COVID-19 Living Evidence Synthesis #6

(Version 10: 23 June 2021)

Question

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

Findings

We present in Table 1 the key findings about vaccine effectiveness in variants of concern (VOC). Five studies have been added since the previous edition of this living evidence synthesis, all of which are signaled by a last-updated date of 23 June 2021 (highlighted in yellow). New studies for VOC: Alpha [B.1.1.7] (4) and Delta [B.1.617.2] (1).

Overall, we have moderate certainty evidence that 2 doses of BNT162b2 [Pfizer] prevented infection from VOC Alpha (range of mean estimates: 70 to 93%) and Beta (88% [95% CI, 61 to 96] - 1 Obs) and prevented severe disease from VOC Alpha (range of mean estimates: 92 to 98%). We have moderate certainty evidence that 2 doses may protect against symptomatic infection from VOC Delta (range of mean estimates 79 to 88%).

We have moderate certainty evidence that 2 doses of mRNA-1273 [Moderna] prevented infection from VOC Alpha (range of mean estimates: 86 to 97%) and low certainty evidence that it prevented infection from VOC Beta (88% [95% CI, 61 to 96] - 1 Obs).

We have moderate certainty evidence that 2 doses of ChAdOx1nCoV-19 [AstraZeneca] prevented infection from VOC Alpha (70.4% [95% CI, 43.6 to 84.5] – 1 RCT) and moderate certainty evidence

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. Each version will include studies and updates to living evidence syntheses identified up to two days before the version release date.

We include studies with clinical outcomes (whether the vaccines prevent infection, severe disease, death, and prevent transmission) and exclude studies that capture only antibody responses.

A full list of included and excluded studies is provided in **Appendix 1**. A glossary is provided in **Appendix 2**. We extract data from each study in duplicate using the template provided in **Appendix 3**.

We critically appraise each study in duplicate using an adapted version of the ROBINS-I tool as described in **Appendix 4**. (The lower the ROBINS-I score, the higher the study quality.)

We summarize the evidence (under heading "Overall") by presenting narrative evidence profiles across studies, with or without pooling as appropriate, and rating our confidence in the effect using GRADE for treatment effect (5 domains to downgrade, 3 to upgrade), starting at low confidence for observational evidence.

A template for the other summary statements (Page 1 under "Findings" and in Table 1 under each VOC) is provided in **Appendix 5**.

Relevance to VOC is determined directly when reported by study authors or indirectly where reasonable assumptions can be made about the variants prevalent in the jurisdiction at the time of the study as described in **Appendix 6**.

We update this document every Wednesday and post it on the COVID-END website. The McMaster/BMJ team maintaining a living evidence synthesis about vaccine efficacy will use our extracted data in their meta-analyses, GRADE assessments, and guideline development. We will incorporate their findings as they become available.

that it does not prevent infection from VOC Beta (10.4% [95% CI, -76.8 to 54.8]- 1 RCT). We have moderate certainty evidence that 2 doses may protect against symptomatic infection from VOC Delta (range of mean estimates: 60 to 61%).

We have moderate certainty evidence that Johnson & Johnson prevented infection from VOC Beta (67% [95% CI, 59 to 73%] - 1 RCT).

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

Overall, 77 studies were appraised and 41 used to complete this summary. The reasons for excluding the remaining 36 studies are reported in Appendix 2

Methods are presented in Box 1 and Appendices 1-5.

Table 1: Key findings about vaccine effectiveness

Vaccine	Effectiveness	Findings
Pfizer	Overall	Compared to placebo, vaccination with BNT162b2 probably reduces the incidence of symptomatic cases of COVID-19 substantially, although there remains uncertainty about the impact of reducing mortality or severe disease. The evidence shows that it may slightly increase the incidence of serious adverse events, and it probably increases the incidence of any adverse event. Review of RCTs (AMSTAR 10/11); *last search date 2021-06-18;* GRADE evidence profile updated on 2021-06-18
	By variant of concern	
	• Alpha	BNT162b2 provided protection against variant Alpha for the following outcomes 14 days after 1st dose: • 46 to 89% from infection (RME) • 100% (95% CI, 81.7 to 100) from severe, critical or fatal disease BNT162b2 provided protection against variant Alpha for the following outcomes at least 7 days after 2nd dose: • 70 to 97% from infection (RME) • 90% from symptomatic infection • 92 to 98% from severe disease (RME) • 94 to 98% from death (RME) (16 Obs) [1][2][3][8][9][10][15][21][22][23][28][31][34][36][37][41]; *last update 2021-06-23*
	• Beta	BNT162b2 provided protection against variant Beta for the following outcomes ≥ 14 days after 1st dose: • 75% (95% CI, 70.5 to 78.9) from infection • 100% (95% CI, 73.7 to 100) from severe, critical or fatal disease

		BNT162b2 provided protection against variant Beta for the following outcomes 35-41 days after 1st dose: • 43% (95% CI, 22 to 59) from symptomatic infection BNT162b2 provided protection against variant Beta for the following outcome 7 days after 2nd dose: • 88% (95% CI, 61 to 96) from symptomatic infection (2 Obs)[23][36]; *last update 2021-06-16*
	• Delta	BNT162b2 provided protection against variant Delta for the following outcome at least 28 days after 1st dose: • 30% (95% CI, 17 to 41) from infection [38] • 33 to 33.2% from symptomatic infection (RME) BNT162b2 provided protection against variant Delta for the following outcome 14 days after 2nd dose: • 79% (95% CI, 75 to 82) from infection [38] • 83 to 87.9% from symptomatic infection (RME) (2 Obs) [29][38]; *last update 2021-06-23*
	• Gamma	no data
	• Epsilon	BNT162b2 provided protection against variant 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 variant 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*
	• R.1	no data
	By special population	
	• HCW, Alpha	BNT162b2 provided protection against variant Alpha for the following outcomes 21 days after 1st dose: • 70% (95% CI, 55 to 85) from infection BNT162b2 provided protection against variant Alpha for the following outcomes 7 days after 2nd dose: • 85 to 96% (95% CI, 74 to 96) from infection • 97% (95% CI, 94 to 99) from symptomatic infection (3 Obs)[11][25][26]; *last update 2021-06-01*
	• Over 65 years, requiring support at home, Alpha	BNT162b2 provided protection against variant Alpha for the following outcomes 7 days after 2nd dose: • 87% (95% CI, 70 to 95) from infection • 97% (95% CI, 88 to 99) from death (1 Obs)[32]; *last update 2021-06-16*
	• Over 70 years, Alpha	BNT162b2 provided protection against variant Alpha for the following outcomes ≥ 21 days after 1st dose: • 67% (95% CI, 57 to 75) from any infection (1 Obs)[35]; *last update 2021-06-16*
	• Over 80 years, Alpha	BNT162b2 provided protection against variant Alpha for the following outcomes 14 to 28 days after 1st dose:

		• 71 to 81% from hospitalization (RME) BNT162b2 provided protection against variant Alpha for the following outcomes 14 days after 2nd dose: • 93% (95% CI, 89 to 95) from hospitalization (2 Obs)[13][20]; *last update 2021-05-21*
	• LTC, Alpha	BNT162b2 provided protection against variant Alpha for the following outcomes 35-48 days after 1st dose: • 70% (aHR 0.3, 95% CI, 0.17 to 0.71) from infection BNT162b2 provided protection against variant Alpha for the following outcomes 7 days after 2nd dose: • 89% (95% CI, 81 to 93) from death (2 Obs)[12][32];*last update 2021-06-16*
	• Over 70 years, Gamma	BNT162b2 provided protection against variant Alpha for the following outcomes ≥ 21 days after 1st dose: • 61% (95% CI, 45 to 72) from any infection (1 Obs)[35]; *last update 2021-06-16*
	• HCW, Beta or Gamma	BNT162b2 provided protection against variant 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 variant 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, Beta	BNT162b2 provided protection against variant Beta for the following outcome >28 days after 2 doses: • 50% (95% CI, 34 to 73) from infection (1 Obs)[24]; *last update 2021-06-01*
	• LTC, R.1	BNT162b2 provided protection against variant R.1 for the following outcomes ≥ 14 days after 2nd dose: • 66.2% (95% CI, 40.5 to 80.8) from infection • 94.4% (95% CI, 44.6 to 99.4) from death (1 Obs); [16] *last update 2021-05-07*
	Transmission	
	• Household of vaccinated individual, Alpha	BNT162b2 reduced transmission of variant 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% (RME) BNT162b2 reduced transmission of variant Alpha from a vaccinated HCW (10 weeks after 2nd dose) to household spouse: • 42.9% (95% CI, 22.3 to 58.1) (3 Obs) [6][14][33]; *last update 2021-06-16*
	• Vaccinated close contacts of COVID+	BNT162b2 reduced transmission to close contacts COVID+ index cases at least 14 days after 2nd dose: • 65% (95% CI, 56 to 73) against any infection

		• 94% (95% CI, 60 to 99) against hospitalization (1 Obs)[40]; *last update 2021-06-23*
	• Vaccinated HCW vs unvaccinated community, Beta and Gamma	BNT162b2 reduced transmission of variants Beta or Gamma from vaccinated HCW compared to unvaccinated community ≥14 days after 1st dose: • 54.7% (95% CI, 44.8 to 62.9) BNT162b2 reduced transmission of variants Beta or Gamma from vaccinated HCW compared to unvaccinated community ≥7 days after 2nd dose: • 84.8% (95% CI, 75.2 to 90.7) (1 Obs) [27]; *last update 2021-06-08*
Moderna	Overall	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 2021-06-18;* GRADE evidence profile updated on 2021-01-25
	By variant of concern	
	• Alpha	mRNA-1273 provided protection against variant Alpha for the following outcomes 14-41 days after 1st dose: • 58.9% (95% CI, -9.7 to 84.5) from infection • 61% (95% CI, 56 to 66) from symptomatic infection mRNA-1273 provided protection against variant Alpha for the following outcomes 7-15 days after 2nd dose: • 86 to 97% from infection (RME) • 90% (95% CI, 88 to 100) from symptomatic infection (5 Obs) [8][23][31][34][37]; *last update 2021-06-23*
	• Beta	mRNA-1273 provided protection against variant 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 variant Beta for the following outcome 7 days after 2nd dose: • 88% (95% CI, 61 to 96) from symptomatic infection (1 Obs) [23]; *last update 2021-06-01*
	• Gamma	No data available
	• Epsilon	mRNA-1273 provided protection against variant 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 variant 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 variant 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
	• Over 70 years, Gamma	mRNA-1273 provided protection against variant 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
Astra Zeneca	Overall	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 2021-06-18;* 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.
	By variant of concern	
	• Alpha	ChAdOx1nCoV-19 provided protection against variant Alpha for the following outcome 21 to 28 after 1st dose: • 65-74% from any infection (1 Obs, moderate to low quality of evidence)[9][10]; ChAdOx1nCoV-19 provided protection against variant Alpha for the following outcome after 2 doses: • 70.4% (95% CI, 43.6 to 84.5) from symptomatic infection (1 RCT, moderate quality) [5]; *last update 2021-04-22*
	• Beta	ChAdOx1nCoV-19 provided protection against variant 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) [4]; *last update 2021-04-14*
	• Delta	ChAdOx1 provided protection against variant Delta for the following outcome at least 28 days after 1st dose: • 18% (95% CI, 9 to 25) from any infection [38] • 33% (95% CI, 23 to 41) from symptomatic infection [38] • 32.9% (95% CI, 19.3 to 44.3) from symptomatic infection [29] ChAdOx1 provided protection against variant Delta for the following outcome 14 days after 2nd dose: • 60% (95% CI, 53 to 66) from any infection [38] • 60 to 61% from symptomatic infection (RME) (2 Obs) [29][38]; *last update 2021-06-23*
	• Gamma	no data
	• Epsilon	no data

	Special populations	
	• Over 80 years, Alpha	ChAdOx1nCoV-19 provided protection against variant Alpha for the following outcomes 14 to 28 days after 1st dose: • 73 to 80% from hospitalization (RME) (2 Obs) [13] [20]; *last update 2021-05-21*
	• LTC, Alpha	ChAdOx1nCoV-19 provided protection against variant Alpha for the following outcomes 35-48 days after 1st dose: • 70% (aHR 0.32, 95% CI, 0.15 to 0.66) from infection (1 Obs)[12]; *last update 2021-04-30*
	Transmission	
	• Household of vaccinated individual, Alpha	ChAdOx1nCoV-19 reduced transmission of variant 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% (RME) (2 Obs) [6][14]; *last update 2021-06-08*
	• Vaccinated close contacts of COVID+	ChAdOx1nCoV-19 reduced transmission to close contacts COVID+ index cases at least 14 days after 2nd dose: • 44% (95% CI, 31 to 54) against any infection • 92% (95% CI, 46 to 99) against hospitalization (1 Obs)[40]; *last update 2021-06-23*
Johnson & Johnson	Overall	[Johnson & Johnson's Janssen vaccine] Vaccination with AD26.COV2.S probably reduces the incidence of symptomatic cases of COVID-19 by around 66%, 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 2021-06-18*. GRADE evidence profile updated on 2021-05-28 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*
	• Gamma	no data
	• Epsilon	no data
Sinovac (Coronavac)	• Overall	[Coronavac vaccine] Compared to placebo, vaccination with CoronaVac probably reduces the incidence of symptomatic cases of COVID-19 by about 50%, close to the lowest level deemed effective by the WHO (www.afro.who.int/news/what-covid-19-vaccine-efficacy) and it may substantially reduce the incidence of hospitalization or severe diseases 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 2021-06-18*; GRADE evidence profile updated 2021-05-09
	By variant of concern	
	• Alpha	no data
	• Beta	no data
	• Gamma	CoronaVac provided protection against variant 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 (1 Obs) [30]; *last update 2021-06-08*
	• Epsilon	no data
	By special population	
	• HCW, Gamma	CoronaVac provided protection against variant 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	• Overall	[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 2021-06-11.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 2021-06-11. GRADE evidence profile updated on 2021-06-11
Novavax	• Overall	[Novavax vaccine] The effects of vaccination against COVID-19 with the Novavax vaccine are currently uncertain. Review of RCTs (AMSTAR 10/11); last search date 2021-06-18; GRADE evidence profile updated on 2021-06-21
	By variant of concern	
	• Alpha	NVX-CoV2373 provided protection against variant Alpha for the following outcome after 2 doses: • 89.7% (95% CI, 80.2 to 94.6) against infection. • No hospitalizations or deaths in vaccinated group • Post hoc: 86.3% (95% CI, 71.3 to 93.5) against confirmed Alpha variant symptomatic infection (1 RCT, moderate quality), [19]; *last update 2021-06-16*
	• Beta	NVX-CoV2373 provided protection against variant Beta for the following outcome after 7 days after 2nd dose: • Post-hoc: 43% (95% CI, -9.8 to 70.4) from infection (1 RCT, moderate quality), [17]; *last update 2021-06-16*
EpiVacCorona	• Overall	[EpiVacCorona] The effects of using vaccination with EpiVacCorona are uncertain. Review of RCTs (AMSTAR 10/11); last search date 2021-06-18; GRADE evidence profile updated on 2021-06-11

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 6.10): What is the efficacy and effectiveness of available COVID-19 vaccines in general and specifically for variants of concern? Hamilton: Health Information Research Unit, 23 June 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 the same VE as the phase III trial 46% (95% CI, 40 to 51) 14 to 20 days after 1st dose and 92% (88 to 95%) 7 days after 2nd dose in a population with an estimated circulation of Alpha. up to 80% against any infection.	Moderate	Cohort Israel, .5 M matched; large population, KM, concordant with trial;2 M excluded (possible overlap with Haas); time and setting for VOC Alpha
2	Haas	BNT162b2 showed the same VE as the phase III trial (91% [>7 days] and against asymptomatic infections [94%], hospitalization [98%] and death [98%], respectively, 14 days after 2nd dose in a population with 94% of Alpha.	Moderate	Cohort Israel, concordant with trial; effect on death (possible overlap with Dagan) Updated May 14 due to final publication; VOC Alpha confirmed in sample
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% B.1.135.	Moderate	Case-control Israel; confirmed VOC; small sample for Beta (no overlap, CHS cohort)
4	Madhi	ChAdOx1 nCoV-19 vaccine had minimal effectiveness against VOC Beta in preventing mild to-moderate Covid-19 after 2nd dose	Moderate quality (RCT)	RCT South Africa; VE 20% in seronegative and 10% in seropositive – 75% (95% CI, 9 to 95) after 1 dose before emergence of variant. Underpowered for 20% efficacy (42 cases)
5	Emary	ChAdOx1nCoV-19 showed VE 70.4% (95% CI, 43.6 to 84.5) for Alpha and 81.5% (95% CI, 67.9 to 89.4) for non-Alpha after 2nd dose	Moderate quality (RCT)	RCT; UK; neutralization of Alpha 9 times lower; no sequencing for 45% of cases; 52 cases (19%) had Alpha variant
6	Shah	ChAdOx1nCoV-19 or BNT162b2 reduced infection in household contacts of vaccinated HCW by about 30% (HR, 0.70, 95% CI, 0.64 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	Moderate	Observational Scotland - (25% of cases had received 2 doses); time and setting for VOC Alpha

		0.16, 95% CI, 0.09 to 0.27) ≥ 14 days after 1st dose		
7	Sadoff	Ad26.COV2.S showed VE 66.9% (95% CI, 59.0 to 73.4) at 14 days and 66.1% (95% CI, 55.0 to 74.8) at 28 days against any infection. 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). VE against VOC Beta was 52.0% and 64.0% at 14 days and 28 days, respectively, and 73.1% for moderate cases and 81.7% for severe cases.	Moderate quality (RCT)	RCT (~40,000) 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 VE was 58.9% (95% CI, −9.7 to 84.5) at 15 days after 1 dose, and 85.7% (95% CI, 67.2 to 93.9) 15 days after 2 dose against any infection.	Moderate	Observational test-negative, case-positive random sampling matched control study. 69% of population at time had VOC Alpha or Epsilon
9	Glampson	ChAdOx1nCoV-19 or BNT162b2 showed VE 74% (HR 0.26, 95% CI, 0.19 to 0.35) and 78% (HR 0.22, 95% CI, 0.18 to 0.27), respectively, 28 days after first vaccination dose against any infection.	Moderate	Observational retrospective cohort, 2 M eligible for population; 389,587 vaccinated (58% Pfizer, 42 AZ); time and setting for VOC Alpha
10	Pritchard	ChAdOx1nCoV-19 or BNT162b2 showed VE of 65% (95% CI, 60 to 70%) 21 days after 1st dose and 70% (95% CI, 62 to 77%) after 2nd dose against any infection. No difference between vaccines or versus people with previous infection. Same effect for Alpha (dominant) or not Alpha.	Moderate	Observational prospective testing; 370,000 participants, 1.6 M tests infections with evidence of high viral shedding Ct<30 (88% reduction after two doses; 95% CI 80 to 93%; P<0.001) and with self-reported symptoms (90% reduction after two doses; 95% CI 82 to 94%; P<0.001). VOC Alpha confirmed
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 in the study population against any infection.	Moderate	Prospective cohort with standardized testing for HCW over all of England; 23,000 participants; time and setting for VOC Alpha
12	Shrotri	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.	Low	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;	Moderate	Test negative case control, Scotland. Single center, 466

		ChAdOx1nCoV-19 showed VE 80.4% (95% CI, 36.4 to 94.5) against hospitalization for 80+ 14 days after 1st dose. 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).		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 in England; 338,887 participants; time and setting for VOC Alpha
15	Goldberg	Prior infection (in unvaccinated) has similar VE against any infection [94.8%], and severe illness [96.4%] as two doses of BNT162b2	Moderate	Individual-level population database in Israel; 6,351,903 participants; likely overlaps with Dagan and Haas; time and setting for VOC Alpha
16	Cavanaugh	VE against infection was 66.2% (95% CI, 40.5% to 80.8%) among residents and among HCP was 75.9% (95% CI, 32.5% to 91.4%). VE against hospitalization was 94.4% (95% CI, 73.9% to 98.8%) among residents; no HCP were hospitalized. Three residents died, two of whom were unvaccinated (VE = 94.4%; 95% CI, 44.6% to 99.4%).	Serious	Outbreak analysis; small sample size
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; 4387 participants 38/41 cases Beta
18	Hitchings	CoronaVac showed VE of 35.1% (95% CI, -6.6 to 60.5) against infection in HCW after 1st dose	Moderate	53,176 HCW in Manaus 75% prevalence of Gamma; 776 (28%) of 2797 PCR were used for the case-controls; infection increased in the first 13 days; rate of previous infection high in the population
19	Heath	NVX-CoV2373 showed VE 89.7% (95% CI, 80.2 to 94.6) against any 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 or ChAdOx1 showed VE 80% (95% CI, 74 to 85) against	Moderate	Screening study of 13,907 hospitalized patients in UK;

		hospitalization 28 days after 1st dose and 92% (95% CI, 87 to 95%) 14 days after 2nd dose for people 80+.		results for age 80+ also reported separately according to vaccine; time and setting for VOC Alpha
21	Bernal (2)	BNT162b2 reduced risk of death in 70+ by 44% (95% CI, 32 to 53) after 1st dose and by 69% (95% CI, 31 to 86) after 2nd dose; single dose ChAdOx1 reduced risk of death by 55% (95% CI, 41 to 66)	Moderate	48,096 cases above age 70+ in England; linked to mortality database; 12.7% BNT162b2 and 8.2% ChAdOx1; time and setting for VOC Alpha
22	Chodick	BNT162b2 showed VE 94% (95% CI, 88 to 97) against infection 7-27 days after 2nd dose; 71% (95% CI, 37 to 87) in immunosuppressed	Moderate	Health care organization in Israel – 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 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 Beta or Gamma 14 days after 1st dose and 88% (95% CI, 61 to 96) 7 days after 2nd dose.	Serious	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
24	Bailly	BNT162b2 showed VE 50% (95% CI, 34 to 73) against infection with Beta >28 days after 2 doses	Moderate	Outbreak in a single LTC in France, 90 participants, all samples genome sequenced for VOD 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 Beta or Gamma 14 to 42 days after 1st dose and 79.2% (95% CI, 64.60 to 87.80) 7 days after 2nd dose	Low	Data-linkage, 25,558 Canadian HCW; evenly split between VOC Gamma and VOC Beta by end of study period
28	Bernal (1)	BNT162b2 reduced risk of infection by confirmed variant Alpha OR 0.40 (95% CI, 0.27 to 0.60) at least 28	Moderate	Test-negative in England, 156,930 participants; time and setting for VOC Alpha

		days after 1st dose and OR 0.10 (95% CI, 0.06 to 0.16) at least 14 days after 2nd dose for people 70+		
29	Bernal (3)	BNT162b2 reduced risk of symptomatic infection by confirmed variant Delta VE 33.2% (95% CI, 8.3 to 51.4) at least 21 days after 1st dose and VE 87.9% (95% CI, 78.2 to 93.2) at least 14 days after 2nd dose. 1st dose. ChAdOx1 reduced risk of symptomatic infection by confirmed variant Delta VE 32.9% (95% CI, 19.3 to 44.3) at least 21 days after 1st dose and VE 59.8% (95% CI, 28.9 to 77.3) 14 days after 2nd dose.	Moderate	Test-negative; 12,675 sequenced cases: 11,621 Alpha and 1,054 Delta. Positive cases after 1 or 2 doses were more likely to be due to variant Delta (OR 1.40, 95% CI, 1.13 to 1.75)
30	Ranzani	CoronaVac reduced risk of symptomatic infection by variant of concern 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 any 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.	Moderate	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 2nd 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 and mRNA-1273 showed VE 97.1% (95% CI, 94.3 to 98.5) against any 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%) and mRNA-1273 showed overall VE 65% (95% CI, 58 to 71) against any infection ≥21 days after 1st dose for 70+: VE 67% (95% CI, 57 to 75) against any infection by VOC Alpha and VE 61% (95% CI, 45 to 72) against any infection by VOC Gamma	Moderate	Test-negative in Canada; 16,993 specimens; out of 1,131 genetically sequenced: 45% VOC Alpha and 28% Gamma; limitations in symptom collection and assessment for covariates
36	Abu-Raddad	BNT162b2 showed VE 89.5% (95% CI, 85.9 to 92.3) against any infection, VE 100% (95% CI, 81.7 to 100) against any severe, critical, or fatal disease by VOC Alpha ≥ 14 days after 1st dose; BNT162b2 showed VE 75% (95% CI, 70.5 to 78.9) against any infection, VE 100% (95% CI, 73.7 to 100) against any severe, critical, or fatal disease by VOC Beta ≥ 14 days after 1st dose	Moderate	Test-negative in Qatar; 17,293 cases; sequencing showed 50% VOC Beta and 45% VOC Alpha between February-March 2021
37	Akhrass	BNT162b2 and mRNA-1273 showed overall VE 60.4% (95% CI, 30 to 78) against any symptomatic infection ≥ 14 days after 1st dose; BNT162b2 and mRNA-1273 showed overall VE 98.2% (95% CI, 90 to 98) against any symptomatic infection ≥ 14 days after 2nd dose	Serious	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 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 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	Low	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	BNT162b2 reported no symptomatic infections in the vaccinated group	Serious	Prospective cohort of adults with autoimmune inflammatory

		(0/686) compared to 0.83% infections in the vaccinated general population control group		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 any 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 any infection and VE 92% (95% CI, 46 to 99) against hospitalization at least 14 days after 1st dose in close contacts of index cases	Moderate	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% (95% CI, 16 to 72) against any infection 13 to 24 days after 1st dose	Low	Data-linkage study in Israel; 351,897 participants; time and setting for VOC Alpha

Section 2: excluded studies	
Author	**Reason for exclusion**
Hollinghurst	serious risk of bias
Moustsen-Helms	prevalence of variants unknown and suspected to be <50%
Guijarro	prevalence of variants unknown and suspected to be <50%
Thompson	prevalence of variants unknown and suspected to be <50%
Salmeron Rios	prevalence of variants unknown and suspected to be <50%
Raches Ella	Phase 1 trial
Geisen	clinical outcomes not reported
Shimabukuro	clinical outcomes not reported
Li	Phase 1 trial
Jacobson	serious risk of bias
Mor	prevalence of variants unknown and suspected to be <50%
Rudolph	prevalence of variants unknown and suspected to be <50%
Britton	prevalence of variants unknown and suspected to be <50%
Gray	prevalence of variants unknown and suspected to be <50%
Regev-Yochay	prevalence of variants unknown and suspected to be <50%
Cabezas	prevalence of variants unknown and suspected to be <50%
Monge	prevalence of variants unknown and suspected to be <50%
Vahidy	prevalence of variants unknown and suspected to be <50%

Bjork	prevalence of variants unknown and suspected to be <50%
Swift	prevalence of variants unknown and suspected to be <50%
Corchado-Garcia	prevalence of variants unknown and suspected to be <50%
Domi	prevalence of variants unknown and suspected to be <50%
Rana	no appropriate comparison group
Pilishville	prevalence of variants unknown and suspected to be <50%
Kaabi	prevalence of variants unknown and suspected to be <50%
Frenck	prevalence of variants unknown and suspected to be <50%
Khawaja	serious risk of bias
Palacios	prevalence of variants unknown and suspected to be <50%
Khan	prevalence of variants unknown and suspected to be <50%
Thompson	prevalence of variants unknown and suspected to be <50%
Haas	modelling study used to estimate cases averted
Voysey	prevalence of variants unknown and suspected to be <50%
Gils	clinical outcomes not reported
Menni	serious risk of bias
Tande	prevalence of variants unknown and suspected to be <50%
Mattar	no appropriate comparison group, prevalence of variants unknown and suspected to be <50%

Appendix 2: Glossary

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 (same as LTCF)

Obs: observational study

RME: range of mean estimates across 2 or more studies

Vaccine effectiveness (VE): measure of how well a vaccine protects people from becoming infected (For example: VE of 92% means that 92% of people be well protected from becoming infected with COVID and 8% of people will still be at risk of becoming infected with COVID)

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 2

Appendix 4: Critical appraisal process

We appraise the quality of the individual studies using 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. It also includes identifying all the confounders and co-interventions potentially relevant to the specific field of investigation (listed below). The table below indicates which domains we consider relevant to the VE&VOC field. We focus our assessment on the most relevant domains, but we consider potential bias arising in any of them.

ROBINS- I Domains	Anticipated relevance of the domain to VE & VOC
Bias due to	
Confounding	high relevance
Selection of participants into the study	intermediate relevance
Classification of interventions	low relevance
Deviations from intended intervention	low relevance
Missing data	high relevance
Measurement of outcomes	high relevance
Selection of the reported result	low relevance

Overarching 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

(*) confirmation of specific variant, or evidence the variant was the dominant circulating strain
(**) before-after studies, where the infection rate in the first 2 weeks after the vaccination are used as control are commonly performed and maybe appraised but are open to confounding and bias.

Aim for this study is to assess the effect of assignment to intervention (most vaccine studies will assess patients who received the vaccine)

List the potential confounding domains relevant to all or most studies

Socio-economic status, age, sex, gender, ethnicity, job role, LTC status, HCW status

List co-interventions that could be different between intervention groups and that could impact on outcomes

Appendix 5: Detailed description of the narrative summary statement

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.

Appendix 6: 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