COVID-19 Living Evidence Synthesis #6

(Version 6: 21 May 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. Three studies have been added since the previous edition of this living evidence synthesis, all of which are signaled by a last-updated date of 21 May 2021 (highlighted in yellow). One new study reporting the effectiveness of Novavax vaccine for preventing infection by B.1.1.7 and two studies updating vaccines (Pfizer and AstraZeneca) for preventing hospitalization or death have been added.

Overall, we have moderate certainty that the Pfizer, Moderna, and AstraZeneca vaccines prevent infection by VOC B1.1.1.7. We have evidence that the Johnson & Johnson vaccine prevents infection by B.1.1.7 and B.1.351, but the degree of certainty is unknown. The AstraZeneca vaccine does not prevent infection associated with B.1.351. There remains uncertainty about the impact of any of the vaccines on severe disease, death or prevention of transmission of the VOC.

We present our methods in Box 1 and Appendices 1-5.

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 illness, death, and prevent transmission) and exclude studies that capture only antibody responses. As to the relevance to VOC, we include studies where direct measures are reported, or where reasonable assumptions can be made about the variants prevalent in the jurisdiction at the time of the study.

A full list of studies included, under appraisal, or excluded as non-contributory, is provided as **Appendix 1**.

We extract data from each study in duplicate (McMaster University and University of Ottawa) using the template provided in **Appendix 2**.

We critically appraise each study in duplicate using a simplified version of the ROBINS-I tool as described in **Appendix 3**. The lower the ROBINS-I score, the higher the study quality.

We summarize the evidence by presenting narrative evidence profiles across studies, with or without pooling as appropriate, and rating our confidence in the effect using the GRADE approach for treatment effect (5 domains to downgrade, 3 to upgrade), starting at low confidence for observational evidence. A more detailed explanation of the narrative summary statement is provided in **Appendix 4**.

We update this document every Friday 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.

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 for any difference in serious adverse effects is uncertain, although the vaccination probably increases the incidence of any adverse event. Review of RCTs (AMSTAR 10/11); *last search date 2021-05-07;* GRADE evidence profile updated on 2021-01-25 Vaccination with the Pfizer/BioNTech vaccine reduces the risk of contracting COVID-19 substantially even after the first dose and it probably reduces the risk of severe COVID-19, whereas its effects on other outcomes are yet to be determined; the incidence of serious adverse events may slightly increase, whereas the incidence of any adverse event substantially increase. Review of RCTs (AMSTAR /11); last search date 2021-05-13
	By variant of concern	
	• B.1.1.7	BNT162b2 showed the same VE as the phase III trial (46 to 60% 14 days after 1st dose) and 85.7 to 92% 7 days or 70 to 94% 14-21 days after 2nd dose) in a population with an estimated circulation of B.1.1.7. up to 80-94%. Severe disease and death were reduced by 92 to 98% and 94 to 98%, respectively after the 2nd dose. Ct>30 reduced by 88% and symptomatic episodes reduce by 90%; no difference with previous infection protection (8 studies, low quality of evidence) [1][2][3][9][10][11][15][16] *last updated 2021-05-14*
	• B.1.351	no data
	• P.1	no data
	• CAL.20C	no data
	• R.1	BNT162b2 shows VE 66.2% (95% CI, 40.5 to 80.8) for any infection and 94.4% (95% CI, 44.6 to 99.4) for death due to variant R.1 in residents of a nursing facility after 2nd dose. 189 people, 1 study. [17] Last update 2021-05-07
	By special population	
	• Healthcare workers	BNT162b2 reduced infection rate in HCW by about 55% compared to non vaccinated people (HR 0.45, 95% CI, 0.42 to 0.49) to 80% (95% CI, 59 to 90) after the 1st dose and 90% (95%, CI 68 to 97) after the 2nd dose; hospitalization after the 1st dose was reduced by 91% (HR

		0.16, 95% CI, 0.09 to 0.27) (2 Obs, low quality of evidence) [6][7] *last update 2021-04-14*
	• HCW, B.1.1.7	A single dose of BNT162b2 vaccine showed VE of 70% (95% CI, 55 to 85) 21 days after 1st dose and 85% (74 to 96) 7 days after two doses in HCW (median age 46, 84% females)[12], *last update 2021-04-30*
	• LTC, B.1.17	VE for BNT162b2 at 35-48 days was (aHR 0.3, 95% CI, 0.17 to 0.71)(median age 86)[13]*last update 2021-04-30*
	• Over 80 years	VE for BNT162b2 was 81% (95% CI, 76 to 85) against hospitalization 28 days after 1st dose and 93% (95% CI, 89 to 95) 7 days after 2nd dose (2 Obs, low quality of evidence)][14] [21], *last update 2021-05-21*
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 2021-05-07;* GRADE evidence profile updated on 2021-01-25 Vaccination with the Moderna vaccine reduces the risk of contracting COVID-19 substantially (but it may reduce this risk with the first dose) and reduces the risk of severe COVID-19, whereas its effects on other outcomes are yet to be determined; the vaccination probably does not increase the incidence of serious adverse events. Review of RCTs (AMSTAR /11); last search date 2021-05-13
	By variant of concern	
	• B.1.1.7	mRNA-1273 VE was 58.9 (95% CI, −9.7 to 84.5) 15 days after 1st dose, and 85.7 (95% CI, 67.2 to 93.9) 15 days after 2nd dose. (1 study, [9] *last updated 2021-04-22*
	• B.1.35.1	no data
	• P.1	no data
	• CAL.20C	no data
Astra Zeneca	Overall	Compared to vaccinating with MedACWY (meningitis vaccine), vaccination with ChAd0x1 probably reduces the incidence of asymptomatic cases of COVID-19 as well as the number of positive tests and may reduce severe or critical disease and hospitalisations. The effects on mortality are uncertain, and adverse effects are probably less frequent. (*)Review of RCTs (AMSTAR 10/11); *last search date 2021-05-07;* 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. Vaccination with the EU Nodes - Astrazeneca/Oxford vaccine reduces the risk of contracting COVID-19 and may reduce the risk of severe COVID-19, whereas its effects on other outcomes are yet to be determined; the vaccination probably does not increase the incidence of serious adverse events. Review of RCTs (AMSTAR /11); last search date 2021-05-13
	By variant of concern	
	• B.1.1.7	ChAdOx1nCoV-19 VE in preventing mild to-moderate Covid-19 from the B.1.1.7 variant was 70.4% (95% CI, 43.6 to 84.5) compared to 81.5% (95% CI, 67.9 to 89.4) versus naïve COVID19; neutralization effect was 9 times lower; VE confirmed at 65-74% after 1st dose in large observational retrospective cohorts (1 RCT, 2 Obs, moderate to low quality of evidence)[5][10][11] *last updated 2021-04-22*
	• B.1.351	ChAdOx1 nCoV-19 vaccine (two doses) had very low efficacy against the B.1.351 variant in preventing mild to-moderate Covid-19 and there is no data on protection against severe disease (1 RCT).[4] *last update 2021-04-14*
	• P.1	no data
	• CAL.20C	no data
	Special populations	
	• LTC, B.1.17	VE for ChAdOx1 at 35-48 days was (aHR 0.32, 95% CI, 0.15 to 0.66) (median age 86)[13] *last update 2021-04-30*
	• Over 80 years	VE for ChAdOx 1 was 73% (95% CI, 60 to 81) against hospitalization 28 days after 1st dose (2 Obs, low quality of evidence)][14] [21], *last update 2021-05-21*
Johnson & Johnson	Overall	[Johnson & Johnson's Janssen vaccine] Synthesis pending. Review of RCTs (AMSTAR 8/9); *last update 2021-05-07* 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 the evidence) [8] 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 updated 2021-05-17*

		Vaccination with the Janssen vaccine reduces the risk of contracting COVID-19 substantially and reduces the risk of severe COVID-19, whereas its effects on other outcomes are yet to be determined; the vaccination increases the incidence of serious adverse events. Review of RCTs (AMSTAR /11); last search date 2021-05-13
	By variant of concern	
	• B.1.1.7	no data
	• B.1.351	VE against VOC 20H/501Y.V2 variant (B.1.351) 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), [8] *last updated 2021-04-22*
	• P.1	no data
	• CAL.20C	no data
Sinovac (Coronavac)	• Overall	[Coronavac vaccine] Compared to placebo, vaccination with CoronaVac probably reduces the incidence of symptomatic cases of COVID-19 by 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. High quality review of RCTs (AMSTAR 10/11); *last search date 2021-05-07;* GRADE evidence profile updated on 2021-05-07 Vaccination with the CoronaVac/Sinovac vaccine reduces the risk of contracting COVID-19 (even after the 1st dose) and it probably reduces the risk of severe COVID-19, whereas its effects on other outcomes are yet to be determined; the incidence of serious adverse events probably does not increase, whereas the incidence of any adverse event is higher. Review of RCTs (AMSTAR /11); last search date 2021-05-13
	By variant of concern	
	• B.1.1.7	no data
	• B.1.351	no data
	• P.1	no data
	• CAL.20C	no data
	By special population	
	• HCW, P.1	CoronaVac provides a 49.6% protection from infection and 35.1% protection from symptomatic infection due to variant P.1 in health care workers =>14 days after 1st dose. ~500 people, 1 study[19]; last update 2021-05-07

Sinopharm	• Overall	Synthesis pending. Review of RCTs (AMSTAR /11); last search date 2021-05-13
Novavax	• Overall	Synthesis pending
	By variant of concern	
	• B.1.1.7	Two doses of NVX-CoV2373 showed VE 89.7% (95% CI, 80.2 to 94.6) against any infection. No hospitalizations or deaths in vaccinated group. Post hoc: VE 86.3% (95% CI, 71.3 to 93.5) against B.1.1.7 variant, 15,187 people, 1 RCT, [20] last updated 2021-05-21
	• B.1.351	NVX-CoV2372 provides a 57.7% protection from infection due to variant B1.351 =>7 days after 2nd dose. 4,387 people, 1 RCT, [18]; last update 2021-05-07

Links to references are provided in Appendix 1

Iorio A, Little J, Linkins L, Abdelkader W, Bennett D, Lavis JN. COVID-19 living evidence profile #6 (version 6.6): What is the efficacy and effectiveness of available COVID-19 vaccines in general and specifically for variants of concern? Hamilton: Health Information Research Unit, 21 May 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 (46-60% 14 days after 1st dose and 92% 7 days after 2nd dose) in a population with an estimated circulation of B.1.1.7. 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)
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 B.1.1.7.	Low	Cohort Israel, concordant with trial; effect on death (possible overlap with Dagan) Updated May 14 due to final publication
3	Kustin	BNT162b2 showed lower relative VE (2.4:1) against B.1.1.7. after 1st dose; and lower VE (8:1) against B.1.351 after 2nd dose in a population with >90% of B.1.1.7 and <1% B.1.135.	Moderate	Case-control Israel, asymmetry in VOC; small sample for B.1.135 (no overlap, CHS cohort).
4	Madhi	Two doses of the ChAdOx1 nCoV-19 vaccine had no efficacy against the B.1.351 variant in preventing mild to-moderate Covid-19.	Moderate	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
5	Emary	ChAdOx1nCoV-19 (two doses) VE against the B.1.1.7 variant was 70.4% (95% CI, 43.6 to 84.5) for B.1.17 and 81.5% (95% CI, 67.9 to 89.4) for non-B.1.1.7.	Low	RCT UK; neutralization of B.1.1.7 9 times lower
6	Shah	ChAdOx1nCoV-19 reduced infection (and hospitalization) in household contacts of vaccinated HCW by about 30% (HR, 0.70, 95% CI, 0.64 to 0.78); BNT162b2 reduced infection in HCW by about 55% (HR 0.45, 95% CI, 0.42 to 0.49)	Moderate	Observational Scotland - (25% of cases had received 2 doses)

		and hospitalization by 91% (HR 0.16, 95% CI, 0.09 to 0.27)		
7	Thompson	BNT162b2 and mRNA-1273 VE in HCW, first-line responder and essential/frontline workers was 80% (95% CI, 59 to 90) after the first dose and 90% (95% CI, 68 to 97) after the second dose against any infection.	Low	Observational US, multicentric Prospective, standardized, weekly PCR testing; small size. 63% Pfizer, 27% Moderna; larger prevalence of infection in male, Hispanic.
8	Sadoff	For Ad26.COV2.S, VE was 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 B.1.351 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.	Low	RCT (~40,000) Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States;
9	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% (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 populaton at time had variants B.1.1.7., {B.1.427, B.1.429).
10	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) 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); variants not assessed, but dominant being B.1.1.7 at that time.
11	Pritchard	ChAdOx1nCoV-19 or BNT162b2 showed VE of 65% (95% CI, 60 to 70%) 21 days after first dose and 70% (95% CI, 62 to 77%) after second dose against any infection. No difference between vaccines or versus people with previous infection. Same effect for B.1.1.1.7 (dominant) or not B.1.1.7.	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)

12	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 two doses in the study population against any infection.	Low	prospective cohort with standardized testing and adjustment for confounders, HCW, all of England; 23,000, 46 yo, 84% females.
13	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	9160 of 10412 frail LTC residents (median 86 yo), 66% Pfizer, 33% AZ. Prospective testing.
14	Hyams	1st BNT162b2 showed VE 71.4% (95% CI, 46.5 to 58 90.6). ChAdOx1nCoV-19 1st dose VE 80.4% (95% CI, 36.4 to 4.5) against hospitalization 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, Scotland. Small sample, single center, 80+ (median age 86). Adjusted/matched Cox
15	Harris	First dose of BNT162b2 or ChAdOx1 (21 days prior) reduced likelihood of transmission by 40-50% for household contacts of HCW	Moderate	Data-linkage and case-control; will have missed asymptomatic infection
16	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; likely overlaps with Dagan and Haas
17	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
18	Shinde	NVX-CoV2372 VE showed VE 57.7% (95% CI, 25.7 to 75.9) against symptomatic infection 7 days after 2nd dose	RCT	4387 participants 39/41 cases B.1.351
19	Hitchings	One dose of CoronaVac showed VE of 35.5% (95% CI, -6.6 to 60.5) against infection in HCW	Serious	53,176 HCW in Manaus 75% prevalence of P.1; 776 (28%) of 2797 PCR were used for the case control;

				infection increased in the first 13 days (Healthcare seeking behaviour, differential test seeking); rate of previous infection high in the population
20	Heath	Two doses of NVX-CoV2373 showed VE 89.7% (95% CI, 80.2 to 94.6) against any infection. No hospitalizations or deaths in vaccinated group.	RCT	15,187 people in UK Post hoc: VE 86.3% (95% CI, 71.3 to 93.5) against B.1.1.7 variant
21	Ismail	Two doses of BNT162b2 or ChAdOx1 showed VE 80% (95% CI, 74 to 85) against hospitalization 28 days after 1st dose and 92% (95% CI, 87 to 95%) 14 days after 2nd dose for people 80+.	Moderate	13,907 hospitalized patients in UK; results for age 80+ also reported separately according to vaccine
22	Bernal	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)	Low	48,096 cases above age 70+ in England; linked to mortality database; 12.7% BNT162b2 and 8.2% ChAdOx1

Section 2: studies under appraisal		
#	**Author**	**Notes**
1		
2		
3		

Section 3: excluded studies			
#	**Author**	**Reason for exclusion**	**Notes**
	Jacobson	Not actionable information, and high risk of bias.	Imprecise information about infection rate, proportion of prevalent variant, amount of missing outcome data.
	Hollinghurst	Serious risk of bias	
	Mor	Moderate risk of bias	Observational USA, multiple LTC; routine screening; no details on

			testing; not variant of concern

Appendix 2: Glossary

HCW: Healthcare workers

LTC: Long-term care

Obs: observational study

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 (under revision)

Vaccine product	BNT = BNT162b2 (Pfizer-BioNTech)
	MOD = mRNA-1273 (Moderna)
	AZ = ChAdOx1-S (AstraZeneca, COVISHIELD)
	JJ = Ad26.COV2 (Janssen [Johnson & Johnson])
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)	gen public/LTC/Households/HCW/Other
Control group	not vaccinated, <7day vacc internal control, none,other
Total (N)	number of all study participants
% female	percent female or NA
LTC	number or NA
HCW	number or NA
Households	number or NA
>80	number older than this age group or unclear or NA
>70	number older than this age group or unclear or NA
>60	number older than this age group or unclear or NA
Notes	about study as a whole
Outcomes	outcomes separated by variant type
Group	group the outcomes in the next few columns applies to: all or subgroup label
Outcomes	confirmed infection/asymptomatic/mild symptomatic/severe symptoms/hosp/ICU/death/biomarkers
1st Dose VE	VE with 95% CI
Days post 1st dose	days post 1st dose when VE measured
2nd Dose VE	VE with 95% CI
Days post 2nd dose	days post 2nd dose when VE measured
Over Study Period	number
Rate per 100 pt years	vaccinated vs control
HR	vaccinated vs control

RR	vaccinated vs control
Biomarkers	antibody titres
PCR-conf	percent PCR confirmed with Ct value if available
NAAT	percent confirmed by NAAT
(repeat above outcome columns for each VARIANT)	
Transmission	infection rates in contacts (overlaps with studies of duration of infectivity)
Viral load	
Detection Frame	
Duration of infectivity	correlation of serial rRT-PCR test results with virus cultures, studies of contracts, modelling studies
Critical appraisal	See appendix 2
Comments	

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, previous COVID19 infection)
Intervention	COVID19 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

Use of PPE; self-isolation

Appendix 5: Detailed description of the narrative summary statement

We aim at providing a lay language, concise, standardized summary statement for each combination of vaccine/VOC for which we found evidence. Where more than one study was found, we will provide a summary statements.

We are reporting on the following clinical outcomes: prevention of infection, severe illness, and death, and prevention of transmission. As a default, we will provide one statement for overall infection prevention and prevention of severe illness (or absence of evidence thereof). Other statements may be added as needed.

We will use the following template whenever possible:

Vaccine X provides a XX% protection from infection and XX% protection from severe illness due to variant Y [optional subgroup: in people such and such] =>dd days after [first/second] dose. # people, #studies, quality.

Examples (not real statement, look for real statements in the synopsis):

Example 1: Moderna (mRNA) provides an 84% protection from infection and >90% protection from severe illness due to the B1.1.7. variant two weeks after the second dose. 12,000 people, one study, moderate confidence.

Example 2: AZ provides a 10% protection from infection due to the B.1.351 variant and unknown protection from severe illness two weeks after the first dose. 50,747 people, one study, high confidence.

Example 3: Pfizer (mRNA) provides a 62-84% protection and >90% protection from severe illness from infection due to the B1.1.7. variant two weeks after the first dose. 250,000 people, seven studies, moderate confidence.

The level of protection is provided whenever possible as % reduction of the risk of infection. Complete protection would be 100% protection, complete absence of protection 0%. How much is enough is a judgement call and may vary case by case. Some vaccines provide incomplete protection against the original strain of COVID19; the same level of protection is the maximum expected for each variant.