose (VOC Delta).	Moderate	Test-negative study in England; 1,475,391 participants; VOC Alpha to VOC Delta (only data for VOC Delta reported here)
93	Patalon	BNT162b2 showed marginal VE 3% (95% CI, -5 to 10) against infection 0 to 6 days after 3rd dose and marginal VE 84.0% (95% CI, 79 to 88) 14 to 20 days after 3rd dose compared to 2 doses.	Moderate	Test-negative study in Israel comparing 2 doses of vaccine versus 3 doses of vaccine; 182,076 participants; time and setting for VOC Delta
94	Kissling	BNT162b2 showed VE 87% (95% CI, 74 to 93) against symptomatic infection 14 days after 2nd dose.	Serious	Test-negative study of adults >65 years in primary care setting in I-MOVE group (England, France, Ireland, the Netherlands, Portugal, Scotland, Spain and Sweden); 4,964 participants; sample sequenced for VOC Alpha.
95	McKeigue	BNT162b2 or mRNA-1273 showed VE 92% (95% CI, 85 to 96) against severe disease in people with no risk conditions and VE 72% (95% CI, 51 to 84) against severe disease in people	Serious	Case-control study of people with clinical risk conditions in Scotland; 50,935 participants; time and setting for VOC Alpha to VOC Delta

		eligible for shielding at least 14 days after 2nd dose. ChAdOx1 showed VE 94% (95% CI, 90 to 96) against severe disease in people with no risk conditions and VE 63% (95% CI, 46 to 75) against severe disease in people eligible for shielding ≥ 14 days after 2nd dose.		
96	Kertes	BNT162b2 showed OR 1.61 (95% CI, 1.45 to 1.79) for infection comparing fully vaccinated Jan to Feb vs fully vaccinated Mar to May.	Serious	Data-linkage study of people fully vaccinated 6 months previously in Israel; 1,423,098 participants; time and setting for VOC Alpha to VOC Delta
97	Barlow	BNT162b2 or mRNA-1273 showed VE 74% (95% CI, 65 to 82) against infection ≥ 14 days after 2nd dose. Ad26.COV2.S showed VE 51% (95% CI, -2 to 76) against infection ≥ 14 days after 2nd dose.	Serious	Test-negative study in Oregon; 1000 participants; time and setting for VOC Delta
98	Chemaitelly (3)	BNT162b2 showed VE 65.8% (95% CI, 63.8 to 67.7) against infection 5 to 9 weeks after 2nd dose; VE 29.7% (95% CI, 21.7 to 36.9) against infection 15 to 19 weeks after 2nd dose and VE 0% (95% CI, 0 to 0) against infection 20 to 24 weeks after 2nd dose. BNT162b2 showed VE 94.2% (95% CI, 91.0 to 96.5) against hospitalization or death 5 to 9 weeks after 2nd dose; VE 86.4% (95% CI, 69.9 to 94.8) against hospitalization or death 15 to 19 weeks after 2nd dose and VE 95.3% (95% CI, 70.5 to 99.9) against hospitalization or death 20 to 24 weeks after 2nd dose.	Serious	Test-negative study in Qatar; 1,472,761 participants; time and setting for VOC Beta to VOC Delta
99	Thompson (3)	BNT162b2 showed VE 90% (95% CI, 86 to 93) against ICU admission ≥14 days after 2nd dose. BNT162b2 showed VE 92% (95% CI, 88 to 94) against hospitalization at 28 to 41 days after 2nd dose and VE 86% (95% CI, 74 to 93) ≥112 days after 2nd dose.	Serious	Test-negative study of adults ≥50 years in the USA; 76,463 participants; time and setting for VOC Alpha

Section 2: excluded studies	
Author	**Reason for exclusion**
Akhrass	Delayed exclusion – Clinical outcomes of interest for this LES not reported
Albahrani	Prevalence of variants unknown and suspected to be <50%
Alencar	Critical risk of bias
Alhamlan	Vaccine effectiveness not reported
Alharbi	Prevalence of variants unknown and suspected to be <50%
Ali	Prevalence of variants unknown and suspected to be <50%
Alkhafaji	Prevalence of variants unknown and suspected to be <50%
Allen	Serious risk of bias
Almufty	Prevalence of variants unknown and suspected to be <50%
Apisarnthanarak	Vaccine effectiveness not reported
Arashiro	Vaccine effectiveness not reported
Ayass	Clinical outcomes of interest for this LES not reported
Baden	Critical risk of bias
Bailly	Delayed exclusion – critical risk of bias
Bajema	Clinical outcomes of interest for this LES not reported
Barchuk	Clinical outcomes of interest for this LES not reported
Bergwerk	Vaccine effectiveness not reported
Bernal (2)	Delayed exclusion – critical risk of bias
Bjork	Prevalence of variants unknown and suspected to be <50%
Blaiszik	Clinical outcomes of interest for this LES not reported
Borobia	Clinical outcomes of interest for this LES not reported
Britton	Prevalence of variants unknown and suspected to be <50%
Brown	Vaccine effectiveness not reported
Bruxvoort	Prevalence of variants unknown and suspected to be <50%
Butt	Prevalence of variants unknown and suspected to be <50%
Butt	Critical risk of bias
Butt (2)	Delayed exclusion – critical risk of bias
Cabezas	Prevalence of variants unknown and suspected to be <50%
Caillard	Clinical outcomes of interest for this LES not reported
Cavanaugh	Delayed exclusion – VOI not VOC
Charmet	Serious risk of bias
Chau	Vaccine effectiveness not reported
Clemens	Prevalence of variants unknown and suspected to be <50%
Corchado-Garcia	Prevalence of variants unknown and suspected to be <50%
Dash	Critical risk of bias
de Gier Brechje	Prevalence of variants unknown and suspected to be <50%
Domi	Prevalence of variants unknown and suspected to be <50%

El Sahly	Prevalence of variants unknown and suspected to be <50%
Ella	Prevalence of variants unknown and suspected to be <50%
El-Sahly	Prevalence of variants unknown and suspected to be <50%
Falsey	Prevalence of variants unknown and suspected to be <50%
Farinholt	Vaccine effectiveness not reported
Fisher	Prevalence of variants unknown and suspected to be <50%
Frenck	Prevalence of variants unknown and suspected to be <50%
Furer	Delayed exclusion – critical risk of bias
Geisen	Clinical outcomes of interest for this LES not reported
Gils	Clinical outcomes of interest for this LES not reported
Gorgels	Prevalence of variants unknown and suspected to be <50%
Gray	Prevalence of variants unknown and suspected to be <50%
Griffin	Vaccine effectiveness not reported
Guijarro	Prevalence of variants unknown and suspected to be <50%
Gupta	Prevalence of variants unknown and suspected to be <50%
Gupta	Vaccine effectiveness not reported
Haas (2)	Modelling study used to estimate cases averted
Hacisuleyman	Critical risk of bias
Hetemaki	Vaccine effectiveness not reported
Hitchings(2)	Delayed exclusion – critical risk of bias
Hollinghurst	Serious risk of bias
Iliaki	Prevalence of variants unknown and suspected to be <50%
Iliaki	Prevalence of variants unknown and suspected to be <50%
Jacobson	Critical risk of bias
John	Prevalence of variants unknown and suspected to be <50%
Jones	Critical risk of bias
Kaabi	Prevalence of variants unknown and suspected to be <50%
Kale	Delayed exclusion – critical risk of bias
Kaur	Delayed exclusion – critical risk of bias
Keegan	Critical risk of bias
Khan	Prevalence of variants unknown and suspected to be <50%
Khawaja	Critical risk of bias
Kojima	Prevalence of variants unknown and suspected to be <50%
Lamprini	Clinical outcomes of interest for this LES not reported
Lefèvre	Critical risk of bias
Li	Phase 1 trial
Li (2)	Clinical outcomes of interest for this LES not reported
Ling	Prevalence of variants unknown and suspected to be <50%
Linsenmeyer	Vaccine effectiveness not reported
Loconsole	Vaccine effectiveness not reported
Luo	Vaccine effectiveness not reported
Marco	Delayed exclusion – critical risk of bias

Mattar	Prevalence of variants unknown and suspected to be <50%
Mazgatos	Critical risk of bias
McEvoy	Prevalence of variants unknown and suspected to be <50%
Menni	Serious risk of bias
Mizrahi	Modelling study
Monge	Prevalence of variants unknown and suspected to be <50%
Mor	Prevalence of variants unknown and suspected to be <50%
Moustsen-Helms	Prevalence of variants unknown and suspected to be <50%
Munitz	Clinical outcomes of interest for this LES not reported
Musser	Vaccine effectiveness not reported
Mutnal	Vaccine effectiveness not reported
Nanduri	Critical risk of bias
Oduwole	Clinical outcomes of interest for this LES not reported
Olmedo	Clinical outcomes of interest for this LES not reported
Palacios	Prevalence of variants unknown and suspected to be <50%
Paris	Prevalence of variants unknown and suspected to be <50%
Pawlowski	Critical risk of bias
Perry	Clinical outcomes of interest for this LES not reported
Pilishville	Prevalence of variants unknown and suspected to be <50%
Piltch-Loeb	Prevalence of variants unknown and suspected to be <50%
Polinski	Delayed exclusion – critical risk of bias
Raches Ella	Phase 1 trial
Rana	Critical risk of bias
Regev-Yochay	Prevalence of variants unknown and suspected to be <50%
Riemersma	Clinical outcomes of interest for this LES not reported
Riley	Critical risk of bias
Rivelli	Clinical outcomes of interest for this LES not reported
Rovida	Critical risk of bias
Rudolph	Prevalence of variants unknown and suspected to be <50%
Salmeron Rios	Prevalence of variants unknown and suspected to be <50%
Sansone	Critical risk of bias
Scobie	Delayed exclusion – critical risk of bias
Sharma	Prevalence of variants unknown and suspected to be <50%
Shimabukuro	Clinical outcomes of interest for this LES not reported
Shrotri	Delayed exclusion – critical risk of bias
Starrfelt	Serious risk of bias
Swift	Prevalence of variants unknown and suspected to be <50%
Tande	Prevalence of variants unknown and suspected to be <50%
Tanriover	Prevalence of variants unknown and suspected to be <50%
Tenforde	Clinical outcomes of interest for this LES not reported
Tenforde (2)	Clinical outcomes of interest for this LES not reported
Thangaraj	Critical risk of bias

Thiruvengadam	Serious risk of bias
Thompson (1)	Prevalence of variants unknown and suspected to be <50%
Thompson (2)	Prevalence of variants unknown and suspected to be <50%
Vahidy	Prevalence of variants unknown and suspected to be <50%
Vasileiou	Clinical outcomes of interest for this LES not reported
Veneti	Clinical outcomes of interest for this LES not reported
Victor	Critical risk of bias
Volkov	Modelling study
Voysey	Prevalence of variants unknown and suspected to be <50%
Waldhorn	Serious risk of bias
Wickert	Critical risk of bias
Williams (2)	Serious risk of bias
Young-Xu	Prevalence of variants unknown and suspected to be <50%
Zacay	Delayed exclusion – critical risk of bias
Zhong	Clinical outcomes of interest for this LES not reported

Appendix 2: Glossary

AZ: AstraZeneca

Alpha: variant of concern B.1.1.7

Beta: variant of concern B.1.351

Delta: variant of concern B.1.617.2

Gamma: variant of concern P.1

Epsilon: variant of concern B.1.427/B.1.429

HCW: Healthcare workers

LTC: Long-term care

LTCF: Long-term care facility

MOD: Moderna

Obs: observational study

OR: odds ratio

PF: Pfizer

RME: range of mean estimates across 2 or more studies

VE (Vaccine effectiveness): measure of how well a vaccine protects people from getting the outcome of interest in real-world practice (For example: VE of 92% against infection means that 92% of people will be protected from becoming infected with COVID and 8% of people will still be at risk of becoming infected with COVID)

VOC: variant of concern

VOI: variant of interest

Appendix 3: Data-extraction template

Vaccine product	
Source	First author of study
Link	DOI or Pubmed ID
Date published	in format YYYY/MM/DD or preprint
Country	
Funding	public or industry
Study details	
Study type	RCT/cohort/data-linkage/test-negative/case-control/other
Surveillance	routine screening Y or N
Population(s)	general public/LTC/Households/HCW/Other
Control group	not vaccinated, <7day vaccinated internal control, none, other
Total (N)	number of all study participants
Female	number or %
LTC	number or %
HCW	number or %
Households	number or %
>80	number or %
>70	number or %
>60	number or %
Outcomes	outcomes separated by VOC type
Outcomes	confirmed infection/asymptomatic/mild symptomatic/severe symptoms/hospitalized/ICU/death
1st Dose VE	VE with 95% CI
Days post 1st dose	days post 1st dose when VE provided
2nd Dose VE	VE with 95% CI
Days post 2nd dose	days post 2nd dose when VE provided
Rates per X person-days/years	vaccinated vs control
HR	vaccinated vs control
RR	vaccinated vs control
Adjusted	Regression, stratification, matching and associated variables
Transmission	infection rates in unvaccinated contacts of vaccinated individuals
Critical appraisal	See Appendix 5

Appendix 4: Process for assigning Variant of Concern to studies

A Variant of Concern is considered to be the dominant (≥50%) strain in a study if any of the following conditions apply:
i) the authors make a statement about prevalence of VOC during the study time frame
ii) time and setting of the study is consistent with a VOC being dominant according to the following open tracking sources:

Nextstrain. Real-time tracking of pathogen evolution. https://nextstrain.org/
Outbreak Info. https://outbreak.info/location-reports

Appendix 5: Research question and critical appraisal process (revised 06 Oct 2021)

Review question:

Participants	People at risk of COVID-19 (usually without but sometimes with previous COVID-19 infection)
Intervention	COVID-19 Vaccine
Comparator	Unvaccinated people (*)
Outcomes	PCR-diagnosis of COVID-19 infection (**); symptomatic disease; hospital/ICU admission; death; transmission

(*) before-after studies, where the infection rate in the first 2 weeks after the vaccination are used as control are (**)
(**) commonly performed and may be appraised confirmation of specific variant, or reasonable evidence the variant was the dominant circulating strain

Critical Appraisal Process

We appraise the quality of the individual studies using an adapted version of ROBINS-I. This tool classifies the Risk of Bias of a study as **Low, Moderate, Serious, Critical, or No Information**. Low Risk of Bias indicates High Quality, and Critical Risk of Bias indicates Very Low (insufficient) Quality. ROBINS-I appraises 7 bias domains and judges each study against an ideal reference randomized controlled trial. To improve the utility of ROBINS-I for assessing studies reporting vaccine effectiveness, we have focused on study characteristics that introduce bias as reported in the vaccine literature. (WHO. Evaluation of COVID-19 vaccine effectiveness. Interim Guidance. 17 March 2021). Studies rated as "serious" or "critical" risk of bias will not be included in the Summary statements on Page 1-2 (exception: if limited data available for an outcome for a VOC). An overall judgement of "serious" or "critical" is given when the study is judged to be at critical risk of bias in at least one domain.

VE Study Characteristics that may introduce bias	Description
Study design ROBINS-I: Bias in selection of participants into study	In cohort studies, people who get vaccinated may differ in health-seeking behaviour from people who do not get vaccinated; using a test-negative study design minimizes this type of bias Examples and typical judgement: • test-negative design with a clearly defined symptomatic study population (low) • test-negative design (mixed or unclear study population) or case-control or cohort design or data-linkage with no concerns (moderate) • cross-sectional design or case-control (concerns about whether controls had same access to vaccines/risk of exposure to COVID or unclear) or cohort design (concerns that exposed and non-exposed were not drawn from the same population) (serious)
Method for confirming vaccination ROBINS-I: Bias in classification of interventions	Questionnaires are prone to recollection bias; Population databases developed for purpose of tracking COVID vaccines minimize this type of bias Examples and typical judgement:

	• database linkage study (low) • Questionnaire with confirmation by an additional method (e.g. registry) of at least a subset of study population (moderate) • Questionnaire without confirmation by an additional method (serious) • Estimating vaccination status based on surveillance data alone (critical)
Databases used for retrieval of COVID test results, participant prognostic factors, and clinical outcomes ROBINS-I: Bias in classification of interventions	Databases developed for collecting data on COVID are less prone to bias due to missing information and m <u>Examples and typical judgement</u>: • database for non-COVID purpose but with individual level data (moderate) • database for non-COVID purpose without individual level data (serious) • no or unclear description of database type (critical)
Assignment of infection start date ROBINS-I: Bias in classification of interventions	Using date of symptom onset (if within 10 days of testing) as infection start date reduces risk of misclassification bias (e.g., vaccinated participant who is reported as COVID+ may have been infected prior to receiving the vaccine or during non-immune period) and sensitivity of assays decreases over time <u>Examples and typical judgement</u>: • using a PCR positive test that was part of an ongoing standardized monitoring system (e.g., within a health network) (low) • using sample date without interview or documented confirmation of symptoms ≤ 10 days (relevant for symptomatic disease only) (serious)
Verification of symptoms ROBINS-I: Bias in classification of interventions	Prospective, standardized collection of symptoms from patients reduces risk of missing information bias; testing within 10 days after symptom onset reduces risk of false-negative COVID test <u>Examples and typical judgement</u>: • using sample date without patient report/ documented confirmation of symptoms ≤ 10 days (relevant for symptomatic disease only) (serious) • if symptomatic COVID is not an outcome (no information)

Accounting for non-immune period (first 14 days after first vaccine dose) ROBINS-I: Bias due to confounding	Reported absence of vaccine effect during non-immune period reduces risk of residual confounding bias Example/common case: • presence of an effect during non-immune period or result not reported (moderate) • unclear that non-immune period was considered (serious)
Inclusion of participants with prior COVID infection ROBINS-I: Bias due to confounding	Exclusion (or separate analysis) of participants with prior COVID infection reduces concern about differences in infectivity as well as risk-taking and health-seeking behaviour Examples and typical judgement: • inclusion of prior infection status as a covariate in the models (moderate) • previously infected not excluded or analyzed separately (serious)
Accounting for calendar time ROBINS-I: Bias due to confounding (time-varying confounding)	Accounting for calendar time reduces bias due to differences in vaccine accessibility and risk of exposure over time Examples and typical judgement: • use of time-varying statistics without explicit mention of adjustment for calendar time (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 ROBINS-I: Bias due to confounding	Adjustment for prognostic factors for COVID infection, severity of disease, and vaccination, such as age, gender, race, ethnicity, socioeconomic factors, occupation (HCW, LTC), and chronic medical conditions Examples and typical judgement: • no or insufficient adjustment for occupation (or number of tests as a surrogate for exposure risk) - exception age>65 or LTCF resident (moderate) • no or insufficient adjustment for socioeconomic factors (or neighborhood or income as a surrogate), race, ethnicity (serious) • no or insufficient adjustment for age (any study population) or chronic medical conditions (LTC)(critical)
Testing frequency ROBINS-I: Bias in measurement of outcomes	Similar frequency of testing between groups reduces risk of bias introduced by detecting asymptomatic infection in one group but not in another (e.g. when only one group undergoes surveillance screening)

	Examples and typical judgement: • no systematic screening but consistent methods for detection in one group vs. the other, e.g., within health networks (moderate) • screening performed for a subset of both study groups (serious) • screening performed routinely in one study group but not in the other (critical)

Appendix 6: Detailed description of the narrative summary statement

We include studies with the following clinical outcomes: prevention of infection, severe disease (as defined by the study investigators), death, and prevention of transmission. These outcomes were selected because they are less susceptible to bias. If data are not available for these specific outcomes, but are available for symptomatic infection and/or hospitalization, data for these additional outcomes are provided temporarily. Studies reporting only antibody responses are excluded.

We aim at providing a lay language, standardized summary statement for each combination of vaccine and VOC for which we found evidence.

Where more than one study was found, we will provide a summary statement with a **range of the estimates across the studies**.

Where a single study provided data, we will provide the **estimate plus 95% confidence interval** for that study. As additional studies are added, the estimate plus confidence interval will be replaced by a range as described above.

In the summaries, "prevented" or "protects" will be applied to mean estimates or range of mean estimates that are greater than or equal to 50%.