Pfizer-BioNTech COVID-19 Vaccine Medical Data Website

Systematic Literature Review Protocol

June 2023

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EMERGENCY USE AUTHORIZATION

Pfizer-BioNTech COVID-19 Vaccine, Bivalent has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals aged 6 months of age and older. The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner. Please see EUA Fact Sheets at www.cvdvaccine-us.com.

Monovalent mRNA COVID-19 vaccines are no longer authorized for emergency use in the United States. FDA and CDC guidance is to check inventory and dispose of monovalent mRNA vaccines according to state and local regulations.

1. Introduction

The information provided is for general informational and educational purposes. Pfizer will use reasonable efforts to include accurate and up-to-date information but makes no warranties or representations of any kind as to accuracy, currency or completeness.

Real-world evidence (RWE) studies that are designed to directly compare COVID-19 vaccines are not included in the website. RWE studies that report data for multiple COVID-19 vaccines without a direct comparison will be included and show only BNT162b2 data. Clinical trial publications may be included if they are non-comparative.

Terms of Use for the Pfizer-BioNTech COVID-19 Vaccine Medical Data website can be accessed here: https://www.pfizer.com/general/terms.

1.1 Objective

The objective of this systematic literature review (SLR) is to identify and select published, peer-reviewed clinical trial data and real-world evidence relevant to Pfizer-BioNTech COVID-19 Vaccine, Original Monovalent BNT162b2 and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) with topic-specific date limits as specified in Appendix 1. Periodic updates are planned as additional publications become available.

1.2 Scope of topics

The scope of the SLR addresses the following research topics to identify studies that meet predefined methodology requirements:

1. General Population - OMICRON: Published, peer-reviewed clinical trial & RWE studies for the Omicron variant
    - Vaccine Effectiveness against Omicron (Monovalent Adult primary series and booster; Pediatrics primary series and booster)

- Vaccine Effectiveness against Omicron (Bivalent Adult and Pediatrics)

2. General Population – Pre-OMICRON: Published, peer-reviewed clinical trial & RWE studies for earlier variants
    - Vaccine Effectiveness (Adult primary series and booster; Pediatrics primary series and booster)
3. Special Populations
    - Pregnant Women – Vaccine Effectiveness from RWE studies
    - Immunocompromised – Vaccine Effectiveness from RWE studies
    - Geriatrics – Vaccine Effectiveness from RWE studies
4. VACCINE SAFETY: Published, peer-reviewed clinical trial & RWE studies related to vaccine safety
    - Clinical Trials – Vaccine Safety
    - Vaccine-associated Myo/pericarditis

2. Methods

2.1 Searching method: Data sources

Peer-reviewed Publication Databases: The searches are conducted in the following databases using the Ovid® SP platform:

- Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline® Daily, and Medline® and Versions. All trademarks are the property of their respective owners.

The search strategy is based on a combination of free text words, indexing terms (e.g., Medical Subject Headings [MESH] terms or Excerpta Medica database [EMBASE] subject heading [EMTREE]) and their relationship using Boolean terms (e.g., 'and', 'or', 'not'). Search strategies for all sources searched are included in Appendix 2.

Citation searching: The search includes cross-checking bibliographies of related sites to identify additional studies that are relevant.

- International Vaccine Access Center (IVAC) & World Health Organization summary of COVID-19 vaccine effectiveness studies: https://view-hub.org/resources

2.2 Searching method: Criteria

The search criteria are presented according to the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Study design) format based on the research topics (Omicron variant; other VE & Safety).

Table 1: PICOTS criteria for studies of outcomes related to the Omicron variant

Criterion	Description

Population	General population infected with the Omicron variant
	• Subgroups of interest:
	  ○ Demographics: Country or region, sex, race/ethnicity
	  ○ Age: 6 months - 4 years of age, 5-11 years of age, 12-15 years of age and 16 years of age and older
	  ○ Population: general population, pregnant women, immunocompromised, geriatric
	  ○ Variant: any Omicron subvariant
	  ○ Prior COVID-19 status: with or without prior SARS-CoV-2 infection

Intervention	• Pfizer-BioNTech COVID-19 Vaccine, Original Monovalent BNT162b2 • Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Comparators	Real-world evidence (RWE) studies that are designed to directly compare COVID-19 vaccines are not included in the website. RWE studies that report data for multiple COVID-19 vaccines without a direct comparison will be included and report only BNT162b2 data. Clinical trial publications may be included if they are non-comparative.

Criterion	Description
Outcome domains*	1. Vaccine Effectiveness 2. Safety • Subgroups: ○ Dose: first dose, second dose, third dose (1st booster), fourth dose (2nd booster) ○ Time interval: time since last dose (in months) Exclude: • Results presented *only* as immunogenicity, neutralization titer, antibody titer • Heterologous primary vaccination or booster studies • Adverse events of interest presented only as number of cases, without a denominator
Time	Bibliographic searches will range from November 24, 2021-current
Inclusion / Exclusion	Include: • Peer-reviewed publications (Letters to Editor and other published correspondence are included if they contain outcome data) 1. Identify an 'earliest start date' timeframe for each vaccine-related topic (e.g. completion of first clinical trial, first identification of a variant of concern, first identification of adverse events of interest) 2. Search MEDLINE/OVID using keywords related to vaccine-related topic, vaccine, and timeframe 3. Compare search results with the list of studies on View-Hub (COVID-19 vaccine medical data website from International Vaccine Access Center, Johns Hopkins and WHO) to identify any missed articles 4. Evaluate Peer-reviewed publications for inclusion a. Screen abstracts to confirm publication matches the topic (completed by medically trained persons) b. Use Newcastle-Ottawa Scale to assess the quality of real-world evidence studies . Studies with NOS score >6 are included. (completed by medically trained persons) Exclude: • Preprints • Biological mechanism studies • Case reports • Clinical series reports • Congress abstracts or posters • Modeling studies • Non-English publications • Press releases

Criterion	Description
Other	• No geographical limit

Table 2: PICOTS criteria for studies of Vaccine effectiveness / Vaccine efficacy and safety outcomes

Criterion	Description

Population	The general population of adults and children (at least 6 months of age) eligible for COVID-19 vaccination
	• Subgroups of interest:
	  ○ Demographics: Country or region, sex, race/ethnicity
	  ○ Age: 6 mo-4 years of age, 5-11 years of age, 12-15 years of age, and 16 years of age and older
	  ○ Population: general population, pregnant women, immunocompromised, geriatric

Intervention	• Pfizer-BioNTech COVID-19 Vaccine, Original Monovalent BNT162b2 • Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Comparators	Real-world evidence (RWE) studies that are designed to directly compare COVID-19 vaccines are not included in the website. RWE studies that report data for multiple COVID-19 vaccines without a direct comparison will be included and report only BNT162b2 data. Clinical trial publications may be included if they are non-comparative.

Outcome domains	**Vaccine effectiveness (VE) / Vaccine efficacy**, defined as:
	1. Any infection
	2. Symptomatic
	3. Asymptomatic
	4. Hospitalization
	5. Severe disease/ICU admission
	6. Death
	Safety, defined as:
	1. General safety – including reactogenicity (local and systemic reactions) and adverse events
	2. Vaccine-associated Myo/pericarditis (presented as proportion with event, incidence rate, reporting rate, rate ratio, or hazard ratio)
	• Subgroups:
	  • Dose: first dose, second dose, third dose (1st booster), fourth dose (2nd booster)
	  • Time interval: time since last dose (in months)
	
	Exclude:
	• Results presented *only* as immunogenicity, neutralization, antibody titer

Criterion	Description
	• Effectiveness/efficacy results reported *only* as hazard ratio, odds ratio, rate ratio or risk difference, and not as VE • Adverse events of interest presented only as number of cases, without a denominator
Time	• Bibliographic searches will range from December 11, 2020-current for Omicron RWE, through August 22, 2022 for pre-Omicron, and with relevant date limits for individual topics (see Appendix 1); • Bibliographic searches for phase 2/3/4 randomized controlled trials will be conducted without a date restriction
Inclusion / Exclusion	Include: • Peer-reviewed publications (Letters to Editor are included if they contain outcome data) 1. Identify an 'earliest start date' timeframe for each vaccine-related topic (e.g. completion of first clinical trial, first identification of a variant of concern, first identification of adverse events of interest) 2. Search MEDLINE/OVID using keywords related to vaccine-related topic, vaccine, and timeframe 3. Compare search results with the list of studies on View-Hub (COVID-19 vaccine medical data website from International Vaccine Access Center, Johns Hopkins and WHO) to identify any missed articles 4. Evaluate Peer-reviewed publications for inclusion a. Screen abstracts to confirm publication matches the topic (completed by medically trained persons) b. Use Newcastle-Ottawa Scale to assess the quality of real-world evidence studies. Studies with NOS score >6 are included. (completed by medically trained persons). Refer to Appendix 3 for additional information. Exclude: • Preprints • Biological mechanism studies • Case reports • Clinical series reports • Congress abstracts or posters • Modeling studies • Non-English publications • Press releases
Other	• No geographical limit

2.3 *Screening method: Title/abstract or Full-text review*

After excluding duplicate citations across the bibliographic databases, records are screened in steps.

Step 1 – Title and abstract review: All unique records identified from the searches are screened based on the predefined PICOTS criteria by two independent reviewers.

Step 2 – Full-text review: Full-text articles for all relevant studies identified from title and abstract screening are assessed using each full-text report based on the predefined PICOTS criteria by two independent reviewers. Discrepancies between reviewers are resolved by a third reviewer adjudication.

2.3 *Screening method: NOS scoring*

In order to select the most representative studies with high quality, for observational studies, the Newcastle-Ottawa Scale[3] (Appendix 3) is applied to evaluate the potential risk of bias, with a total maximum score of 9, and only studies with low risk of bias (score 7-9) are considered for study data extraction.

2.5 *Data extraction*

Extraction of data from the included studies is conducted using the standardized data extraction template. The data extracted from the included studies includes the information outlined in Table 4.

Table 3: Variables to be extracted from each study for content curation

Criterion	Description
Citation information	• Study ID • Tab name • Topic • Author(s) • Title • Journal or source name • Date of publication • Level of evidence: RCT or RWE; peer-reviewed • Trial registration; linked study IDs (if applicable)
Study overview	• Study name or network • Country • Study sponsor • Study design • Study period: start and end date of data collection • Source of population/data • Study objectives

Criterion	Description
	• Primary endpoint and definition • Summary of Conclusions and Limitations
Patient characteristics	• Study population category • Study population description • Inclusion/exclusion criteria • Total sample size • Vaccinated sample size • Age group • Mean or median age • Comorbidities • Prior history of COVID-19 infection
Vaccine characteristics	• Vaccine(s) • Vaccine dose • Comparator • Vaccine primary series • Booster type if applicable • Variant
Outcomes	**<u>Vaccine effectiveness / Vaccine efficacy:</u>** 1. Any infection 2. Symptomatic infection 3. Asymptomatic infection 4. Hospitalization 5. Severe/ICU admission 6. Death • For each VE outcome: ○ Study-specific definition ○ Metric for estimate and variance, e.g., VE (%), 95% confidence interval • Estimate – VE estimate only • Lower bound • Upper bound ○ Timepoint, time since last vaccination **<u>Safety and AE of Interest:</u>** 1. General safety: reactogenicity (local/systemic reactions), adverse events 2. Vaccine-associated Myo/pericarditis as a specific serious adverse event • For each safety outcome: ○ Study-specific definition

Criterion	Description
	○ Metric for estimate and variance, e.g., %, 95% confidence interval • Estimate - proportion with event, incidence rate, or reporting rate; rate ratio or hazard ratio • Lower bound • Upper bound ○ Timepoint, time since last vaccination **<u>Outcomes related to the Omicron variant:</u>** 1. Vaccine Effectiveness (e.g., hospitalization, severe COVID, death) • For each Omicron variant-related outcome: ○ Study-specific definition ○ Metric for estimate and variance, e.g., %, rate, rate ratio, 95% confidence interval • Estimate • Lower bound • Upper bound ○ Timepoint, time since last vaccination Predefined subgroups may include: • Vaccine: Pfizer-BioNTech COVID-19 Vaccine, Original Monovalent BNT162b2 and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) • Dose: 1st dose, 2nd dose, third dose (1st booster), fourth dose (2nd booster) • Time interval since last dose • Variant • Prior history of COVID-19 infection • Age: 6 mo-4 years of age, 5-11 years of age, 12-15 years of age, and 16 years of age and older • Sex • Race/ethnicity • Country

2.4 QC of extracted data

Accuracy of extracted data is completed for the following key variables:

- Study information: citation information, study name, level of evidence (e.g., peer-reviewed journal article), sponsor

- Study design: country, study dates, type (observational or interventional)
- Study population: sample size (total number, number vaccinated, number vaccinated by vaccine type), age (group, mean or median), comorbidities, variant
- Vaccine information: vaccine type, dose, timing interval
- Outcomes reported: VE, safety, subgroups
- Supporting information: study objective, outcome definition, inclusion/exclusion criteria, summary of conclusions and limitations, table/figure footnotes (if applicable)

Appendix 1 Date Limits for Study Selection

Category	Pfizer-BioNTech COVID-19 vaccine key dates	Start date for literature search/study selection
Omicron	**WHO: 11/24/2021**	**11/24/2021**
Pediatric	**EUA 12-15yo: 5/10/2021** **EUA 5-11yo: 10/29/2021** **EUA 6mo-4yo: 6/17/2022**	**5/10/2021**
Boosters	ACIP 12y/SIC: 8/13/2021 EUA 65yo/IC: 09/22/2021 **ACIP 18yo+: 10/21/2021** EUA 18yo+: 11/19/2021 EUA 16yo+: 12/9/2021 EUA 12yo+: 01/3/2022 **EUA Bivalent 12yo+: 08/31/2022** **EUA Bivalent 5yo+: 10/12/2022** **EUA Bivalent 6mo+: 12/8/2022** **EUA Bivalent: 04/18/2023**	**10/21/2021**
Vaccine Safety (general) **Vaccine Effectiveness**	**EUA 16yo+: 12/11/2020** Approval: 08/23/2021	**12/11/2020**
Myo/pericarditis	Case reports: 04/2021 **ACIP: 06/23/2021**	**06/23/2021**

Appendix 2 Search Strategy for OvidSP

Database(s) searched: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

1. RWE for Omicron

#	Concept	Search string
1	Population – COVID-19	COVID-19/ or ("COVID-19" or "Coronavirus disease 2019" or "Coronavirus 2019" or "SARS-CoV-2").ti,ab.
2	Outcomes of interest	(effectiv* or hospitali* or admit* or admission or death or mortality or "severe disease" or "severe illness" or "ICU admission" or "intensive care" or severity or breakthrough or transmission or transmit* or "prior infection").ti,ab.
3	Population + intervention + outcomes	1 and 2
4	Limit by language	limit 3 to english language
5	Limit by publication type	4 not (commentary or editorial or "case report*" or "case stud*" or "conference abstract").sh,hw,xs,pt.
6	Limit by date	limit 5 to rd=20211124-present
7	Omicron	6 and (Omicron or "B.1.1.529").ti,ab.
8	RWE	(Observational or Retrospective or Registry or registries or database* or "claims data" or "health record*" or data or surveillance or Prospective or 'cohort study' or cohort or cross-sectional or 'cross sectional' or "case-control" or "case control" or "real world" or rwe or rwd).ab,ti,hw,sh,xs,pt. or exp epidemiologic studies/ or exp case control study/ or exp observational study/ or exp longitudinal study/ or exp prospective study/ or exp retrospective study/
9	Limit to RWE	7 and 8

2. RCT for vaccine efficacy and safety

#	Concept	Search string
1	Population – COVID-19	COVID-19/ or ("COVID-19" or "Coronavirus disease 2019" or "Coronavirus 2019" or "SARS-CoV-2").ti,ab.
2	Intervention	(Pfizer or BioNTech or "Pfizer-BioNTech" or "Pfizer/BioNTech" or BNT162b2 or TOZINAMERAN or Comirnaty").ti,ab.
3	Outcomes of interest	(efficacy or safety or reactogenicity or adverse).ti,ab.
4	Population + intervention + outcomes	1 and 2 and 3
5	Limit by language	limit 4 to english language
6	Limit by publication type	5 not (commentary or editorial or "case report*" or "case stud*" or "conference abstract").sh,hw,xs,pt.
7	RCT	("randomized controlled trial").pt,xs,sh,hw. or (rct or randomi*).mp. or "placebo controlled".ab,ti. or ((randomi* or placebo or phase) adj3 (controll* or trial*)).ab,ti. or exp randomized controlled trial/
8	Limit to RCT	6 and 7

3. RWE for vaccine effectiveness and general safety

#	Concept	Search string
1	Population – COVID-19	COVID-19/ or ("COVID-19" or "Coronavirus disease 2019" or "Coronavirus 2019" or "SARS-CoV-2").ti,ab.
2	Intervention	(Pfizer or BioNTech or "Pfizer-BioNTech" or "Pfizer/BioNTech" or BNT162b2 or TOZINAMERAN or Comirnaty").ti,ab.
3	Outcomes of interest	(effectiv* or hospitali* or admit* or admission or death or mortality or "severe disease" or "severe illness" or "ICU admission" or "intensive care" or "testing positive" or "positive case*" or "documented infection" or "confirmed infection" or "symptomatic infection").ti,ab. or (reactogenicity or safety or adverse or "local reaction*" or "systemic event*" or "systemic reaction*").ti.
4	Population + intervention + outcomes	1 and 2 and 3
5	Limit by language	limit 4 to english language
6	Limit by publication type	5 not (commentary or editorial or "case report*" or "case stud*" or "conference abstract").sh,hw,xs,pt.
7	Limit by date	limit 6 to rd=20201211-20220822 for pre-Omicron
8	RWE	(Observational or Retrospective or Registry or registries or database* or "claims data" or "health record*" or data or surveillance or Prospective or 'cohort study' or cohort or cross-sectional or 'cross sectional' or "case-control" or "case control" or "real world" or rwe or rwd).ab,ti,hw,sh,xs,pt. or exp epidemiologic studies/ or exp case control study/ or exp observational study/ or exp longitudinal study/ or exp prospective study/ or exp retrospective study/
9	Limit to RWE	7 and 8

4. RWE for Myo/pericarditis

#	Concept	Search string
1	Population – COVID-19	COVID-19/ or ("COVID-19" or "Coronavirus disease 2019" or "Coronavirus 2019" or "SARS-CoV-2").ti,ab.
2	Intervention	(Pfizer or BioNTech or "Pfizer-BioNTech" or "Pfizer/BioNTech" or BNT162b2 or TOZINAMERAN or Comirnaty).ti,ab. or vaccin*.ti.
3	Outcomes of interest	(myocarditis or myopericarditis or pericarditis").ti,ab.
4	Population + intervention + outcomes	1 and 2 and 3
5	Limit by language	limit 4 to english language
6	Limit by publication type	5 not (commentary or editorial or "case report*" or "case stud*" or "conference abstract").sh,hw,xs,pt.
7	Limit by date	limit 6 to rd=20210413-present
8	RWE	(Observational or Retrospective or Registry or registries or database* or "claims data" or "health record*" or data or surveillance or Prospective or 'cohort study' or cohort or cross-sectional or 'cross sectional' or "case-control" or "case control" or "real world" or rwe or rwd).ab,ti,hw,sh,xs,pt. or exp epidemiologic studies/ or exp case control study/ or exp observational study/ or exp longitudinal study/ or exp prospective study/ or exp retrospective study/
9	Limit to RWE	7 and 8

Appendix 3 Newcastle-Ottawa Scale

Cohort or other observational studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories, and two star for the Comparability domain. A maximum of nine stars can be given to each study.

Selection

1) Representativeness of the exposed cohort (vaccinated)

a)* truly representative of the general population in the community – national database/samples,

b)* somewhat representative of the general population in the community – state or regional database/samples, health care system, samples from multiple sites

c) selected group of users – samples from a single site; select group of population, e.g., nurses, health care workers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort (unvaccinated)

a)* drawn from the same community as the exposed cohort

b) drawn from a different source (e.g. historical control)

c) no description of the derivation of the non exposed cohort

d) no non exposed cohort

3) Ascertainment of exposure (vaccination)

a)* vaccine administered at the institute or by study protocol

b)* secure record (medical/vaccination records)

c) interview or self report

d) no description

4) Demonstration that outcome of interest (SARS-CoV-2 infection and related outcomes; safety events) was not present at start of study

a)* yes

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis (multiple selection)

a)* study controls for age and comorbid conditions

b)* study controls for any additional factor

c) not controlled for the above factors

Outcome

1) Assessment of outcome (SARS-CoV-2 infection and related outcomes; safety events)

a)* independent blind assessment (e.g., COVID-19 test onsite or from testing institute; independent assessment of myocarditis)

b)* record linkage (e.g., medical record)

c) interview or self report

d) no description

2) Was follow-up long enough for outcomes to occur

a)* yes (efficacy/effectiveness: at least 14 days following last dose of vaccination; safety: at least 7 days following vaccination)

b) no

3) Adequacy of follow up of cohorts

a)* complete follow up - all subjects accounted for

b)* subjects lost to follow up unlikely to introduce bias - small number lost - > 80 %

follow up, or description provided of those lost)

c) follow up rate < 80% and no description of those lost

d) no statement

Case-control studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories, and two star for the Comparability domain. A maximum of nine stars can be given to each study.

Selection

1) Is the case (SARS-CoV-2 infection and related outcomes; safety events) definition adequate?

a)* yes, with independent validation (e.g., COVID-19 test onsite or from testing institute; independent assessment of myocarditis)

b)* record linkage (e.g., medical record)

c) interview or self report

d) no description

2) Representativeness of the cases (SARS-CoV-2 infection and related outcomes; safety events)

a)* consecutive or obviously representative series of cases (national, state, or regional database/samples, health care system, samples from multiple sites)

b) potential for selection biases or not stated (samples from a single site; select group of population, e.g., nurses, health care workers)

3) Selection of Controls (no SARS-CoV-2 infection or related outcomes; no safety events)

a)* community controls drawn from the same source

b) hospital controls or controls drawn from a different source

c) no description

4) Definition of Controls (no SARS-CoV-2 infection or related outcomes; no safety events)

a)* no history of disease (endpoint)

b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis (multiple selection)

a)* study controls for age and comorbid conditions

b)* study controls for any additional factor

c) not controlled for the above factors

Exposure

1) Ascertainment of exposure (vaccination)

a)* vaccine administered at the institute or by study protocol

b)* secure record (medical/vaccination records)

c) interview or self report

d) no description

2) Same method of ascertainment of exposure for cases and controls

a)* yes

b) no

3) Non-response rate or missing exposure information

a)* same rate for both groups

b) non respondents described; missing information described

c) rate different and no designation