COVID-19 Living Evidence Synthesis #6

(Version 4: 7 May 2021)

Question

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

Findings

We present in Table 1 the key findings about vaccine effectiveness. Three rows in the table have been updated since the previous edition of this living evidence synthesis, all of which are signaled by a last-updated date of 5 May 2021 (highlighted in yellow). New data were added for Pfizer efficacy against the R.1 variant. Second, efficacy data for NVX-CoV2372 against B1.351 and CoronaVac against P.1 have been reviewed. We have therefore added rows for a new variant of concern R1 and for the new Indian variant B.1.617.2.

Overall, we have moderate confidence that the Pfizer vaccine is effective against VOC B1.1.1.7 and low quality evidence it is protective against the R.1 variant. We have moderate confidence that the Johnson & Johnson vaccine is effective against B1.351, the Moderna vaccine is effective against the B1.1.7., and that the AZ vaccine is not effective and NVX-CoV2372 moderately effective against mild-to-moderate COVID-19 associated with B1.351. We have low confidence that CoronaVac is moderately effective against B1.351. We do not have data relating to VOC for other vaccines/variants combinations. Overall, the evidence shows higher protection versus symptomatic disease than infection rate. The sample sizes for included studies are such that vaccine effects on mortality cannot yet be reliably estimated for variants of concern. We present our methods in Box 1 and Appendices 1-4.

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 and 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. High quality review of RCTs (AMSTAR 10/11); *last update 2021-03-26*
	By variant of concern	
	• B.1.1.7	BNT162b2 showed the same VE as the phase III trial (46-60% 14 days after 1st dose) and 85.7-92% 7 days or 70-94% 14-21 days after 2nd dose) in a population with an estimated circulation of B.1.1.7. up to 80-94%. Neutralization effect was 2.4 lower after 2nd dose in a population with >90% B.1.1.7. Ct>30 reduced by 88% and symptomatic episodes reduce by 90%; no difference with previous infection protection (6 studies, moderate to low quality of the evidence)[1][2][3][11][12][13]*last updated 2021-04-22*
	• B.1.351	There are not yet clinical data, but neutralizing experiments showed a 8 times lower VE BNT162b2 in a population with <1% B.1.351 (1 study, low quality of the evidence)[3] *last update 2021-04-14*
	• P.1	no data
	• CAL.20C	no data
	R.1	BNT162b2 provides a 66.2% protection from infection and **94.4%** protection from severe illness due to variant R.1 in residents of a nursing facility after second dose. 189 people, 1 study, low quality. [17] *last update 2021-05-07*
	B.1.617.2	
	By special population	
	• Healthcare workers	BNT162b2 was VE in reducing the infection rate in HCW by about 55% (HR 0.45, 95% CI 0.42 – 0.49) to 80% (95% CI 59-90) after the first dose and 90 (95% CI 68-97) after the second dose; hospitalization after the first dose was reduced by 91% (HR 0.16, 95% CI 0.09 – 0.27) (2 studies, moderate to low quality of the evidence) [6][8] *last update 2021-04-14*
	• HCW, B.1.1.7	A single dose of BNT162b2 vaccine showed vaccine effectiveness of 70% (95% CI 55–85) 21 days after first dose and 85% (74–96) 7 days after two doses in HCW (median age 46, 84% females)[14], *last update 2021-04-30*

	• LTC, B.1.17	VE for BNT162b2 at 35-48 days was (aHR 0·35 [0·17, 0·71])(median age 86)[15][16] *last update 2021-04-30*
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. High quality review of RCTs (AMSTAR 10/11); *last update 2021-03-26*
	By variant of concern	
	• B.1.1.7	mRNA-1273 VE was 58.9 (−9.7, 84.5) 15 days after 1 dose, and 85.7 (67.2, 93.9) 15 days after 2 dose. (1 study, moderate quality of the evidence, [11] *last updated 2021-04-22*
	• B.1.35.1	no data
	• P.1	no data
	• CAL.20C	no data
	R.1	
	B.1.617.2	
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 rare but serious. (*) High quality review of RCTs (AMSTAR 10/11); *last update 2021-03-26*. (*) judgement on adverse adjusted to account for Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT).
	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 74.6% (95% CI, 41.6 to 88.9) compared to 84.1% (95% CI, 71 to 91) versus naïve COVID19; neutralization effect was 9 times lower; VE confirmed at 65-74% after one dose in large observational retrospective cohorts (1 RCT, 2 Obs, moderate to low quality of the evidence)[5][12][13] *last updated 2021-04-22*
	• B.1.351	ChAdOx1 nCoV-19 vaccine (two doses) had no efficacy against the B.1.351 variant in preventing mild to-moderate Covid-19 (1 RCT, moderate quality of the evidence). [4] *last update 2021-04-14*
	• P.1	no data
	• CAL.20C	no data
	R.1	
	B.1.617.2	
	Special populations	

	• LTC, B.1.17	VE for ChAdOx1 at 35-48 days was (aHR 0·32 [0·15-0·66] (median age 86)[15][16] *last update 2021-04-30*
Johnson & Johnson	Overall	[Johnson & Johnson's Janssen vaccine] Synthesis pending. High quality review of RCTs (AMSTAR 8/9); *last update 2021-04-23* 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% (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) [10] Rare but serious thrombotic side effects were reported (data not systematically reviewed). *last updated 2021-04-30*
	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, moderate quality of the evidence) [10] *last updated 2021-04-22*
	• P.1	no data
	• CAL.20C	no data
	R.1	
	B.1.617.2	
Sinovac (Coronavac)	• Overall	[Coronavac] Synthesis pending. High quality review of RCTs (AMSTAR 8/9); *last update 2021-04-23*
	• By variant of concern	
	• B.1.1.7	no data
	• B.1.351	no data
	• 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 firstdose. ~500 people, 1 study, very low quality.[19]; *last update 2021-05-07*
	• CAL.20C	no data
	• R.1	
	• B.1.617.2	
NVX-CoV2372	• Overall	Synthesis pending.
	• By variant of concern	
	• B.1.1.7	no data

	• B.1.351	NVX-CoV2372 provides a 57.7% protection from infection due to variant B1.351 =>7 days after second dose. 4387 people, 1 RCT, [18] Low quality(*); *last update 2021-05-07*. (*) because one study only.
	• P.1	no data
	• CAL.20C	
	• R.1	
	• B.1.617.2	

Links to references are provided in Appendix 1

Iorio A, Little J, Linkins L, Abdelkader W, Bennett D, Lavis JN. COVID-19 living evidence syntheisis #6 (version 6.4): What is the efficacy and effectiveness of available COVID-19 vaccines in general and specifically for variants of concern? Hamilton: Health Information Research Unit, 7 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%	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 (90% [>7 days] and 94% [14 days] after second dose) against asymptomatic infections and death [91%] in a population with 94% of B.1.1.7.	Low	Cohort Israel, concordant with trial; effect on death (possible overlap with Dagan)
3	Kustin	BNT162b2 showed lower relative VE (2.4:1) against B.1.1.7. after first dose; and lower VE (8:1) against B.1.351 after second dose in a population with >90% of B.1.1.7 and <1% B.1.135	Moderate	C-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% (9-95%) 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 was VE in reducing the infection rate (and hospitalization) in household of vaccinated HCW by about 30% (HR .70, 95% CI 0.64 – 0.78); BNT162b2 was VE in reducing the infection rate in HCW by about 55% (HR 0.45, 95% CI 0.42 – 0.49) and	Moderate	Obs Scotland - (25% of cases 2 doses)

		hospitalization by 91% (HR 0.16, 95% CI 0.09 – 0.27)		
7	Hollinghurst	ChAdOx1nCoV-19 in people >60 dwelling in LTC reduced infection rate to 1.05%, with 90% of cases occurring within 4 weeks of vaccination;	Serious	Obs Wales – 75% cases AZ
8	Thompson	BNT162b2 and mRNA-1273 VE in HCW, first line responder and essential/frontline workers was 80% (95% CI 59-90) after the first dose and 90 (95% CI 68-97) after the second dose	Low	Obs US, multicentric Prospective, standardized, weekly PCR testing; small size. 63% Pfizer, 27% Moderna; larger prevalence of infection in male, Hispanic.
9	Mor	BNT162b2 or mRNA-1273 VE in LTC reduced cumulative number of confirmed infections by 5.2 per 100 at risk at 7 weeks post vaccination in the early group	Moderate	Obs USA, multiple LTC; routine screening; no details on testing
10	Sadoff	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% (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). 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.	Low	RCT Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States;
11	Andrejko	BNT162b2 or mRNA-1273 VE was 58.9 (−9.7, 84.5) 15 days after 1 dose, and 85.7 (67.2, 93.9) 15 days after 2 dose	Moderate	Obs test-negative, case-positive random sampling matched control study. 69% of population at time had variants B.1.1.7., {B.1.427, B.1.429).
12	Glampson	ChAdOx1nCoV-19 or BNT162b2 showed a 74% (HR 0.26 (0.19-0.35)) and 78% (HR 0.22 (0.18-0.27)) 28 days after first vaccination dose, compared to unvaccinated subjects.	Moderate	Obs 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.

13	Pritchard	ChAdOx1nCoV-19 or BNT162b2 showed VE as infection reduction of 65% (60-70%) 21 days after first dose and 70% (62-77%) after second dose, compared to unvaccinated subjects. 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	Obs 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)
14	Hall (SIREN)	A single dose of BNT162b2 vaccine showed vaccine effectiveness of 70% (95% CI 55–85) 21 days after first dose and 85% (74–96) 7 days after two doses in the study population.	Low	prospective cohort with standardized testing and adjustment for confounders, HCW, all of England; 23,000, 46 yo, 84% females.
15	Shrotri	Similar effect sizes were seen for ChAdOx1 (aHR 0·32 [0·15-0·66] and BNT162b2 (aHR 0·35 [0·17, 0·71]) vaccines at 35-48 days.	Low	9160 of 10412 frail LTC residents (median 86 yo), 66% Pfizer, 33% AZ. Prospective testing.
16	Hyams	First dose vaccine effectiveness of BNT162b2 was 71.4% (95% confidence interval [CI] 46.5-58 90.6). ChAdOx1nCoV-19 first dose vaccine effectiveness was 80.4% (95% CI 36.4-94.5). When effectiveness analysis for BNT162b2 was restricted to the period covered by ChAdOx1nCoV-19, the estimate was 79.3% (95% CI 47.0-92.5).	Moderate	Test negative case control, Scotland. Small sample, single center, median age 86. Adjusted/matched Cox
17	Cavanaugh	The estimated VE against SARS-CoV-2 infection among residents was 66.2% (95% CI = 40.5%–80.8%) and among HCP was 75.9% (95% CI = 32.5%–91.4%). VE against symptomatic COVID-19 was 86.5% (95% CI = 65.6%–94.7%) among residents and 87.1% (95% CI = 46.4%–96.9%) among HCP. VE against hospitalization was 94.4% (95% CI = 73.9%–98.8%) among residents; no HCP were hospitalized. Three residents died, two of whom were unvaccinated (VE = 94.4%; 95% CI = 44.6%–99.4%).	Serious	variant R1 – outbreak analysis =small sample size
18	Shinde	NVX-CoV2372 vaccine efficacy was	RCT	4387 participants

		57.7% (25.7-75.9) for symptomatic infection by B1.351 7 days after 2nd dose.		39/41 cases B1.351
19	Hitchings	Estimated vaccine effectiveness of CoronaVac at least one dose against any SARS-CoV-2 infection was 35.1% (95% CI, -6.6 - 60.5) in the same time period. Vaccination with at least one dose was associated with a 0.50-fold reduction (adjusted vaccine effectiveness, 49.6%; 95% CI, 11.3 - 71.4) in the odds of symptomatic SARS-CoV-2 infection during the period 14 days or more after receiving the first dose.	Serious	53,176 participants, HCW in Manaus 75% prevalence of P1 test-negative case control; 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

Section 2: studies under appraisal

#	Author	Notes
1		
2		
3		

Section 3: excluded studies

#	Author	Reason for exclusion	Notes
1	Jacobson	Not actionable information, and high risk of bias.	Imprecise information about infection rate, proportion of prevalent variant, amount of missing outcome data.
2	Bjok	No VOC data	
3	Swift	No VOC data	

Appendix 2: 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 3: 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 4. 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 single summary statement.

We are reporting on clinical outcomes (whether the vaccines prevent infection, severe illness and death, and prevent 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.