COVID-19 Living Evidence
Synthesis # 8
(Version 8.1: 14 December 2021)

Question

What is the effectiveness of available COVID-19 vaccines for children and adolescents, including variants of concern?

Findings

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

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

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

Overall, 7 studies were appraised and 3 used to complete this summary. The reasons for excluding the remaining 4 studies are reported in the second section of Appendix 2.

Box 1: Our approach

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

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

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

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

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

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

Pfizer/Comirnaty [BNT162b2]

- **Overall**
  - We have low certainty evidence that 1 dose **BNT162b2** prevented infection from SARS-CoV-2 (non dominant variant) (67% [95% CI, 50 to 78] - 1 Obs) in adolescents age 12 to 15 years [3]
  - We have low certainty evidence that 2 doses of **BNT162b2** prevented infection from SARS-CoV-2 (non dominant variant) (91% [95% CI, 88 to 93] - 1 Obs) in adolescents age 12 to 15 years [3]

- **VOC Delta**
  - We have low certainty evidence that 1 dose of **BNT162b2** prevented infection from VOC **Delta** (59% [95% CI, 52 to 65] - 1 Obs) in adolescents age 12 to 18 years[2]
  - We have low certainty evidence that 2 doses of BNT162b2 prevented infection from VOC **Delta** (range of mean estimates: 90 to 92% - 2 Obs) in adolescents age 12 to 18 years [1][2]

Until the date of publication of this report, we have no information on the effectiveness of other vaccines in a population under 18 years of age.

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

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

Colour indicates level of certainty based on the evidence

High certainty evidence	Moderate certainty evidence	Low certainty evidence
pooling of low to moderate risk of bias RCTs or pooling of observational studies with low risk of bias and consistent findings	single RCT with low to moderate risk of bias or >one observational study with low to moderate risk of bias and at least partially consistent findings	single RCT or observational study with serious risk of bias or multiple low to serious risk of bias observational studies with inconsistent findings

Outcome (and vaccine)	Vaccine Effectiveness (2 doses unless otherwise stated) for each combination of vaccine, variant, and outcome					
	Overall	**Alpha**	**Beta**	**Gamma**	**Delta**	**Omicron**
Any Infection						
Pfizer	91%				90 - 92%	
Moderna						
CoronaVac						
Symptomatic Infection (reported when data on "any infection" is limited)						
Pfizer						
Moderna						
CoronaVac						
Transmission						
Pfizer						
Moderna						
CoronaVac						
Severe Disease (may include death for some studies)						
Pfizer						
Moderna						
CoronaVac						
Death						
Pfizer						
Moderna						
CoronaVac						

*Single dose
**mean estimate of effect less than the lowest acceptable limit for vaccine effectiveness as determined by WHO
AZ, AstraZeneca

Table 2: Key findings about vaccine effectiveness

Vaccine	Effectiveness	Findings
Pfizer/ BioNTech **Comirnaty** **[BNT162b2]**	Overall	BNT162b2 provided protection against infection for the following outcomes at least 14 days after 1st dose in adolescents age 12 to 15: ● 67% (95% CI, 50 to 78) from infection ● 100% (95% CI, 100 to 100) from hospitalization BNT162b2 provided protection against hospitalization for the following outcomes at least 7 days after 2nd dose in adolescents age 12 to 15: ● 91% (95% CI, 88 to 93) from infection ● 81% (95% CI, -55 to 98) from hospitalization (1 Obs) [3]; *last update 2021-12-13*
	By variant of concern	
	● Delta	BNT162b2 provided protection against VOC Delta for the following outcomes at least 14 days after 1st dose: ● 59% (95% CI, 52 to 65) from infection BNT162b2 provided protection against VOC Delta for the following outcomes at least 7 days after 2nd dose: ● 90 to 92% against infection (RME) (2 Obs) [1][2]; *last update 2021-11-17 from COVID-19 living evidence synthesis #6 (version 6.25)*
Moderna **Spikevax** **[mRNA-1723]**	Overall	No data
AstraZeneca [ChAd0x1] **Vaxzevria** **Serum Institute of India [Covishield]***	Overall	No data
Johnson & Johnson [AD26.COV2.S]*	Overall	No data
Sinovac [CoronaVac]	Overall	No data
Sinopharm (Wuhan) [WIV04]* **Sinopharm (Beijing) [HBO2] [BBIBP-CorV]***	Overall	No data
Novavax [NVX-CoV2373]*	Overall	No data

FBRI [EpiVacCorona]*	Overall	No data
Bharat Biotech [Covaxin] [BBV152]*	Overall	No data
Gamaleya [Sputnik V] [Gam-COVID-Vac]*	Overall	No data

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

*As of the date of publication, these vaccines have not been approved for the population of children and adolescents.

Flórez ID[1,2], Velásquez-Salazar P[1], Martínez JC[1], Linkins L[3], Abdelkader W[3], Iorio A[3], Lavis J[3], Patiño-Lugo DF[1]. COVID-19 living evidence synthesis #8 (version 1): What is the effectiveness of available COVID-19 vaccines in children and adolescents in general and specifically for variants of concern? Evidence and Deliberation Unit for Decision Making (UNED), University of Antioquia & Health Information Research Unit (HIRU), McMaster University, 14 December 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.

[1] Faculty of Medicine, University of Antioquia, Colombia

[2] School of Rehabilitation Science, McMaster University, Canada

[3] Faculty of Health Sciences, McMaster University, Canada

Appendix 1: Summary of Study Findings and Appraisals

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	Glatman-Freedman	BNT162b2 showed VE 91.5% (95% CI, 88.2 to 93.9) against infection at least 8 days after 2nd dose in adolescents age 12 to 15 years. There were no deaths in either group.	Serious	Population cohort in Israel of adolescents age 12 to 15 years; 2,034,591 vaccinated person-days and 13,623,714 unvaccinated person-days; time and setting for VOC Delta
2	Reis	BNT162b2 showed VE 59% (95% CI, 52 to 65) against infection 14 to 20 days after 1st dose in adolescents age 12 to 18. BNT162b2 showed VE 90% (95% CI, 88 to 92) against infection 7 to 21 days after 2nd dose in adolescents age 12 to 18.	Moderate	Case-control study in Israel; 94,354 vaccinated matched to 94,354 unvaccinated adolescents age 12 to 18; time and setting for VOC Delta
3	Tartof	BNT162b2 showed VE 67% (95% CI, 50 to 78) against infection and VE 100% (95% CI, 100 to 100) against hospitalization at least +14 days after 1st dose in adolescents age 12 to 15 years. BNT162b2 showed VE 91% (95% CI, 88 to 93) against infection and VE 81% (95% CI, -55 to 98) against hospitalization at least +7 days after 2nd dose in adolescents age 12 to 15 years.	Moderate	Retrospective Cohort in USA of 3,436,957 Kaiser Permanente Southern California (KPSC) healthcare system members ≥12 years of age between Dec 14, 2020 – Aug 8, 2021. The cohort included 122,779 adolescents age 12 to 15 years. The primary exposure was being fully vaccinated, defined as receiving 2 doses of BNT162b2 with ≥7 days after the second dose. Over the study period, 28.4% of 9,147 specimens sent for whole genome sequencing (WGS) and viral lineage designation were Delta.

Section 2: excluded studies	
Author	**Reason for exclusion**
Tang	Did not report the vaccine effectiveness in <18 years (and without enough data to calculate it)
Naleway	Did not report results according to vaccine type
Chadeau-Hyam	Vaccine effectiveness not reported/Modelling study
Chadeau-Hyam 1	Vaccine effectiveness not reported/Modelling study

Appendix 2: Glossary

AZ: AstraZeneca

Alpha: variant of concern B.1.1.7

Beta: variant of concern B.1.351

Delta: variant of concern B.1.617.2

Gamma: variant of concern P.1

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

MOD: Moderna

Obs: observational study

OR: odds ratio

PF: Pfizer

RME: range of mean estimates across 2 or more studies

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

VET: vaccine effectiveness against transmission

VOC: variant of concern

VOI: variant of interest

Appendix 3: Data-extraction template

Vaccine product	
Source	First author of study
Link	DOI or Pubmed ID
Date published	in format YYYY/MM/DD or preprint
Country	
Funding	public or industry
Study details	
Study type	RCT/cohort/data-linkage/test-negative/case-control/other
Surveillance	routine screening Y or N
Control group	not vaccinated, <7day vaccinated internal control, none, other
Total (N)	number of all study participants
Female	number or %
< 3 years	number or %
3 - 5 years	number or %
5 - 12 years	number or %
> 12 years	number or %
Outcomes	outcomes separated by VOC type
Outcomes	confirmed infection/asymptomatic/mild symptomatic/severe symptoms/hospitalized/ICU/death
1st Dose VE	VE with 95% CI
Days post 1st dose	days post 1st dose when VE provided
2nd Dose VE	VE with 95% CI
Days post 2nd dose	days post 2nd dose when VE provided
Rates per X person-days/years	vaccinated vs control
HR	vaccinated vs control
RR	vaccinated vs control
Adjusted	Regression, stratification, matching and associated variables
Transmission	infection rates in unvaccinated contacts of vaccinated individuals
Critical appraisal	See Appendix 5

Appendix 4: Process for assigning Variant of Concern to studies

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

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

Appendix 5: Research question and critical appraisal process (revised 12 Dec 2021)

Review question:

Participants	People aged under 18 years at risk of COVID-19 (usually without but sometimes with previous COVID-19 infection)
Intervention	COVID-19 Vaccine
Comparator	Unvaccinated children and adolescents (*)
Outcomes	PCR-diagnosis of COVID-19 infection; symptomatic disease; hospital/ICU admission; death; transmission

(*) Eligible studies must have a comparison group (unvaccinated; non-immune period; time since vaccination; 2 doses vs 3 doses); before-after studies, where the infection rate in the first 2 weeks after the vaccination are used as control are commonly performed and may be appraised

Key exclusion criteria

Studies that address the question of interest but from which the information of children cannot be separated from that of adults.
Comparison of one vaccine vs another (e.g. relative effectiveness) is not eligible.
Studies reporting only antibody responses are excluded.

Critical Appraisal Process

We appraise the quality of the individual studies using an adapted version of ROBINS-I. This tool classifies the Risk of Bias of a study as **Low, Moderate, Serious, Critical, or No Information**. Low Risk of Bias indicates High Quality, and Critical Risk of Bias indicates Very Low (insufficient) Quality. ROBINS-I appraises 7 bias domains and judges each study against an ideal reference randomized controlled trial. To improve the utility of ROBINS-I for assessing studies reporting vaccine effectiveness, we have focused on study characteristics that introduce bias as reported in the vaccine literature. (WHO. Evaluation of COVID-19 vaccine effectiveness. Interim Guidance. 17 March 2021). Studies rated as "critical" risk of bias will not be included in the Summary statements on Page 1-2 (exception: if limited data available for an outcome for a VOC). An overall judgement of "serious" or "critical" is given when the study is judged to be at serious or critical risk of bias in at least one domain or "serious" in 3 separate ROBINS-I domains.

VE Study Characteristics that may introduce bias	Description
Study design ROBINS-I: Bias in selection of participants into study	In cohort studies, people who get vaccinated may differ in health-seeking behaviour from people who do not get vaccinated; using a test-negative study design minimizes this type of bias Examples and typical judgement: • test-negative design with a clearly defined symptomatic study population (low) • test-negative design (mixed or unclear study population) or case-control or cohort design or data-linkage with no concerns (moderate) • cross-sectional design or case-control (concerns about whether controls had same access to vaccines/risk of exposure to

	COVID or unclear) or cohort design (concerns that exposed and non-exposed were not drawn from the same population) (serious)
Method for confirming vaccination ROBINS-I: Bias in classification of interventions	Questionnaires are prone to recollection bias; Population databases developed for purpose of tracking COVID vaccines minimize this type of bias <u>Examples and typical judgement</u>: • database linkage study (low) • Questionnaire with confirmation by an additional method (e.g. registry) of at least a subset of study population (moderate) • Questionnaire without confirmation by an additional method (serious) • Estimating vaccination status based on surveillance data alone (critical)
Databases used for retrieval of COVID test results, participant prognostic factors, and clinical outcomes ROBINS-I: Bias in classification of interventions	Databases developed for collecting data on COVID are less prone to bias due to missing information and misclassification <u>Examples and typical judgement</u>: • database for non-COVID purpose but with individual level data (moderate) • database for non-COVID purpose without individual level data (serious) • no or unclear description of database type (critical)
Assignment of infection start date ROBINS-I: Bias in classification of interventions	Using date of symptom onset (if within 10 days of testing) as infection start date reduces risk of misclassification bias (e.g., vaccinated participant who is reported as COVID+ may have been infected prior to receiving the vaccine or during non-immune period) and sensitivity of assays decreases over time <u>Examples and typical judgement</u>: • using a PCR positive test that was part of an ongoing standardized monitoring system (e.g., within a health network) (low) • using sample date without interview or documented confirmation of symptoms ≤ 10 days (relevant for symptomatic disease only) (serious)
Verification of symptoms ROBINS-I: Bias in classification of interventions	Prospective, standardized collection of symptoms from patients reduces risk of missing information bias; testing within 10 days after symptom onset reduces risk of false-negative COVID test <u>Examples and typical judgement</u>: • using sample date without patient report/ documented confirmation of symptoms ≤ 10 days (relevant for symptomatic disease only) (serious) • if symptomatic COVID is not an outcome (no information)
Accounting for non-immune period (first 14	Reported absence of vaccine effect during non-immune period reduces risk of residual confounding bias

days after first vaccine dose) ROBINS-I: Bias due to confounding	<u>Example/common case</u>: • presence of an effect during non-immune period or result not reported (moderate) • unclear that non-immune period was considered (serious)
Inclusion of participants with prior COVID infection ROBINS-I: Bias due to confounding	Exclusion (or separate analysis) of participants with prior COVID infection reduces concern about differences in infectivity as well as risk-taking and health-seeking behaviour <u>Examples and typical judgement</u>: • inclusion of prior infection status as a covariate in the models (moderate) • previously infected not excluded or analyzed separately (serious)
Accounting for calendar time ROBINS-I: Bias due to confounding (time-varying confounding)	Accounting for calendar time reduces bias due to differences in vaccine accessibility and risk of exposure over time <u>Examples and typical judgement</u>: • use of time-varying statistics without explicit mention of adjustment for calendar time (moderate) • not taken into account but short-time frame (e.g. ≤2 months) (serious) • not taken into account and time frame >2 months (critical)
Adjustment for prognostic factors ROBINS-I: Bias due to confounding	Adjustment for prognostic factors for COVID infection, severity of disease, and vaccination, such as age, gender, race, ethnicity, socioeconomic factors, occupation (HCW, LTC), and chronic medical conditions <u>Examples and typical judgement</u>: • no or insufficient adjustment for occupation (or number of tests as a surrogate for exposure risk) -exception age>65 or LTCF resident (moderate) • no or insufficient adjustment for socioeconomic factors (or neighborhood or income as a surrogate), race, ethnicity (serious) • no or insufficient adjustment for age (any study population) or chronic medical conditions (LTC)(critical)
Testing frequency ROBINS-I: Bias in measurement of outcomes	Similar frequency of testing between groups reduces risk of bias introduced by detecting asymptomatic infection in one group but not in another (e.g. when only one group undergoes surveillance screening) <u>Examples and typical judgement</u>: • no systematic screening but consistent methods for detection in one group vs. the other, e.g., within health networks (moderate) • screening performed for a subset of both study groups (serious) • screening performed routinely in one study group but not in the other (critical)

Appendix 6: Detailed description of the narrative summary statement

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

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

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

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

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