**COMIRNATY (COVID-19 mRNA VACCINE)**
**RISK MANAGEMENT PLAN**

RMP Version number: 17.0

Data lock point for this RMP, see below:

| Age group[a] | Module SIII. Clinical Trial Exposure | Module SVII.3. Details of Important Risks |
|---|---|---|
| **Comirnaty LP. 8.1 (monovalent)** | | |
| Individuals:<br>6 months to <5 years of age<br>5 to 11 years of age<br>12 years of age and older | N/A | 18 June 2025<br>Pfizer safety database (non-CT dataset)<br>Stratified by product, age group and without booster doses counted |
| **Comirnaty KP.2 (monovalent)** | | |
| Individuals:<br>6 months to <5 years of age<br>5 to 11 years of age<br>12 years of age and older | N/A | 18 June 2025<br>Pfizer safety database (non-CT dataset)<br>Stratified by product, age group and without booster doses counted |
| **Comirnaty JN.1 (monovalent)** | | |
| Individuals:<br>6 months to <5 years of age<br>5 to 11 years of age<br>12 years of age and older | N/A | 18 June 2025<br>Pfizer safety database (non-CT dataset)<br>Stratified by product, age group and without booster doses counted |
| **Monovalent Omicron XBB.1.5** | | |
| Individuals:<br>6 months to <5 years of age<br>5 to 11 years of age<br>12 years of age and older | N/A | 18 June 2025<br>Pfizer safety database (non-CT dataset)<br>Stratified by product, age group and without booster doses counted |
| **bivalent BNT162b2 (original/Omi BA.1 and BA.4/BA.5)** | | |
| Individuals:<br>6 months to <5 years of age<br>5 to 11 years of age<br>12 years of age and older | N/A | 18 June 2025<br>Pfizer safety database (non-CT dataset)<br>Stratified by product, age group and without booster doses counted |
| **Comirnaty original (monovalent)** | | |
| Individuals:<br>6 months to <5 years of age<br>5 to 11 years of age<br>12 years of age and older | N/A | 18 June 2025<br>Pfizer safety database (non-CT dataset)<br>Stratified by product, age group and without booster doses counted |
| **bivalent BNT162b2 (original/Omi BA.4/BA.5)** | | |
| 12 years of age and older bivalent BNT162b2 (original/Omi BA.4/BA.5) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg) as primary series or 4th dose | 12 October 2022 Cohort 2<br>31 Oct 2022 Cohort 3<br>Study C4591044 | 12 October 2022 Cohort 2<br>31 Oct 2022 Cohort 3<br>Pfizer Clinical Database - Study C4591044 |
| 5-<12 years of age bivalent BNT162b2 (original/Omi BA.4/BA.5) modified vaccine (BNT162b2 + BNT162b2 OMI 10 µg) as 4th dose | 25 November 2022<br>[C4591048 Substudy D (group 2)] | 25 November 2022<br>Pfizer Clinical Database - Study C4591048 (SSD group 2) |

| | | |
|---|---|---|
| 6 months to <5 years of age bivalent BNT162b2 (original/Omi BA.4/BA.5) modified vaccine (BNT162b2 + BNT162b2 OMI 3 µg) as 4th dose | 25 November 2022 [C4591048 Substudy B, (group 2)] | 25 November 2022<br>Pfizer Clinical Database - Study C4591048 (SSB group 2) |
| **Comirnaty original (monovalent) + bivalent BNT162b2 (original/Omi BA.1)** | | |
| 12 years of age and older booster dose of a bivalent BNT162b2 (original/Omi BA.1) modified vaccine (BNT162b2 + BNT162b2 OMI 30 µg) | Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022 C4591031 (Substudy E).<br><br>11 March 2022 C4591031 (Substudy D – Cohort 2) | Sentinel cohort 05 April 2022 and expanded cohort cut-off date: 16 May 2022<br>Pfizer Clinical Database - Study C4591031 (Substudy E).<br><br>11 March 2022<br>Pfizer Clinical Database - Study C4591031 (SSD – Cohort 2) |
| **Comirnaty original (monovalent)** | | |
| 6 months to <5 years (Primary series) | 16 July 2021 (Phase 1)<br>29 April 2022 (Phase 2/3)<br><br>23 February 2023 (Phase 2/3, 6MPD3) | 29 April 2022<br>Pfizer Clinical Database – Study C4591007 (Phase 2/3) |
| 5 to <12 years of age (Primary series) | 06 September 2021 | 06 September 2021<br>Pfizer Clinical Database |
| Booster (3rd) dose in 5 to <12 years of age | 22 March 2022 (Phase 2/3) | 22 March 2022<br>Pfizer Clinical Database Study C4591007 |
| 12-15 years of age, including severely immunocompromised (Primary series) | 13 March 2021 (Pfizer Clinical Database) | 30 September 2021<br>Pfizer Safety Database (CT dataset) |
| Booster (3rd) dose in 12-15 years of age (6 months post dose 3 data) | 03 November 2022 (Study C4591001) | 03 November 2022<br>Pfizer Clinical Database, Study C4591001 |
| Booster (3rd) dose in 12-17 years of age 1 month post dose 3 | 14 July 2022 (C4591031 Substudy C) | |
| 16 years and older, including severely immunocompromised (Primary series) | 13 March 2021 (Pfizer Clinical Database)<br><br>23 October 2020 (BioNTech Clinical Database) | 30 September 2021<br>Pfizer Safety Database (CT dataset) |
| Booster (3rd) dose in 16 years and older[b] | 17 June 2021 (Study C4591001) | 17 June 2021<br>Pfizer Clinical Database - Study C4591001 |
| SV Post-Authorization Experience: 18 June 2025 | | |

a. Detailed language is included in the SmPC.

b. The safety and immunogenicity of a booster dose (third dose) of Comirnaty in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

Date of final sign off: 16 April 2026

Rationale for submitting an updated RMP (v 17.0): Upversion of previous RMP v 16.1 that

integrated RMP v 15.2 and posology change from single 10µg dose to 2-dose 10µg for 2 years to <5 years of age participants[1].

This comprehensive RMP update, which is based on the previously approved RMP v 16.0, encompasses a Type II variation (EMA/VR/0000320534) procedure that incorporates the posology change from 3 µg to 10 µg and dosing regimen simplification based on study C4591048 Substudy A (Groups 1-5):

1) from 3-dose to 2-dose primary course for 6 months to <2 years of age and

2) from 3-dose to 2-dose primary course for 2 years to <5 years of age.

Consequently, all references to the 3µg strength for all approved variant-adapted presentations have been removed, alongside consequential removal of study C4591048 as an additional pharmacovigilance activity in fulfilment of PAM-MEA-057.3 commitment. Further changes to the content of the RMP were also performed.

Summary of significant changes in the RMP version:

| **RMP Part/Module** | **RMP v 17.0 Major Changes** |
|---|---|
| PART I PRODUCT(S) OVERVIEW | |
| | Removal of 3 µg presentation for all approved variant-adapted formulations;<br>Removal of all XBB1.5 presentations;<br>Removal of Toppac (plastic) PFS JN.1 presentation;<br>Addition of posology change and dose regimen simplification. |
| PART II SAFETY SPECIFICATION | |
| PART II.Module SI Epidemiology of the Indication(s) and Target Populations | Removal of XBB1.5 presentation. |
| PART II.Module SII Non-Clinical Part of the Safety Specification | No changes made. |
| PART II.Module SIII Clinical Trial Exposure | No changes made. |
| PART II.Module SIV Populations Not Studied in Clinical Trials | No changes made. |
| PART II.Module SV Post-Authorisation Experience | No changes made. |
| PART II.Module SVI Additional EU Requirements for the Safety Specification | No changes made. |
| PART II.Module SVII Identified and Potential Risks | SVII.2: reactogenicity data from C4591048 SSA included. |
| PART II.Module SVIII Summary of the Safety Concerns | No changes made. |

[1] Reference is made to the CHMP Rapporteur's preliminary assessment report Request for Supplementary Information dated 23 March 2026 for the Type II variation procedure EMA/VR/0000320534.

| RMP Part/Module | RMP v 17.0 Major Changes |
|---|---|
| PART III PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES) | |
| III.1 Routine Pharmacovigilance activities. | Removal of 3 µg presentation for all approved variant-adapted formulations, Removal of all XBB1.5 presentations Removal of Toppac (plastic) PFS JN.1 presentation. |
| III.2 Additional Pharmacovigilance Activities<br>and<br>III.3 Summary Table of Additional Pharmacovigilance Activities | Updated to remove study C4591048 |
| PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES | |
| | No changes made. |
| PART V PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) | |
| V.1 Routine Risk Minimisation Measures<br><br>V.2 Additional Risk Minimisation Measures<br><br>V.3 Summary of Risk Minimisation Measures | Updated based on the changes made in Part II and PART III, as applicable. |
| PART VI PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN | |
| I The Medicine and What It Is Used For<br><br>II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks | Removal of XBB.1.5 presentation.<br>Updated based on the changes made in PART II, III and V. |
| PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN | |
| Annex 2 and 3: removal of study C4591048.<br>Annex 8: Changes to reflect the updates. | |

Other RMP versions under evaluation: None

Details of the currently approved RMP:

RMP version number: 16.0

Approved with procedure number: EMA/VR/0000302705

Date of approval: CHMP Opinion: 10 April 2026

QPPV name[2]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[2] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 1MPD | 1-month post dose |
| 6MPD3 | 6-month post dose 3 |
| ACIP | Advisory Committee on Immunisation Practices |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AESI | adverse event of special interest |
| AI/AN | American Indian/Alaska Native |
| AKI | Acute kidney injury |
| ALC-0159 | 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide |
| ALC-0315 | ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) |
| aPV | Additional pharmacovigilance |
| AR | Annual Report |
| ARDS | acute respiratory distress syndrome |
| ATC | Anatomical Therapeutic Chemical |
| BALB | Bagg albino |
| BC | Brighton Collaboration |
| BEST | Biologics effectiveness and safety |
| BLA | Biologics license application |
| BMI | body mass index |
| BP | blood pressure |
| CAKI | Covid-associated acute kidney injury |
| CDC | Centers for Disease Control and Prevention |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CKD | Chronic kidney disease |
| CLL | Chronic lymphocytic leukaemia |
| CONSIGN | COVID-19 infectiOn aNd medicineS In preGNancy |
| COPD | Chronic obstructive pulmonary disease |
| COVID-19 | Coronavirus Disease 19 |
| CP | (SDEA) Contractual Party |
| CRF | Case report form |
| CRP | C-reactive protein |
| CRRT | Continuous renal replacement therapy |
| CSR | Clinical Study Report |
| CT | Clinical Trial |
| DART | Developmental and reproductive toxicology |
| DCA | Data Capture Aid |
| DHPC | Direct Healthcare Professional Communication |
| DLP | Data Lock Point |
| DoD | Department of Defense |
| DSPC | 1,2-Distearoyl-sn-glycero-3-phosphocholine |
| ECDC | European Center for Disease Control |
| ECMO | Extracorporeal membrane oxygenation |
| eCTD | electronic Common Technical Document |
| ED | Emergency department |
| EDH | Epidural hematoma |
| EEA | European Economic Area |
| eGFR | estimated Glomerular filtration rate |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |

| Abbreviation | Definition |
|---|---|
| EUA | Emergency use authorization |
| FDA | (US) Food and Drug Administration |
| GLP | Good laboratory practice |
| GSAID | Global Initiative on Sharing All Influenza Data |
| HbA1c | glycated Haemoglobin A1c |
| HBV | Hepatitis B Virus |
| HCO | Health care organization |
| HCP | Healthcare Professional |
| HCV | Hepatitis C Virus |
| HER | Electronic health records |
| HIV | Human Immunodeficiency Virus |
| HMA | Heads of Medicines Agencies |
| IA | Interim analysis |
| IB | Investigator's Brochure |
| ICD | International Classification of Diseases |
| ICU | Intensive care unit |
| IFN | Interferon |
| Ig | Immunoglobulin |
| IIR | Investigator Initiated Research |
| IL | Interleukin |
| IM | intramuscular(ly) |
| IMD | Index of multiple deprivation |
| IMV | Invasive mechanical ventilation |
| IND | Investigational New Drug |
| INN | International Non-proprietary Name |
| IQR | Interquartile Range |
| IRR | Incidence rate ratio |
| ISARIC | International Severe Acute Respiratory and Emerging Infection |
| IV | Intravenous |
| JAMA | Journal of American Medical Association |
| JP | Japan |
| KTR | Kidney transplant recipient |
| LAC | Los Angeles County |
| LDH | Lactic acid dehydrogenase |
| LNP | Lipid nanoparticle |
| LSV | Last Subject Visit |
| M/O | Multiple/Other |
| MA | Marketing Authorisation |
| MAA | marketing authorization applicant |
| MAH | Marketing Authorisation Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MERS | Middle East respiratory syndrome |
| MERS-CoV | Middle East respiratory syndrome-coronavirus |
| MHRA | (UK) Medicines and Healthcare products Regulatory Agency |
| MHS | Military Health System |
| MIS | Multisystem inflammatory syndrome |
| MIS-C | Multisystem inflammatory syndrome in children |
| MIS-C/A | Multisystem inflammatory syndrome in children and adults |
| MIS-N | Multisystem inflammatory syndrome in neonates |
| MOA | Mechanism of action |
| modRNA | nucleoside-modified messenger ribonucleic acid |
| mRNA | Messenger RNA |

| Abbreviation | Definition |
|---|---|
| MR-proADM | Mid-regional pro-adrenomedullin |
| N/A | Not Applicable; Not Available |
| NA | Not Applicable; Not Available |
| NCHS | National center for health statistics |
| NCMD | National child mortality database |
| NDA | New drug application |
| NH/PI | Native Hawaiian/Other Pacific Islander |
| NHLBI | National Heart, Lung and Blood Institute |
| NHP | Nonhuman primate |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institutes of Health |
| NIS | Non interventional study |
| NSCLC | Non-small-cell lung carcinoma |
| OCS | Oral corticosteroids |
| OMI | Omicron |
| OTIS | Organization of Teratology Information Specialists |
| PAM | Post-Authorisation Measure |
| PASC | Post-Acute Sequelae of COVID-19 |
| PASS | Post-Authorisation Safety Study |
| PBS | Phosphate Buffered Saline |
| PC | Product complaint |
| PCORnet | National Patient-Centered Clinical Research Network |
| PCR | Polymerase chain reaction |
| PEDSnet | Pediatric Learning Health System |
| PFS | Pre-filled syringe |
| PHN | Pediatric Heart Network |
| PK | Pharmacokinetic |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| PSUSA | Periodic safety update report single assessment |
| PT | (MedDRA) Preferred Term |
| PTSD | Posttraumatic stress disorder |
| PVP | Pharmacovigilance Plan |
| Q&A | Question and Answer |
| RA | Regulatory Authority |
| RBC | Red blood cell |
| RCA | Regional citrate anticoagulation |
| RMP | Risk Management Plan |
| ROW | Rest of World |
| RR | Relative risk |
| SAE | Serious Adverse Event |
| SARS | Severe acute respiratory syndrome |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| sBLA | Supplemental Biologic License Application |
| SIIV | Seasonal inactivated influenza vaccine |
| siRNA | Small-interfering RNA |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Query |
| SMSR | Summary monthly safety report |
| SPEAC | Safety Platform for Emergency vACcines |
| SS | Substudy |

| Abbreviation | Definition |
|---|---|
| SSR | Summary safety report |
| suPAR | Soluble urokinase plasminogen activator receptor |
| T1d | type 1 diabetes mellitus |
| TESSy | The European Surveillance System |
| TME | Targeted medical event |
| TNF | Tumour necrosis factor |
| TRIS | Tromethamine Buffer or (HOCH2)3CNH |
| UK | United Kingdom |
| UNICEF | United Nations International Children's Emergency Fund |
| US | United States |
| V8 | Variant 8 |
| V9 | Variant 9 |
| VAC4EU | Vaccine monitoring Collaboration for Europe |
| VAED | Vaccine-associated enhanced disease |
| VAERD | Vaccine-associated enhanced respiratory disease |
| VAERS | Vaccine Adverse Event Reporting System |
| VDS | Vaccine Safety Datalink |
| VmCf | Vaccine monitoring Collaboration for |
| VRBPAC | Vaccines and Related Biological Products Advisory Committee |
| VSD | Vaccine Safety Datalink |
| WBC | White blood cells |
| WHO | World Health Organization |
| WOCBP | Women of child-bearing potential |
| WT | Wild type |

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## PART I. PRODUCT(S) OVERVIEW

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Bretovameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron JN.1).<br><br>Cemivameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron KP.2).<br><br>The mRNA encoding LP.8.1 is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron LP.8.1). |
| **Pharmacotherapeutic group(s) (ATC Code)** | J07BN01 |
| **Marketing Authorisation Holder** | BioNTech Manufacturing GmbH |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | Comirnaty |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product:** | Chemical class<br><br>Nucleoside-modified messenger RNA is formulated in LNP |
| | Summary of mode of action<br><br>The nucleoside-modified messenger RNA in Comirnaty is formulated in LNPs, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19. |
| | Important information about its composition<br><br>**Comirnaty:**<br>is nucleoside-modified messenger RNA formulated in LNPs;<br>is a white to off-white dispersion<br>(pH:6.9 – 7.9).<br><br>**Excipients for all presentations**<br>((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)<br>2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)<br>1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)<br>Cholesterol<br>Trometamol<br>Trometamol hydrochloride<br>Sucrose<br>Water for injections |

| | |
|---|---|
| **Hyperlink to the Product Information:** | Please refer to Module 1.3.1 |
| **Indication in the EEA** | Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older. |
| **Dosage in the EEA** | **Comirnaty JN.1**<br><br>*Individuals 12 years of age and older*<br>Comirnaty JN.1 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.<br><br>*Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)*<br>Comirnaty JN.1 10 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.<br><br>*Infants and children 6 months to 4 years of age who have not received a COVID-19 vaccine*<br>Comirnaty JN.1 10 micrograms/dose is administered intramuscularly as a primary course of 2 doses. It is recommended to administer the second dose 8 weeks after the first dose.<br><br>For further posology details see SmPC Section 4.2.<br><br>**Comirnaty KP.2**<br><br>*Individuals 12 years of age and older*<br>Comirnaty KP.2 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.<br><br>*Children 5 to 11 years of age (i.e. 5 years to less than 12 years of age)*<br>Comirnaty KP.2 10 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.<br><br>*Infants and children 6 months to 4 years of age who have not received a COVID-19 vaccine*<br>Comirnaty KP.2 10 micrograms/dose is administered intramuscularly as a primary course of 2 doses. It is recommended to administer the second dose 8 weeks after the first dose.<br><br>For further posology details see SmPC Section 4.2.<br><br>**Comirnaty LP.8.1**<br><br>*Individuals 12 years of age and older*<br>Comirnaty LP.8.1 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.<br><br>*Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)*<br>Comirnaty LP.8.1 10 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.<br><br>*Infants and children 6 months to 4 years of age who have not received a COVID-19 vaccine*<br>Comirnaty LP. 8.1 10 micrograms/dose is administered intramuscularly as a primary course of 2 doses. It is recommended to administer the second dose 8 weeks after the first dose |

| | |
|---|---|
| | For further posology details see SmPC Section 4.2. |
| **Pharmaceutical form and strengths** | **Comirnaty JN.1**<br><br>30 micrograms/dose dispersion for injection (Grey cap)<br>- Single dose: each vial contains 1 dose of 0.3 mL<br>- Multidose vials (2.25mL): each vial contains 6 doses of 0.3 mL<br><br>30 micrograms/dose dispersion for injection in pre-filled syringe (Refrigerated Glass): each syringe contains 1 dose of 0.3 mL<br>The drug product does not require dilution for administration.<br><br>10 micrograms/dose dispersion for injection (Blue cap)<br>- Single dose: each vial contains 1 dose of 0.3 mL<br>- Multidose vials: each vial contains 6 doses of 0.3 mL<br>The drug product does not require dilution for administration.<br><br>10 micrograms/dose concentrate for dispersion for injection (Orange cap)<br>- Multidose vials: each vial contains 10 doses of 0.2 mL<br>The drug product requires dilution for administration<br><br>**Comirnaty KP.2**<br><br>30 micrograms/dose dispersion for injection (Grey cap)<br>- Single dose: each vial contains 1 dose of 0.3 mL<br>- Multidose vials (2.25mL): each vial contains 6 doses of 0.3 mL<br><br>30 micrograms/dose dispersion for injection in pre-filled syringe (Refrigerated Glass): each syringe contains 1 dose of 0.3 mL. The drug product does not require dilution for administration<br><br>10 micrograms/dose dispersion for injection (Blue cap)<br>- Single dose: each vial contains 1 dose of 0.3 mL<br>- Multidose vials: each vial contains 6 doses of 0.3 mL<br>The drug product does not require dilution for administration.<br><br>**Comirnaty LP.8.1**<br><br>30 micrograms/dose dispersion for injection (Grey cap)<br>- Multidose vials (2.25mL): each vial contains 6 doses of 0.3 mL<br><br>30 micrograms/dose dispersion for injection in pre-filled syringe (Refrigerated Glass): each syringe contains 1 dose of 0.3 mL. The drug product does not require dilution for administration<br><br>10 micrograms/dose dispersion for injection (Blue cap)<br>- Single dose: each vial contains 1 dose of 0.3 mL<br>- Multidose vials: each vial contains 6 doses of 0.3 mL<br>The drug product does not require dilution for administration. |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

## PART II. SAFETY SPECIFICATION

### Module SI. Epidemiology of the Indication(s) and Target Population (s)

### Indication

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older (Comirnaty JN.1, Comirnaty KP.2 and Comirnaty LP.8.1).

### Incidence:

The coronavirus disease of 2019 (COVID-19), caused by a novel coronavirus labelled as SARS-CoV-2, first emerged in December 2019[1]. The number of infected cases rapidly increased and spread throughout the world. On 30 January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern and thus a pandemic.[2] Estimates of SARS-CoV-2 incidence change rapidly. The MAH obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organization that collects COVID-19 data from official reports and publishes current global and country specific statistics online.[3]

As of 13 April 2024, the overall number of people who had been infected with SARS-CoV-2 was over 704 million worldwide.[4] Table 1 shows the incidence and prevalence as of 13 April 2024 for the US, UK, and EU-27 countries. In the EU and the UK, as of 13 April 2024, the total number of confirmed cases had accumulated to 212 million, or 413,283 per 1,000,000 people. Across 27 countries in the EU, Romania and Poland reported the lowest incidence rates while France, Slovenia, and Austria reported the highest.[4]

## Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 13 April 2024

| | Total Cases | Incidence: Total Cases/ 1,000,000 | Active Cases | Prevalence: Active Cases/ 1,000,000 | Total Deaths | Mortality: Deaths / 1,000,000 | Population |
|---|---|---|---|---|---|---|---|
| **Global** | 704,753,890 | 90,413 | 22,123,398 | 2,711 | 7,010,681 | 899.4 | 8,161,972,572[a] |
| **EU-27** | 187,384,280 | 420,917 | 682,765 | 1,534 | 1,263,437 | 2,838 | 445,181,267 |
| **UK** | 24,910,387 | 363,666 | 0 | 0 | 232,112 | 3,389 | 68,497,907 |
| **EU-27 + UK** | 212,294,667 | 413,283 | 682,765 | 1,329 | 1,495,549 | 2,911 | 513,679,174 |
| **US** | 111,820,082 | 333,985 | 786,167 | 2,348 | 1,219,487 | 3,642 | 334,805,269 |
| **EU-27 Countries** | | | | | | | |
| Austria | 6,081,287 | 670,727 | 3,811 | 420 | 22,542 | 2,486 | 9,066,710 |
| Belgium | 4,861,695 | 416,659 | 521 | 45 | 34,376 | 2,946 | 11,668,278 |
| Bulgaria | 1,339,851 | 195,753 | 8,159 | 1,192 | 38,748 | 5,661 | 6,844,597 |
| Croatia | 1,309,728 | 322,650 | 32,609 | 8,033 | 18,687 | 4,604 | 4,059,286 |
| Cyprus | 681,110 | 556,741 | 0 | 0 | 1,365 | 1,116 | 1,223,387 |
| Czech Republic | 4,759,041 | 443,246 | 318 | 30 | 43,517 | 4,053 | 10,736,784 |
| Denmark | 3,183,756 | 545,636 | 0 | 0 | 8,814 | 1,511 | 5,834,950 |
| Estonia | 628,070 | 475,123 | N/A | N/A | 3,001 | 2,270 | 1,321,910 |
| Finland | 1,516,117 | 272,930 | 170 | 31 | 11,958 | 2,153 | 5,554,960 |
| France | 40,138,560 | 612,013 | 0 | 0 | 167,642 | 2,556 | 65,584,518 |
| Germany | 38,828,995 | 462,891 | 405,368 | 4833 | 183,027 | 2,182 | 83,883,596 |
| Greece | 6,101,379 | 591,412 | N/A | N/A | 37,869 | 3,671 | 10,316,637 |
| Hungary | 2,230,232 | 232,164 | 29,029 | 3022 | 49,048 | 5,106 | 9,606,259 |
| Ireland | 1,734,582 | 345,521 | 170 | 34 | 9,491 | 1,891 | 5,020,199 |
| Italy | 26,723,249 | 443,445 | 165,544 | 2747 | 196,487 | 3,261 | 60,262,770 |
| Latvia | 982,505 | 531,418 | 4,384 | 2371 | 6,715 | 3,632 | 1,848,837 |
| Lithuania | 1,397,806 | 525,154 | 431 | 162 | 9,897 | 3,718 | 2,661,708 |
| Luxembourg | 391,232 | 609,044 | N/A | N/A | 1,232 | 1,918 | 642,371 |
| Malta | 121,420 | 273,448 | 386 | 869 | 885 | 1,993 | 444,033 |
| Netherlands | 8,635,786 | 501,747 | 195 | 11 | 22,992 | 1,336 | 17,211,447 |
| Poland | 6,661,991 | 176,524 | N/A | N/A | 120,598 | 3,196 | 37,739,785 |
| Portugal | 5,643,062 | 556,484 | 127 | 13 | 28,126 | 2,774 | 10,140,570 |
| Romania | 3,529,735 | 185,470 | 657 | 35 | 68,929 | 3,622 | 19,031,335 |
| Slovakia | 1,877,605 | 343,872 | 0 | 0 | 21,224 | 3,887 | 5,460,193 |
| Slovenia | 1,356,546 | 652,803 | 22 | 11 | 7,100 | 3,417 | 2,078,034 |
| Spain | 13,914,811 | 297,840 | 30,634 | 656 | 121,760 | 2,606 | 46,719,142 |
| Sweden | 2,754,129 | 269,511 | 230 | 23 | 27,407 | 2,682 | 10,218,971 |

a. "World population based on https://www.worldometers.info/world-population/world-population-by-year/. accessed on 15 August 2024"

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported.[5] Further, access to at-home rapid testing kits[6] suggests that the true estimate of cases is estimated to be larger than formally reported counts. The numbers should therefore be interpreted with caution.[7]

**Prevalence:**

The prevalence of SARS-CoV-2 infection is defined as active cases per 100,000 people including confirmed cases in people who have not recovered or died. On 13 April 2024, the overall prevalence estimates for the EU-27 is 1,534 active cases per 100,000.[4] The range of reported prevalence for EU-27 was 0 to 8,033 per 100,000, although this wide range may reflect a difference in reporting quality across countries. Cyprus, Denmark, France, and Slovakia reported the lowest prevalence while, Croatia, Germany, and Hungary reported the highest. It should be noted that Cyprus, Denmark, France, and Slovakia reported 0 active cases on 13 April 2024, leading to a prevalence estimate of 0 per 100,000 population.

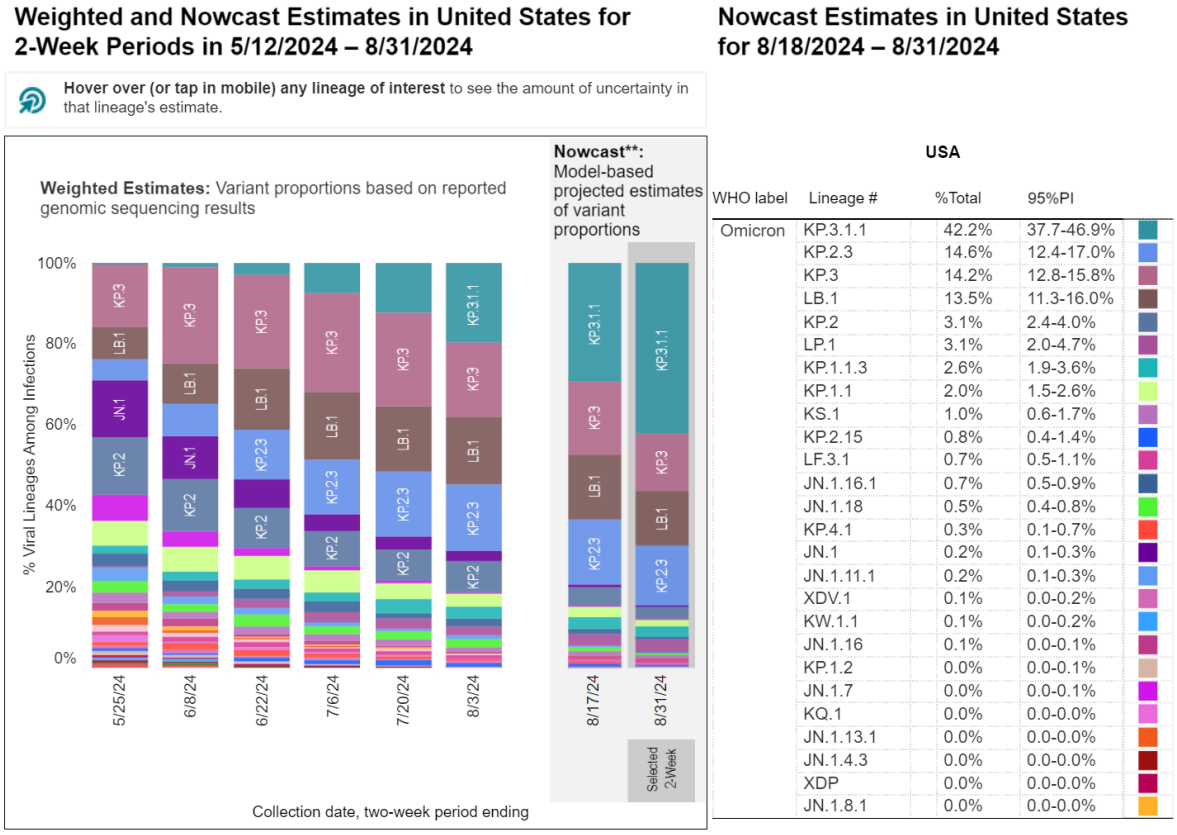
Variant-specific data

Since the end of 2021, nearly all SARS-CoV-2 infections have been caused by descendant strains of the Omicron variant. Before the 2023-2024 season, the Omicron XBB.1.5 variant dominated globally.[3] In early 2024, the Omicron JN.1 variant emerged as the most prevalent. Currently as of 21 July 2024, the most common variants globally as estimated by the World Health Organization were KP.3 (29.4%) and JN.1 (25.7%).[8]

In the US, the most common variant as of 31 August 2024 was the KP.3.1.1 lineage, accounting for 42.2% of SARS-CoV-2 specimens sequenced. The variants from all SARS-CoV-2 specimens sequenced by the US CDC during the week ending 31 August 2024 can be found in Figure 1 along with the variant proportions identified from the week of 12 May 2024 through the week of 31 August 2024.[9]

[3] https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---30-august-2023

**Figure 1. Variant proportions for all SARS-CoV-2 specimens sequenced by the CDC during the week of 12 May 2024 through 31 August 2024**



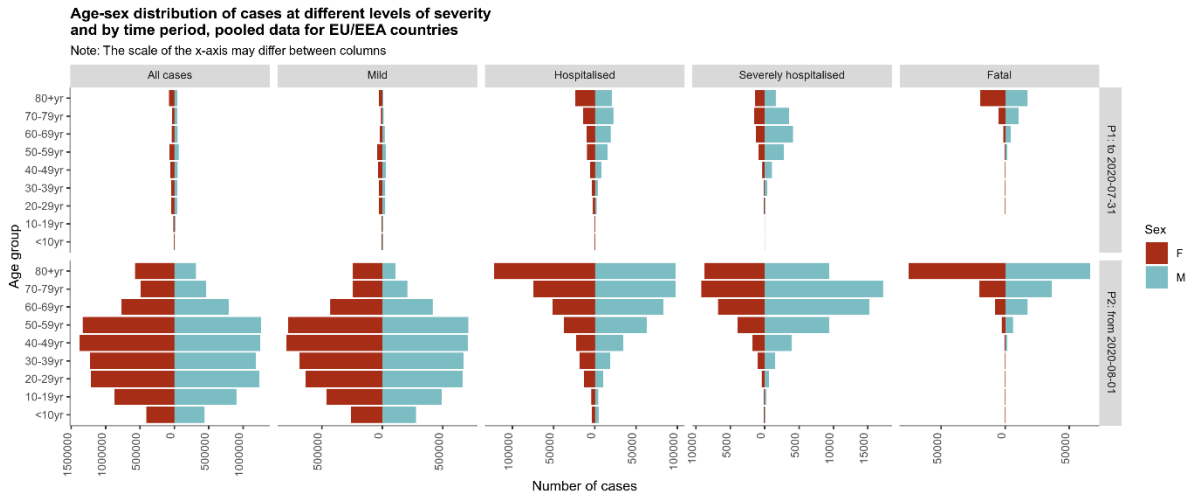

| WHO label | Lineage # | %Total | 95%PI |
|---|---|---|---|
| Omicron | KP.3.1.1 | 42.2% | 37.7-46.9% |
| | KP.2.3 | 14.6% | 12.4-17.0% |
| | KP.3 | 14.2% | 12.8-15.8% |
| | LB.1 | 13.5% | 11.3-16.0% |
| | KP.2 | 3.1% | 2.4-4.0% |
| | LP.1 | 3.1% | 2.0-4.7% |
| | KP.1.1.3 | 2.6% | 1.9-3.6% |
| | KP.1.1 | 2.0% | 1.5-2.6% |
| | KS.1 | 1.0% | 0.6-1.7% |
| | KP.2.15 | 0.8% | 0.4-1.4% |
| | LF.3.1 | 0.7% | 0.5-1.1% |
| | JN.1.16.1 | 0.7% | 0.5-0.9% |
| | JN.1.18 | 0.5% | 0.4-0.8% |
| | KP.4.1 | 0.3% | 0.1-0.7% |
| | JN.1 | 0.2% | 0.1-0.3% |
| | JN.1.11.1 | 0.2% | 0.1-0.3% |
| | XDV.1 | 0.1% | 0.0-0.2% |
| | KW.1.1 | 0.1% | 0.0-0.2% |
| | JN.1.16 | 0.1% | 0.0-0.1% |
| | KP.1.2 | 0.0% | 0.0-0.1% |
| | JN.1.7 | 0.0% | 0.0-0.1% |
| | KQ.1 | 0.0% | 0.0-0.0% |
| | JN.1.13.1 | 0.0% | 0.0-0.0% |
| | JN.1.4.3 | 0.0% | 0.0-0.0% |
| | XDP | 0.0% | 0.0-0.0% |
| | JN.1.8.1 | 0.0% | 0.0-0.0% |

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all 2-week period displayed. While all lineages are tracked by CDC, those named lineages not enumerated in this graphic are aggregated with their parent lineages, based on Pango lineage definitions, described in more detail here: https://web.archive.org/web/20240116214031/https://www.pango.network/the-pango-nomenclature-system/statement-of-nomenclature-rules.

**Demographics of the population in the proposed indication and risk factors for the disease:**

Data on the age and sex distributions of COVID-19 cases in Europe by severity of symptoms as posted on 04 November 2021 are shown in Figure 2,[10] which captures over 80% of the official number of cases reported by ECDC epidemic intelligence.[11] The number of hospitalized, severely hospitalized, and fatal COVID-19 cases increased with age and was the most prevalent in individuals aged 50 years and older. The distribution of cases by sex was generally similar among males and females, although there were slightly more men who were severely hospitalized due to COVID-19.

**Figure 2. Age-Sex distribution of COVID-19 Cases as Different Levels of Severity, Pooled data for EU/EEA countries. Case-based Data from TESSy produced on 04 November 2021[a]**




Note: "mild" = a case that has not been reported as hospitalized or a case that resulted in death.

a. Data from ECDC. COVID-19 Surveillance report. Week 43, 2021. 04 November 2021. "2.2 Age-sex pyramids" Accessed 26 March 2022.

US distributions of reported COVID cases and deaths as of 28 December 2022 are stratified by demographics and presented in Table 2 and Table 3.[12] Only cases and deaths with information reported to the CDC were included in these summaries. Similar to the data in Europe, the US data highlight that individuals of all ages, sexes, and races were diagnosed with COVID-19, but the proportion of deaths is highest among individuals aged 50 years and older.

**Table 2. Distribution of Cases (n=94,447,829) by Age, Sex, Race, and Cross-Tabulated Age and Sex -- United States as of 28 December 2022[a]**

| Event | Age Group | Age % | Sex | Sex % | Race | Race[b] % | Age Group | Females % | Males % | Other % |
|---|---|---|---|---|---|---|---|---|---|---|
| Cases | 0-4 | 3.6 | Females | 53.8 | H/L | 24.7 | 0-4 | 47.9 | 52.1 | <0.1 |
| | 5-11 | 6.5 | Males | 46.2 | AI/AN | 0.9 | 5-11 | 48.8 | 51.2 | <0.1 |
| | 12-15 | 4.5 | Other | <0.1 | Asian | 4.4 | 12-15 | 50.5 | 49.5 | <0.1 |
| | 16-17 | 2.6 | | | Black | 12.4 | 16-17 | 52.8 | 47.2 | <0.1 |
| | 18-29 | 20.4 | | | NH/PI | 0.3 | 18-29 | 55.4 | 44.6 | <0.1 |
| | 30-39 | 16.7 | | | White | 53.4 | 30-39 | 55 | 45 | <0.1 |
| | 40-49 | 14.2 | | | M/O | 3.9 | 40-49 | 54.8 | 45.1 | <0.1 |
| | 50-64 | 18.5 | | | | | 50-64 | 53.5 | 46.5 | <0.1 |
| | 65-74 | 7.3 | | | | | 65-74 | 52.6 | 47.4 | <0.1 |
| | 75-84 | 3.8 | | | | | 75-84 | 53.8 | 46.2 | <0.1 |
| | 85+ | 1.9 | | | | | 85+ | 62.9 | 37.1 | <0.1 |

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 64% of cases, age available for 99% of cases, and sex available for 96.7% of cases.

b. Except for Hispanics/Latinos, all categories refer to non-Hispanics.

Abbreviations: AI/AN=American Indian/Alaska Native, H/L=Hispanic/Latino, M/O=Multiple/Other, NH/PI=Native Hawaiian/Other Pacific Islander.

**Table 3. Distribution of Deaths (n=937,757) by Age, Sex, Race, and Cross-Tabulated Age and Sex -- United States as of 28 December 2022[a]**

| Event | Age Group | Age % | Sex | Sex % | Race[b] | Race % | Age Group | Females % | Males % | Other % |
|---|---|---|---|---|---|---|---|---|---|---|
| Deaths | 0-4 | 0.1 | Females | 45 | H/L | 17.1 | 0-4 | 46.4 | 53.6 | <0.1 |
| | 5-11 | 0.1 | Males | 55 | AI/AN | 0.9 | 5-11 | 43.8 | 56.2 | <0.1 |
| | 12-15 | 0.1 | Other | <0.1 | Asian | 3.2 | 12-15 | 51.9 | 48.1 | <0.1 |
| | 16-17 | <0.1 | | | Black | 13.2 | 16-17 | 38.3 | 61.7 | <0.1 |
| | 18-29 | 0.7 | | | NH/PI | 0.2 | 18-29 | 39.6 | 60.4 | <0.1 |
| | 30-39 | 1.8 | | | White | 63.2 | 30-39 | 39 | 61 | <0.1 |
| | 40-49 | 4.1 | | | M/O | 2.2 | 40-49 | 37.4 | 62.6 | <0.1 |
| | 50-64 | 17.8 | | | | | 50-64 | 38 | 62 | <0.1 |
| | 65-74 | 22.4 | | | | | 65-74 | 40.6 | 59.4 | <0.1 |
| | 75-84 | 26 | | | | | 75-84 | 44.1 | 55.9 | <0.1 |
| | 85+ | 27 | | | | | 85+ | 56 | 44 | <0.1 |

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 83% of deaths, age data available for 99% of deaths, and sex available for 97% of deaths.
b. Except for Hispanics/Latinos, all categories refer to non-Hispanics.
Abbreviations: AI/AN=American Indian/Alaska Native, H/L=Hispanic/Latino, M/O=Multiple/Other, NH/PI=Native Hawaiian/Other Pacific Islander.

As of January 20, 2022, Omicron had been identified in all EU/EEA countries.[13] The median age of the 155,150 cases reported to TESSy by EU/EEA countries up to that point was 30 (interquartile range 20–33) years; 7% were aged 60 years and above and 50% were male.[14]

A study using data from 17 of 18 regional health agencies in France that examined 468 confirmed cases of the Omicron variant from 23 November 2021 to 11 January 2022 found that cases were of a median age of 35 years, 55% female, and only 16% had pre-existing conditions (hypertension, obesity, diabetes, chronic respiratory disease, renal insufficiency, cancer, immunosuppression, liver disease, heart disease, neuromuscular condition, pregnancy, or other condition).[14]

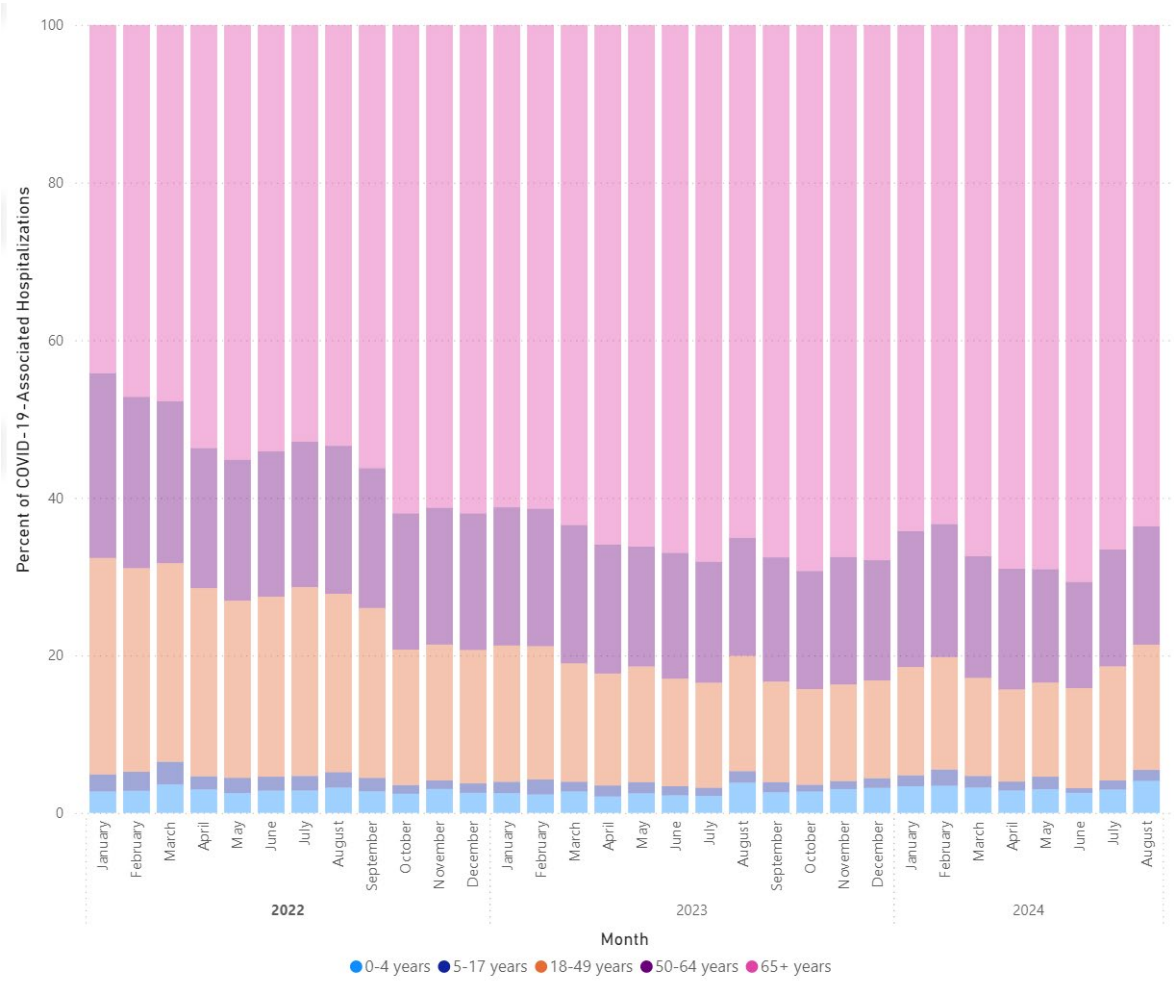
A CDC study of Omicron transmission within households in 4 US jurisdictions found that age was not related to transmission: Omicron attack rates were high across all ages regardless of vaccination status.[15] Additionally, one US-based electronic health record study from a large community health system found that the mean age and gender distribution of persons infected with the Omicron variant of the COVID 19 virus was similar to that of persons infected with prior strains. Infected patients had a mean age 57.7, 58.8 and 61.0 years for the pre-Delta (March 2020–June 2021), Delta (July–November 2021), and Omicron periods (December 2021-February 2022), respectively, and were male 51.0%, 53.3% and 50.3 % for the pre-Delta, Delta and Omicron periods, respectively.[16] However, other studies report that Omicron patients were younger and more likely to be female.[17, 18]

In terms of race/ethnicity, a CDC study of 14 states found that during the Omicron-predominant period, peak hospitalization rates among non-Hispanic African American adults were nearly four times the rate of non-Hispanic White adults and was the highest rate observed among any racial and ethnic group during the pandemic.[19]

This same 14-state CDC study found that, compared with the Delta-predominant period, the proportion of unvaccinated hospitalized African American adults increased during the Omicron-predominant period.

By August 2024, the most common variants were descendant strains of the Omicron variant, such as KP.3 and JN.1. In 2024, most hospitalizations due to COVID-19 continue to be among individuals aged 65 years and older. Figure 3 displays the CDC's estimated percent of hospitalizations stratified by age group in the US. Additionally, the CDC estimates that the distribution of COVID-19 hospitalizations by sex and race/ethnicity have not varied substantially since the onset of Omicron in 2022.[20]

**Figure 3. CDC Estimated Percent of COVID-19 Hospitalizations by Age Group in the US from January 1, 2022 to August 1, 2024**




Paediatric-specific data

While research earlier in the pandemic tended to focus on adults, more recent data have given greater attention to children and adolescents. For the period January 01 - March 31, 2021 across 14 states, the CDC's Coronavirus Disease 2019 (COVID-19) - Associated Hospitalization Surveillance Network (COVID-NET) database recorded 204 adolescents

aged 12-17 who were hospitalized for likely primarily COVID-19-related reasons.[21] The 204 adolescents were 47.5% male consistent with the COVID case sex distribution across all ages and disproportionately from minorities, with 31.4% Hispanic and 35.8% non-Hispanic African Americans.[21]

Another CDC report described demographic trends in US COVID-19 incidence among 15,068 cases aged 0-24 years across 16 jurisdictions during the period 01 January 2020 through 31 December 2020.[22] The report broke down incidence by age groups and 2020 sub-periods that are presented in Table 4. The table shows that early in 2020, 5-9-year-old were experiencing less COVID-19 than 0-4-year-old, but by the end of the year this pattern had reversed. Compared to 5-9-year-old, the age categories 10-14, 15-19, and 20-24 years old showed progressively greater incidence rates, a pattern that held throughout 2020. Other US paediatric data are generally consistent with the CDC findings.

**Table 4. COVID-19 incidence and rate ratios, by age group among persons aged <25 years across three periods of 2020 in 16 U.S. jurisdictions**

| 2020 Sub-Period | Age Group (years) | Number of Cases | Cases per 100,000 population (95% CI) | Rate Ratio (95% CI) |
|---|---|---|---|---|
| **Jan 1 - Apr 30** | 0-4 | 956 | 21 (20-23) | 1.28 (1.17-1.41) |
| | 5-9 | 772 | 17 (16-18) | Reference |
| | 10-14 | 1,184 | 25 (23-26) | 1.49 (1.36-1.63) |
| | 15-19 | 3,267 | 67 (65-70) | 4.03 (3.72-4.36) |
| | 20-24 | 8,889 | 175 (171-178) | 10.47 (9.72-11.26) |
| **May 1 - Aug 31** | 0-4 | 14,017 | 314 (309-319) | 1.01 (0.98–1.03) |
| | 5-9 | 14,406 | 312 (307-317) | Reference |
| | 10-14 | 20,490 | 430 (424-436) | 1.38 (1.35–1.41) |
| | 15-19 | 50,210 | 1,034 (1,025-1,043) | 3.32 (3.26–3.38) |
| | 20-24 | 78,655 | 1,547 (1,536-1,557) | 4.96 (4.88–5.05) |
| **Sep 1 - Dec 31** | 0-4 | 33,595 | 752 (744–760) | 0.71 (0.70–0.72) |
| | 5-9 | 48,824 | 1,056 (1,047–1,066) | Reference |
| | 10-14 | 76,922 | 1,615 (1,604–1,627) | 1.53 (1.51–1.55) |
| | 15-19 | 149,660 | 3,083 (3,067–3,098) | 2.92 (2.89–2.95) |
| | 20-24 | 187,825 | 3,693 (3,677–3,710) | 3.50 (3.46–3.53) |

Table 5 summarizes demographic results for a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems.[23] The table shows that, among the paediatric population, children aged 12-17 were more frequently infected than those under age 12. African Americans and Hispanics had elevated frequencies of testing positive relative to their proportion of the cohort.

**Table 5. Demographics of 135,794 US individuals under age 25 tested for COVID-19 by 08 September 2020**

| | Patients, n (%) | | |
|---|---|---|---|
| **Characteristic** | **COVID-19 negative (n=130,420)** | **COVID-19 positive, Asymptomatic or mild illness (n=5,015)** | **COVID-19 positive, Severe illness (n=359)** |
| **Age, years** | | | |
| <1 | 17,431 (13) | 494 (10) | 72 (20) |
| 1-4 | 32,619 (25) | 808 (16) | 40 (11) |
| 5-11 | 35,617 (27) | 1,029 (21) | 72 (20) |
| 12-17 | 32,362 (25) | 1,521 (30) | 117 (33) |
| 18-24 | 12,391 (10) | 1,163 (23) | 58 (16) |
| **Sex** | | | |
| Female | 61,637 (47) | 2,527 (50) | 172 (48) |
| Male | 68,701 (53) | 2,485 (50) | 187 (52) |
| Other or Unknown | 82 (0.06) | 3 (0.06) | 0 |
| **Race/ethnicity** | | | |
| Hispanic | 14,156 (11) | 918 (18) | 108 (30) |
| API | 4,471 (3) | 151 (3) | 9 (3) |
| Black or AA | 18,646 (14) | 1,424 (28) | 119 (33) |
| White | 77,540 (60) | 1,988 (40) | 97 (27) |
| Multiple | 3,883 (3) | 126 (3) | 5 (1) |
| Other or Unknown | 11,724 (9) | 408 (8) | 21 (6) |

AA=African American, API=Asian or Pacific Islander

## ***Risk Factors***

Human-to-human transmission of SARS-CoV-2 occurs primarily through respiratory droplets and direct contact.[24] Thus, the risk of initial infection increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation.[25] People living in long-term care facilities or high-density apartment homes or working in occupations with close proximity to others (e.g. healthcare, transportation), have a higher risk of infection.[25,26] Among children, the primary source of infection is an infected adult living in the same household[27], but age is not associated with risk of initial infection among people aged 5 years and older based on current data from the CDC.[28,29]

According to the CDC, some ethnic minority groups have a higher risk of infection (Table 6).[29] Male sex is also a significant risk factor for severe disease and mortality due to COVID-19.[30] In addition, there is evidence that high-risk human leukocyte antigen haplotypes, higher expression of angiotensin-converting enzyme polymorphisms, and several genes of cellular proteases increase the risk of susceptibility and severity of COVID-19.[31,32] Lastly, recent narrative reviews and meta-analyses indicate that Blood type O is associated with lower rates of SARS-CoV-2 infection; whereas type A is frequently described as a risk factor and is most often associated with COVID-19 severity and mortality.[33,34]

**Table 6. Risk for COVID-19 Infection, Hospitalization, and Death in US by Age Group and by Race/Ethnicity as of 28 December 2022**

| | | Rate ratios[a] | |
|---|---|---|---|
| **Age Group (years)** | **Cases[b]** | **Hospitalization[c]** | **Death[d]** |
| 0-4 | 0.5 | 0.6 | 0.2 |
| 5-17 | 0.7 | 0.2 | 0.1 |
| 18-29[e] | Ref | Ref | Ref |
| 30-39 | 1 | 1.5 | 3.5 |
| 40-49 | 0.9 | 1.9 | 10 |
| 50-64 | 0.8 | 3.1 | 25 |
| 65-74 | 0.6 | 4.8 | 60 |
| 75-84 | 0.6 | 8.6 | 140 |
| 85+ | 0.7 | 15 | 350 |
| **Race/Ethnicity** | | | |
| | **Cases[f]** | **Hospitalization[g]** | **Death[h]** |
| Non-Hispanic White | Ref | Ref | Ref |
| American Indian or Alaska Native, non-Hispanic | 1.5 | 2.5 | 2.1 |
| Asian, non-Hispanic | 0.8 | 0.7 | 0.8 |
| Black or African American, non-Hispanic | 1.1 | 2.1 | 1.6 |
| Hispanic or Latino | 1.5 | 1.9 | 1.7 |

a. Rates for age groups are expressed as whole numbers, with values less than 10 rounded to the nearest integer, two-digit numbers rounded to nearest multiple of five, and numbers greater than 100 rounded to two significant digits. Rates for race/ethnicity groups are rounded to the nearest tenth.
b. Includes all cases reported by state and territorial jurisdictions (through 06 December 2022, accessed on 13 December 2022). The denominators used to calculate rates were based on the 2019 Vintage population (https://www.census.gov/newsroom/press-releases/2019/popest-nation.html).
c. Includes all hospitalizations reported through COVID-NET (from 01 March 2020 through 04 December 2022, accessed on 13 December 2022). Rates were standardized to the 2000 US standard COVID-NET catchment population.
d. Includes all deaths in National Center for Health Statistics (NCHS) provisional death counts (through 03 December 2022, accessed on 13 December 2022. The denominators used to calculate rates were based on the 2019 Vintage population.
e. Rate ratios for each age group are relative to the 18-29-year age category. This group was selected as the reference group because it has accounted for the largest cumulative number of COVID-19 cases compared to other age groups.
f. Case level surveillance data from state, local and territorial public health jurisdictions (data through 7 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate. Calculations use only the 65% of case reports that have race and ethnicity; this can result in inaccurate estimates of the relative risk among groups.
g. Includes all hospitalizations reported through COVID-NET (1 March 2020 through 3 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2020 US standard COVID-NET catchment population.
h. Includes all deaths in National Center for Health Statistics Provisional Death Counts (data through December 3, 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate.

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status.[28,29,31,35-41] Among adults, these risks increase for every 10-year age group above age 39.[28,42]

Table 6 also gives estimated rate ratios for COVID-19 hospitalisation and death by race/ethnicity relative to white, non-Hispanic persons in the US. Based on regularly updated data from the CDC, the highest risk of hospitalization and death occurred in those who were American Indian or Alaska native persons (RR = 2.5 for hospitalization, RR =2.1 for death), when compared to those who were non-Hispanic white.

These differences in risk among ethnic groups may be attributed to differences in underlying factors that are correlated with race/ethnicity including socioeconomic status, access to health care, and occupation-related virus exposure.[29]

Children aged 5-17 typically experience a milder disease course and have lower risk of hospitalization or death.[29,38,42] Further, among a cohort of children hospitalised with COVID-19 in the United States from March 2020 to May 2021, infants and children 6 months - 4 years of age had a similar risk of severe disease as children ages 12 - 17 years.[43]

Risk of severe or fatal COVID-19 disease is also higher among persons who are current or former smokers, have lower socioeconomic status, have no or public insurance, or live-in neighbourhoods with higher rates of limited English proficiency.[24,36,40,44-46] The CDC has also recognised other socio-demographic groups who may need to take extra precautions against COVID-19 due to increased risk for severe illness: pregnant women; breastfeeding mothers; people with disabilities or those who are clinically frail; people with developmental, behavioural or substance abuse disorders; and newly resettled refugee populations.[47]

Among adults, risk for severe or fatal COVID-19 disease increases with the presence of chronic medical conditions, including obesity, chronic lung diseases (e.g., COPD), hypertension, cardiovascular disease, diabetes, cancer, liver disease, neurological diseases (e.g., stroke or dementia), chronic kidney disease, anaemia, sickle cell disease, immunosuppression, HIV, mycotic infection, vitamin D deficiency higher scores on the WHO Clinical Progression Scale and Charlson Comorbidity Index [35,36,40,42,48-62]

**US FDA approved or authorized treatment options**

Through January 2023, other COVID-19 vaccines were authorized and recommended for use in the United States including vaccines from Moderna (NCT04470427), and Johnson & Johnson/Janssen (NCT04505722). Others may subsequently be approved. The Pfizer-BioNTech COVID-19 vaccine, Comirnaty, received FDA approval on 23 August 2021 for individuals 16 years of age and older[63] and received an emergency use authorization (EUA) in children 5 through 11 years of age on 29 October 2021.[64] Novavax Adjuvanted COVID-19 Vaccine received an EUA on 13 July 2022 for those 18 years of age and older.[65]

EUA authority was also used to make treatments available in patients with COVID-19 ahead of formal approval. These products include direct treatment for COVID-19 infections and for other medical conditions in infected persons (Table 7).[65]

## Table 7. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

| Date of Issuance | Drug or Non-Vaccine Biologic | Authorized Use |
|---|---|---|
| 4/30/2020 | Fresenius Medical, multiFiltrate PRO System and multiBic/multiPlus Solutions [also listed under Medical Device EUAs]. | To provide continuous renal replacement therapy (CRRT) to treat patients in an acute care environment during the COVID-19 pandemic. |
| 5/1/2020 | Remdesivir for Certain Hospitalized COVID-19 Patients (EUA reissued August 28, 2020, October 1, 2020, and October 22, 2020) | For emergency use by licensed healthcare providers for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. On October 22, 2020, FDA approved remdesivir (Veklury) for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. |
| 5/8/2020 | Fresenius Kabi Propoven 2% | To maintain sedation via continuous infusion in patients older than age 16 with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting. |
| 8/13/2020 | REGIOCIT replacement solution that contains citrate for regional citrate anticoagulation (RCA) of the extracorporeal circuit | To be used as a replacement solution only in adult patients treated with continuous renal replacement therapy (CRRT), and for whom regional citrate anticoagulation is appropriate, in a critical care setting |
| 8/23/2020 | COVID-19 convalescent plasma (EUA reissued February 23, 2021, March 9, 2021, and December 28, 2021) | COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings. |
| 11/19/2020 | Baricitinib (Olumiant) (Revised December 20, 2021) | For emergency use by healthcare providers for the treatment COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). |
| 11/21/2020 | REGEN-COV (Casirivimab and Imdevimab) (EUA reissued February 3, 2021, February 25, 2021, June 3, 2021, July 30, 2021, September 9, 2021, and November 17, 2021) | Casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death. |
| 2/9/2021 | Bamlanivimab and Etesevimab (EUA reissued February 25, 2021, August 27, 2021, September 16, 2021, December 3, 2021, and December 22, 2021) | Bamlanivimab and etesevimab administered together for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death. |
| 3/12/2021 | Propofol-Lipuro 1% | To maintain sedation via continuous infusion in patients greater than age 16 with suspected or confirmed COVID-19 who require mechanical ventilation in an ICU setting. |

## Table 7. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA

| Date of Issuance | Drug or Non-Vaccine Biologic | Authorized Use |
|---|---|---|
| 5/26/2021 | Sotrovimab<br>(EUA reissued October 8, 2021, and December 16, 2021) | For the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death. |
| 6/24/2021 | Actemra (Tocilizumab) | For the treatment of COVID-19 in hospitalized adults and paediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). |
| 12/8/2021 | Evusheld (tixagevimab co-packaged with cilgavimab)<br>(EUA reissued December 20, 2021) | For emergency use as pre-exposure prophylaxis for prevention of COVID-19 in adults and paediatric individuals (12 years of age and older weighing at least 40 kg):<br>- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and<br>- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or<br>- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s). |
| 12/22/2021 | Paxlovid<br>(nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) | Paxlovid is authorized for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalisation or death. |
| 12/23/2021 | Molnupiravir | Molnupiravir is authorized for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalisation or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. |
| 2/11/2022 | Bebtelovimab | Bebtelovimab is authorized for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. |

**Table 7. Drugs or Non-Vaccine Biologics with Emergency Use Authorization or Full Approval from the FDA**

| Date of Issuance | Drug or Non-Vaccine Biologic | Authorized Use |
|---|---|---|
| 11/08/2022 | Kineret | Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR). |
| 4/4/2023 | Gohibic | Gohibic[4] is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO). |

**Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

***Symptoms of COVID-19***

Symptoms of COVID-19 infection can range from very mild (or no symptoms) to severe or fatal.[66-69] The most common symptoms for symptomatic infected persons are fever, dry cough, and fatigue; upper respiratory tract symptoms can include pharyngalgia, headaches, and myalgia.[24] Current data indicate that about 80% of COVID-19 patients are asymptomatic or have mild-to-moderate symptoms, while about 15% develop more severe disease requiring hospitalization and about 5% require ventilation support.[24] In addition, 10–20% of COVID-19-infected persons experience persistent or new symptoms for periods of weeks to years.[24]

The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection when compared to household transmission or other healthcare facilities.[69] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults (Table 8).[70,71] However, it has been noted that in older people, COVID-19 clinical presentation is extremely heterogeneous and atypical signs and symptoms such as hyporexia / apyrexia, confusion, delirium, and pre-syncope / syncope are more common than in middle-aged and younger persons.[72] A recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic, while a recent systematic review that examined 1,140 cases of COVID-19 in children from 23 published studies found that 11% of cases were asymptomatic. Among symptoms, fever was reported in 48%, cough 37%, any nasopharyngeal symptom 22%.[73]

[4] https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products

The most common symptoms in hospitalized patients are fever (42-80%), shortness of breath (35-71%), fatigue (33-62%), cough (77-84%), chills (63%), myalgias (63%), headache (59%), and diarrhoea (33%).[74-77]

Many children who develop COVID-19 have no symptoms or experience mild symptoms such as low-grade fever, fatigue, and cough.[78] A recent meta-analysis of 32 studies found that the proportions with specific symptoms in paediatric patients were as follows: fever 33%, cough 25%, rhinorrhoea 13%, fatigue 9%, dyspnoea 9%, diarrhoea 6%, headache 9%, sore throat 7% and vomiting 7%.[79] By variant, Khemiri et al report that the signs and symptoms of infection observed in paediatric patients with Delta and Omicron variants are the same as those observed in children infected before the emergence of these variants.[80]

**Table 8. Signs and Symptoms among 291 Paediatric (age <18 years) and 10,944 Adult (age 18–64 years) Patients[a] with laboratory confirmed COVID-19 — United States, February 12–April 2, 2020**

| | No. (%) with sign/symptom | |
|---|---|---|
| **Sign/Symptom** | **Paediatric** | **Adult** |
| Fever, cough, or shortness of breath[b] | 213 (73) | 10,167 (93) |
| Fever[c] | 163 (56) | 7,794 (71) |
| Cough | 158 (54) | 8,775 (80) |
| Shortness of breath | 39 (13) | 4,674 (43) |
| Myalgia | 66 (23) | 6,713 (61) |
| Runny nose[d] | 21 (7.2) | 757 (6.9) |
| Sore throat | 71 (24) | 3,795 (35) |
| Headache | 81 (28) | 6,335 (58) |
| Nausea/Vomiting | 31 (11) | 1,746 (16) |
| Abdominal pain[d] | 17 (5.8) | 1,329 (12) |
| Diarrhea | 37 (13) | 3,353 (31) |

a. Cases were included in the denominator if they had a known symptom status for fever, cough, shortness of breath, nausea/vomiting, and diarrhoea. Total number of patients by age group: <18 years (N = 2,572), 18–64 years (N = 113,985).
b. Includes all cases with one or more of these symptoms.
c. Patients were included if they had information for either measured or subjective fever variables and were considered to have a fever if "yes" was indicated for either variable.
d. Runny nose and abdominal pain were less frequently completed than other symptoms; therefore, percentages with these symptoms are likely underestimates.

Among non-hospitalised children <18 years of age, 89% experienced one or more typical symptoms of COVID, including fever, cough, shortness of breath, and 22% experienced all three.[75] Approximately 17% to 40% of those hospitalised with COVID-19 experience severe symptoms necessitating intensive care[74,81,82] with 31% of children hospitalised experiencing severe COVID-19 that necessitates intensive care or invasive ventilation or ends in death. Risk factors for severe COVID-19 in hospitalised children include presence of a comorbid condition, younger age, and male sex.[74,83] More than 75% of patients hospitalised with COVID-19 require supplemental oxygen.[84]

According to American Medical Association (AMA), COVID symptoms have become less severe over time and as a result of the emergence of Omicron and its sub-variants.[85] Symptoms such as the temporary loss of taste and smell can still happen in some instances,

but it has become less common with the Omicron variant and subvariants. Other symptoms may include fever, chills, fatigue, muscle or body aches, sore throat, nausea or vomiting and diarrhoea. Symptoms can last between five to seven days but vary from person to person.[85] Sub variants of Omicron, including XBB.1.5 and JN.1, might be less likely to result in severe disease because of two reasons: (1) they tend to remain in the upper respiratory tract thereby reducing the occurrence of lower respiratory tract disease[86] or (2) because populations have some level of immunity from vaccines or prior infection.[85]

***Progression and Timeline of Mild to Moderate Disease***

Mild to moderate disease is defined as the absence of viral pneumonia and hypoxia. For those who develop symptoms, the incubation period is usually 4 to 5 days, with 97.5% experiencing symptoms within 11 days of exposure.[87,88] The average time from exposure to diagnosis was 3.7 days among 107 close contacts of Omicron-positive case patients, with 70% being diagnosed by 5 days, and 99.1% being diagnosed by 10 days.[89] Those with mild COVID-19 recover at home with supportive care and guidance to self-isolate. Those with moderate disease are monitored at home and are sometimes recommended to be hospitalised if conditions worsen. Data on rates of re-infection are limited but variants may lead to increased risk of re-infection in the future. [73,87,90]

***Progression and Timeline of Severe Disease Requiring Hospitalisation***

Those with severe disease will require hospitalisation to manage their illness. Based on data that have been systematically collected for the entire US by the CDC through 10 August 2024, the overall rate of COVID-19 associated hospitalizations was 174.8 per 100,000 people for the 2023-2024 season.[91] For the 50th week of 2022, 7.6 per 100 000 population (country range: 1.3 - 19.5) were hospitalised due to COVID-19 in 14 countries of the EU/EEA with available data.[92] As of 24 March 2022, 0.1-1.5% of children who tested positive for COVID-19 have been hospitalized (for any diagnosis) based on data reported from 25 states and New York City reporting, and 0.00%-0.01% of children with COVID-19 have died based on data reported from 46 states, New York City, Puerto Rico and Guam.

Studies early in the pandemic demonstrated that time from onset of illness to ARDS was 8-12 days and time from onset of illness to ICU admission was 9.5-12 days.[87] In 9 countries of the EU/EEA with available data, 0.5 per 100 000 population (country range: 0.1-1.3) were in the ICU due to COVID-19 during Week 49 2022.[92]

A large number of patient characteristics (demographic/personal, comorbid conditions, complications of COVID) have been identified as being risk factors of severe COVID, or death from COVID (Table 9).

**Table 9. Factors associated with severe disease in those with COVID-19**

| Demographic Characteristics | Comorbid Conditions | Complications of COVID-19 |
|---|---|---|
| Male gender[30,40,41,49,93,94]<br>Older age[38,40,49,93-95]<br>Ethnic minorities [40,42,49,93,95]<br>Lower socioeconomic status [40,49]<br>Obesity [24,38,40,44,49-51,54,55,95]<br>Smoking[40,45,46,57]<br>Blood group type A[33,34] | Disability/clinical frailty/worse scores on health/comorbidity scales [40,95,96]<br>Cardiovascular disease[24,40,58,94,97]<br>Hypertension[24,40,52-54,57,94,97]<br>Dyslipidemia[54,58]<br>Chronic lung diseases / asthma[40,57,58,93,94,97]<br>Diabetes/higher hemoglobin a1c level[24,40,54,57,58,93,94,97]<br>Cancer[49,57,95,97]<br>Liver disease[49,56,57,95,97]<br>Neurological diseases (e.g., stroke or dementia)[38,40,49,58,95,97]<br>Chronic kidney disease or failure/ elevated baseline creatinine[24,38,40,49,58,93,95,97]<br>Autoimmune disease [40,49,58,97]<br>Immunosuppression/immune compromised[40,49,62,95]<br>Organ transplant[49,57,95]<br>Mycotic infection[97,98]<br>HIV[95]<br>Sickle cell disease[95]<br>Vitamin D deficiency[50,61]<br>Certain genetic polymorphisms[32,99] | Cardiac injury/elevated troponin[38,93,94,97]<br>Arrhythmia[100]<br>Shock[97]<br>Pulmonary embolism[48]<br>Respiratory failure/hypoxia [38,97]<br>GI bleeding[97]<br>Anemia[97]<br>Disseminated intravascular coagulation[97]<br>Rhabdomyolysis[97]<br>Bacterial infection/sepsis[97]<br>Higher neutrophil-to-lymphocyte ratio[101]<br>Electrolyte disturbance[97]<br>Elevated glycated hemoglobin [102]<br>Neutrophilia[38,101]<br>Lymphopenia [38,57,93]<br>Thrombocytopenia [38,93,97,101]<br>High circulating histone levels [103]<br>Lower serum iron or total iron banding capacity[104]<br>Higher serum ferritin levels[104]<br>Presence of infiltrate by chest imaging[59,93]<br>High SARS-CoV2 viral load[93] |

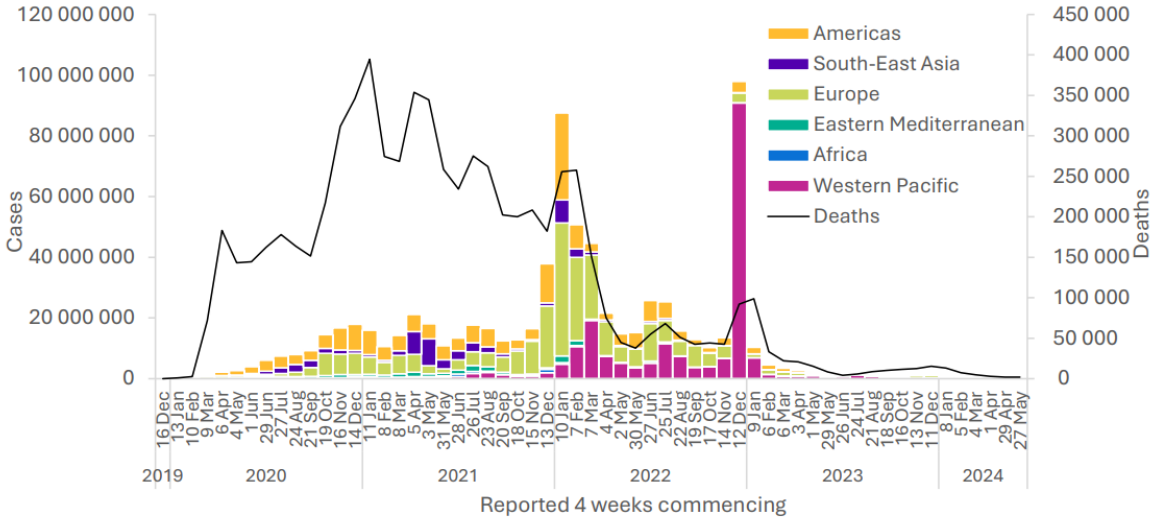
In paediatric patients, COVID infection is much less likely to lead to severe disease or mortality.[105] However, a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C) can present 2-6 weeks after infection in a small subset of children.[106,107] MISC-C is characterized by symptoms of inflammation and fever, with impacts across the body including gastrointestinal, respiratory, and neurological systems and, requires a higher rate of critical care support.[108]

## ***Mortality***

Mortality data of COVID-19 is presented in Table 1. As of 13 April 2024, there were 2,838 deaths per 1,000,000 in the EU-27.[4]

Mortality rates have declined over time, presumably due to an improved understanding of COVID-19 and its management.[109] The number of COVID-19 deaths reported by World Health Organization as of 23 June 2024 are shown in Figure 4.[110]

**Figure 4. COVID-19 cases and global deaths reported by World Health Organization as of 23 June 2024**




According to a 2020 meta-analysis of paediatric studies published through October 2020, the mortality for paediatric patients 0.1-2%.[67,111] In a study from January through June 2020 using the National Child Mortality Database (NCMD) in England, 5.7% of 437 children 0-17 years of age who died were SARS-CoV-2 PCR-positive and those who died of COVID-19 were older and were more likely to be non-White ethnicity.[112]

***Complications of COVID-19 and Long-COVID***

Complications of COVID-19 include impaired function of the heart/cardiovascular system,[113-116] brain/neurological system,[114,115] lung, gastrointestinal/hepatobiliary system,[116] kidney,[117,118] metabolic/endocrine systems,[119] and coagulation system.[120-122]

Complications affecting the heart/cardiovascular system that have been observed include acute myocardial injury, acute coronary syndromes, venous and arterial thrombosis, cardiomyopathy, arrhythmia, myocarditis, pericarditis, heart failure, pulmonary hypertension, and right ventricular dysfunction.[123] One recent review reports that the proportions of patients experiencing some of these complications are as follows: cardiac dysrhythmias in 17 to 44%, cardiac injury with increases in blood troponin in 22 to 40%, myocarditis in 2 to 7%, heart failure in 4 to 21%, and thromboembolic events in 15 to 39%.[124] Another recent review indicates that injury to the myocardium has been reported in up to 30% of hospitalized COVID-19 patients and up to 55% in those with pre-existing cardiovascular disease.[125]

In addition, it has been reported that long-term follow-up of COVID-19 patients has revealed increased incidence of arrhythmia, heart failure, acute coronary syndrome, right ventricular dysfunction, and myocardial fibrosis.[123]

Neurologic complications of COVID-19 infection have also been extensively studied.

Dimitriadis et al examined neurologic manifestations in critically ill COVID-19 patients in a prospective, multicenter, observational registry study of such patients admitted to 19 German ICUs between April 2020 and September 2021. During the study period, among the 15 ICUs that reported a total of 2681 admissions, 340 patients (12.7%) developed neurologic manifestations, the most common being encephalopathy (including delirium, disorder of consciousness, hypoxic encephalopathy, encephalopathy not further described), cerebrovascular disorders (including ischemic stroke, intra-cerebral haemorrhage, subarachnoid haemorrhage, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, cerebral venous sinus thrombosis, cerebral microbleeds, subdural hematoma) and neuromuscular disorders (including polyneuropathy or myopathy, Guillain–Barré syndrome, myasthenia, myositis).[114]

A meta-analysis on the incidence of seizures among COVID-19 patients by Hussaini et al included a total of 11,526 patients from 21 published articles. A total of 255 (2.2%; 95% CI 0.05-0.24, $p < 0.01$) patients presented with seizures as the first manifestation of COVID-19. Only 71 of the 255 patients had previously been diagnosed with epilepsy.[115]

A systematic review by Sourani A et al.[126] reported that 71.4% of COVID-19 patients from seven datasets, presented with spinal epidural hematoma (EDH). Of them, three patients were treated conservatively, while four received neurosurgical intervention. Also, patients with pain and sensorimotor deficits responded fully to the given treatment (100%). However, no response was observed by the sphincter to the given treatment (0%). Long-term follow-up resulted in a good recovery in 71% of patients. SARS-CoV-2-associated spontaneous spinal haemorrhage is a rare complication of infection, with an often-insidious presentation that requires high clinical suspicion.

Another rare infection[127] in COVID-19 patients included mucormycosis. The overall mortality rate in COVID-19–associated mucormycosis patients was found to be 38.9%.

There are also psychological complications of COVID-19 infection. Khraisat et al conducted a meta-analysis to estimate the pooled prevalence of mental disorders among COVID-19 survivors. The analysis included 27 studies with a total sample size of 9605 COVID-19 survivors. The prevalence rates (95% CI) for psychological complications were as follows: overall psychological distress 36% (22–51%), post-traumatic stress disorder 20% (16–24%), anxiety 22% (18–27%), depression 21% (16–28%), and sleeping disorders 35% (29–41%).[128] Also, a recent narrative review of the literature on post-acute neurologic sequelae of COVID-19 indicates that common conditions include persistent fatigue, headaches, “brain fog”, depression, and anxiety.[129]

Shih et al reported that patients with COVID-19 can have GI and hepatobiliary manifestations, which are often mild and transient, although they can occasionally be severe. The most common consequential GI manifestation is ischemic enterocolitis.

Abnormal liver chemistries occur in 14-53% of COVID-19 patients, both at admission and during hospitalization. Typically, liver function test elevations are mild and recover without specific treatment.

Rarely patients with COVID- 19 may present with acute liver failure, develop primary liver disease during their illness, or develop post- COVID-19 cholangiopathy (a form of secondary sclerosing cholangitis).[116]

Mallhi et al performed a review of 42 published systematic reviews on COVID-associated acute kidney injury (CAKI). They found that the incidence of CAKI ranged from 4.3% to 36.4% overall among COVID-19 patients, 36%–50% in kidney transplant recipients (KTRs), and up to 53% in patients with severe or critical illness.[117] Matsumoto and Prowle in their review of the literature on CAKI report that large observational studies and meta-analyses report an AKI incidence of 28-34% in all inpatients and 46-77% in patients admitted to the ICU. The majority of survivors recovered their kidney function by hospital discharge; however, they remained at increased risk of future AKI, a decline in estimated glomerular filtration rate (eGFR), and chronic kidney disease. Moreover, even in the absence of overt AKI a significant proportion of survivors of COVID-19 hospitalisation had reduced eGFR on follow-up.[118]

The risk of new onset diabetes mellitus was reported to be 66% (95% CI 1.38; 2.00) higher among survivors of COVID-19 compared with controls in a meta-analysis of eight studies consisting of 4,270,747 COVID-19 patients and 43,203,759 controls.[119]

Other complications of COVID-19 include haemolytic anaemia,[130] endocrine disorders (including the thyroid, pancreas, adrenal, neuroendocrine, gonadal, and parathyroid glands) [131,132], musculoskeletal disorders including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness,[133] opportunistic infections,[62] and adverse pregnancy outcomes including preterm labour and caesarean delivery without any intrauterine infection, and severe neonatal asphyxia.[134]

A recent narrative review of coagulopathy associated with COVID-19 infection indicates thrombosis occurs as a result of the virus invading endothelial cells causing local complement activation and inflammation which leads to microvascular thrombi (both venous and arterial), which may eventually lead to widespread macrovascular thrombotic injury and in some cases end-organ failure.[121]

Based on a meta-analysis of 42 studies, the risk of thromboembolism was 21% overall and 31% in the ICU, with the pooled odds of mortality being 74% higher among those who experienced thromboembolism compared to those who did not.[135]

*Complications of COVID-19 in paediatric populations*

In children, multisystem inflammatory syndrome has been observed to be temporally associated with COVID-19 infection and often develop a rash following resolution of COVID-19.[67,136,137] Complications include coronary artery aneurysms, cardiac dysfunction, and multiorgan inflammatory manifestations with similarities to Kawasaki disease and other inflammatory conditions.

Neonates born to mothers with SARS-CoV-2 infection during pregnancy have also demonstrated a multisystem inflammatory syndrome with raised inflammatory markers and multi-organ dysfunction, especially of the heart.[138]

As of 03 January 2023, there were 9,333 cases of MIS-C reported to health departments in the United States with 76 deaths reported among those who met the MIS-C case definition.[139] Additional symptoms of MIS-C include abdominal pain, bloodshot eyes, chest tightness or pain, diarrhoea, lethargy, headache, low blood pressure, neck pain, and vomiting.[140]

A recent narrative review of thromboembolic events (TEs) as complications of COVID-19 in children used data from 62 studies, describing 138 patients. Venous TEs represented the majority (54%), followed by arterial thrombosis (38%, mainly arterial ischemic stroke), and intra-cardiac thrombosis (8%). Within the venous TEs group, pulmonary embolism was the most frequent, followed by deep venous thrombosis, central venous sinus thrombosis, and splanchnic venous thrombosis.[141] A systematic review with meta-analysis of four studies to determine the incidence of thrombotic events in children and adolescent patients with COVID-19 infection reported that among 1,128 COVID-19 positive paediatric patients, nearly half of them developed inflammatory sequelae and 7.35% had thrombotic events.[142]

Recent studies have also shown that paediatric patients with COVID-19 are at increased risk of diabetes mellitus, particularly in the 30 days after their COVID-19 infection.[143,144]

*Complications of Long-COVID*

COVID-19 symptoms can persist weeks or months beyond the acute infection.[145,146]
The NICE guideline scope published on 30 October 2020 defined "Long-COVID" signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more and for which signs and symptoms are not explained by an alternative diagnosis).[146]

A meta-analysis of 31 studies published until September 17, 2020 prior to the emergence of the Omicron variant among patients between 18 to 49 years of age found that COVID-19 symptoms were experienced for 14 days to 3 months post-infection, including persistent fatigue (39-73%), breathlessness (39-74%), decrease in quality of life (44-69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39-83%), evidence of peri-/perimyo-/myocarditis (3-26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5-3.4% in controls), and incomplete recovery of olfactory and gustatory dysfunction (33-36%).[147]

Yang et al conducted a meta-analysis of 72 studies with a total of 88,769 patients to examine the occurrence of different symptoms up to one year of follow-up for previously hospitalized patients with COVID-19. A total of 167 sequelae related to COVID-19 were identified, the more common ones being fatigue 27.5%, somnipathy 20.1%, anxiety 18.0%, dyspnoea 15.5%, PTSD 14.6%, hypomnesia 13.4%, arthralgia 12.9%, depression 12.7%, alopecia 11.2%.

The prevalence of most symptoms declined after > 9 months of follow-up, but fatigue and somnipathy persisted in 26.2% and 15.1% of patients, respectively.[148]

The incidence of Long-COVID progressively increases from non-hospitalized to hospitalized individuals to those hospitalized and treated in the ICU.

It varies from 16 and 53% of patients and occurs more frequently in patients after infection with the Alpha or Delta variants in comparison with patients infected with the Omicron variant.[124] Major organ damage post-discharge among adults hospitalized for COVID-19, including incident cardiac, pulmonary, liver, acute and chronic kidney, stroke, diabetes, and coagulation disorders were consistently greater in adults hospitalised for COVID-19 compared with non-COVID-controls in a meta-analysis of nine studies with follow-up of patients ranging from 4 to 22 weeks post-discharge.[149]

Cardiovascular sequelae in post-acute COVID-19 include dyspnoea, chest pain, sinus bradycardia / dysrhythmias, palpitations and/or tachycardia, cerebrovascular disorders, pericarditis, myocarditis, ischemic heart disease, heart failure, thromboembolic events, right ventricular dysfunction, myocardial fibrosis, hypertension,.[113,123,124]

Pulmonary symptoms and complications seen in long-COVID include dyspnoea (occurring in 15% of non-hospitalized patients and up to 81% of previously hospitalized patients), cough, chest pain, or decreased exercise tolerance.[150]

A systematic review and meta-analysis assessed the long-term neurocognitive effects of COVID-19 in three studies comprised of 3,304 post-COVID-19 patients. Persistent neurological / cognitive sequelae of Covid-19 infection included headache 27.8%, fatigue 26.7%, myalgia 23.14%, anosmia 22.8%, dysgeusia 12.1%, sleep disturbance 63.1%, confusion 32.6%, difficulty concentrating 22%, and psychiatric symptoms like PTSD 31%, feeling depressed 20%, and suicidality 2%.[151]

Dangayach et al reports in a narrative review of the literature that neurologic complications in post-acute COVID-19 range from persistent fatigue, headaches, “brain fog”, depression, anxiety, and postural orthostatic tachycardia even in patients with mild disease.[129]

Musculoskeletal disorders with long-COVID, including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, and muscle weakness, were noted in review of systematic reviews and meta-analyses that included 24 studies.[133]

*Complications of Long-COVID in paediatric populations*

It has been estimated that up to 25% of the >14,000,000 children with COVID-19 in the year 2019 have developed persistent symptoms of fatigue, post-exertional malaise, neurologic and cognitive symptoms, and other symptoms that interfere with activities of daily living for months after their initial illness; however more recent data suggest that the proportion of paediatric COVID-19 patients with long-term sequelae/symptoms is in the range of 3-10%.[152]

Post-acute COVID symptoms in children with asymptomatic or mild disease appear to be less severe than in adults, with the most common symptoms being a post-viral cough (4%), fatigue (2%), or both symptoms (1%) with the duration of symptoms lasting 3 to 8 weeks.[153-155]

Pellegrino et al performed a systematic literature review up to 15 February 2022 to summarize long-COVID evidence and to assess prevalence and clinical presentation in children and adolescents.

Twenty-two articles were included; 9 studies provided a control group. The authors found high variability in terms of prevalence (1.6–70%). The most frequently reported symptoms were fatigue (2–87%), headache (3.5–80%), arthro-myalgias (5.4–66%), chest tightness or pain (1.4–51%), and dyspnoea (2–57.1%). Five studies reported limitations in daily function due to long-COVID; most studies did not detect evidence of long-term pulmonary sequelae in these patients.[156]

**Important co-morbidities:**

As mentioned previously, there are a number of common comorbidities in patients with COVID-19; many of these conditions are also associated with more severe disease or progression of disease.

Important comorbidities in those with more severe disease/hospitalised COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, chronic liver disease and autoimmune disease.[24,40,50,51,54-58,89,93,97,157-160]

Prevalence of these conditions have been reported to be lower in mild cases and higher among fatal cases, as shown for European countries in Table 10 using TESSy data posted on 12 August 2021 below.[161]

**Table 10. Preconditions among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 12 August 2021**

| | EU/EEA, reported on 12 August 2021 | | | |
|---|---|---|---|---|
| | **Mild** | **Hosp** | **Severe** | **Fatal** |
| Total N | 1,948,252 | 356,472 | 52,365 | 109,878 |
| Asplenia (%) | 0 | 0 | 0 | 0 |
| Asthma (%) | 0.6 | 1.2 | 1.3 | 1.2 |
| Cancer, malignancy (%) | 3.1 | 9.1 | 10 | 11.1 |
| Cardiac disorder, excluding hypertension (%) | 9.1 | 23.7 | 22.8 | 29.4 |
| Chronic lung disease, excluding asthma (%) | 1.8 | 3.6 | 4.4 | 3.6 |
| Current smoking (%) | 0.9 | 0.1 | 0.2 | 0 |
| Diabetes (%) | 5 | 17.1 | 20.5 | 19.2 |
| Haematological disorders (%) | 0 | 0.2 | 0.1 | 0.1 |
| HIV/other immune deficiency (%) | 0.2 | 0.7 | 0.7 | 0.5 |
| Hypertension (%) | 0.8 | 2.9 | 3.2 | 3.8 |
| Kidney-related condition, renal disease (%) | 0.3 | 1.8 | 1.9 | 2.7 |
| Liver-related condition, liver disease (%) | 0.3 | 0.7 | 0.7 | 0.6 |
| Neuromuscular disorder, chronic neurological (%) | 0.7 | 1.8 | 1.4 | 2.4 |
| Obesity (%) | 0.1 | 0.2 | 0.5 | 0.2 |
| Other endocrine disorder, excluding diabetes (%) | 0.3 | 0.2 | 0.1 | 0.1 |
| Rheumatic diseases including arthritis (%) | 0 | 0 | 0 | 0 |
| Tuberculosis (%) | 0 | 0 | 0 | 0 |
| None (%) | 76.7 | 36.7 | 32.3 | 25 |

Abbreviation: Hosp = Hospitalised

Table 11 below summarises comorbidities among US COVID-19 patients in a retrospective cohort study conducted among 629,953 individuals tested for COVID-19 in a large health system in the US Northwest between 01 March and 31 December 2020.[44]

The most common comorbidities were similar in the full cohort and among those who tested positive: obesity, hypertension, diabetes, and asthma. Among those hospitalised for COVID-19, a large number of comorbidities had elevated prevalence compared to the full cohort and those who tested positive: obesity, hypertension, diabetes, kidney disease, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease.

**Table 11. Comorbidities in Individuals tested for COVID-19 in the Providence St. Joseph Health System – States of California, Oregon, and Washington, 01 March–31 December 2020**

| Comorbidity | Tested (N= 629,953) % | Positive (N= 54,645) % | Hospitalised (N= 8,536) % |
|---|---|---|---|
| Hypertension | 23.3 | 19.8 | 40.2 |
| Diabetes | 9.4 | 10.9 | 28.3 |
| Weight | | | |
| Underweight | 2.1 | 1.7 | 3.1 |
| Normal | 29.0 | 23.9 | 24.3 |
| Overweight | 31.7 | 32.6 | 30.3 |
| Class 1 Obesity | 19.8 | 22.3 | 21.2 |
| Class 2 Obesity | 9.6 | 11.1 | 10.9 |
| Class 3 Obesity | 7.7 | 8.6 | 10.3 |
| Asthma | 6.5 | 5.3 | 6.7 |
| Chronic Obstructive Pulmonary Disease | 4.0 | 2.6 | 8.3 |
| Coronary Artery Disease | 5.5 | 3.6 | 9.7 |
| Myocardial Infarction | 2.2 | 1.6 | 5.5 |
| Congestive Heart Failure | 5.3 | 3.9 | 13.2 |
| Kidney Disease | 5.6 | 5.3 | 17.2 |
| Liver Disease | 3.1 | 2.5 | 4.0 |
| Cancer | 6.1 | 3.0 | 6.3 |

In a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems, the proportion of obese individuals was similar among those who tested negative (18%) and among mild or asymptomatic COVID-19 cases (19%), but clearly elevated among severe COVID-19 cases (37%).[23] Those with severe cases of COVID-19 more commonly had chronic conditions in at least two body systems, with 25% of COVID-19 negative individuals, 17% mild or asymptomatic cases, and 38% of severe cases having multiple chronic conditions. More recent data provide insight into comorbidities among the paediatric population. For the period January 01- March 31, 2021 across 14 states, the CDC's COVID-NET database recorded 204 adolescents aged 12-17 who were hospitalized for likely primarily COVID-related reasons.[21] Among the 204 adolescents, 70.6% had at least one major underlying medical condition, the most common conditions being obesity (35.8%), chronic lung diseases including asthma (30.9%), and neurologic disorders (14.2%).[21]

A recent systematic review and meta-analysis using published reports through August 25, 2021 revealed that prematurity in young infants (RR, 2.00; 95% CI, 1.63-2.46), obesity (RR, 1.43; 95% CI, 1.24-1.64), diabetes (RR, 2.26; 95% CI, 1.95–2.62), chronic lung disease (RR, 2.62; 95% CI, 1.71-4.00), heart disease (RR, 1.82; 95% CI, 1.58-2.09), neurologic disease (RR, 1.18; 95% CI, 1.05-1.33), and immunocompromised status (RR, 1.44; 95% CI, 1.01–2.04) were significant comorbidities associated with severe COVID-19 (intensive care unit admission, invasive mechanical ventilation, and/or death) in children.[162]

The most common comorbidities do not vary substantially by variant. A US electronic medical record study was conducted of adults (≥18 years) with a diagnosis of COVID-19 (ICD-10 code U07.1) hospitalized in a single health care system from 05 March 2020 to 05 February 2022 to evaluate hospitalized patients with COVID-19.[16] The study period was constructed based on the most prevalent SARS-CoV-2 variant at the time as follows: March 2020 - June 2021 (pre-Delta), July - November 2021 (predominantly-Delta), and December 2021 - February 2022 (predominantly-Omicron). The prevalence of most common comorbidities of the study population, stratified by the variant that was predominant at the time of patient admission are shown in Table 12.[16]

**Table 12. Prevalence (%) of most common comorbid conditions among patient hospitalized for COVID-19 in a single health care system from March 5th, 2020, to February 5th, 2022, by predominant variant at the time of admission**

| | **Pre-Delta** | **Delta** | **Omicron** |
|---|---|---|---|
| | n=7112 | n=860 | n=1556 |
| Obesity (BMI > 30) | 43.4 | 43.3 | 38.0 |
| Morbid obesity (BMI > 40) | 8.5 | 8.9 | 8.6 |
| Myocardial infarction | 8.5 | 13.4 | 14.5) |
| Congestive heart failure | 14.9 | 20.9 | 25.1 |
| Peripheral vascular disease | 10.5 | 13.0 | 16.3 |
| Cerebrovascular disease | 12.6 | 16.2 | 17.9 |
| Dementia | 12.4 | 12.3 | 16.1 |
| Chronic pulmonary disease | 21.3 | 24.9 | 29.4 |
| Mild liver disease | 9.5 | 11.2 | 11.1 |
| Diabetes without complications | 21.7 | 16.2 | 13.9 |
| Diabetes with complications | 15.5 | 20.0 | 23.2 |
| Renal disease | 19.7 | 24.5 | 31.5 |
| Non-metastatic cancer | 5.0 | 7.0 | 8.4 |

## Module SII. Non-Clinical Part of the Safety Specification

Nonclinical evaluation of BNT162b2 (COVID-19 mRNA vaccine) included pharmacology (mouse immunogenicity and NHP immunogenicity and challenge studies), pharmacokinetic (series of biodistribution, metabolism and pharmacokinetic studies), and toxicity (2 GLP rat repeat-dose toxicity) studies in vitro and in vivo. A GLP DART study was also completed. No additional toxicity studies are planned for COVID-19 mRNA vaccine. Mouse immunogenicity studies were also conducted with variant modified vaccines.

Nonclinical studies in mice and NHP for COVID-19 mRNA vaccine demonstrated both a strong neutralizing antibody response and a Th1-type $CD4^+$ and an $IFN\gamma^+$ $CD8^+$ T-cell response. The Th1 profile is characterised by a strong IFNγ, but not IL-4, response indicating the absence of a potentially deleterious Th2 immune response and is a pattern favored for vaccine safety and efficacy.[163] Rhesus macaques (Study VR-VRT-10671) that had received two IM immunisations with 100 µg COVID-19 mRNA vaccine or saline 21 days apart were challenged with $1.05 \times 10^6$ plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal and intratracheal routes.[164] COVID-19 mRNA vaccine provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease enhancement. Variant-modified vaccines (BNT162b2 Beta, BNT162b2 Omicron BA.1, and BNT162b2 Omicron BA.4/BA.5) evaluated either as monovalent formulations or also as bivalent formulations (Original + Variant) elicited robust neutralizing antibody responses in mice. Responses were generally highest against the variant matched to the vaccine; bivalent formulations provided a greater breadth of the antibody response in naïve mice compared to monovalent formulations. When administered as a 3rd dose booster to mice that received 2 prior doses of BNT162b2, Omicron BA.4/BA.5 variant vaccines elicited a more balanced response against Omicron sublineages compared to a booster with an Omicron BA.1 variant vaccine.

An intravenous rat PK study, using an LNP with the identical lipid composition as COVID-19 mRNA vaccine, demonstrated that the novel lipid excipients in the LNP formulation, ALC-0315 and ALC0159, distribute from the plasma to the liver. While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC0159. Further studies indicated- metabolism played a role in the elimination of ALC0315. Biodistribution was assessed using luciferase expression as a surrogate reporter formulated like COVID-19 mRNA vaccine, with the identical lipid composition. After IM injection of the LNP formulated RNA encoding luciferase in BALB/c mice, luciferase protein expression was demonstrated at the site of injection 6 hours post dose and expression decreased over time to almost reach background levels after 9 days. Luciferase was detected to a lesser extent in the liver; expression was present at 6 hours after injection and was not detected by 48 hours after injection. After IM administration of a radiolabelled LNP-mRNA formulation containing ALC-0315 and ALC-0159 to rats, the percent of administered dose was also greatest at the injection site. Outside of the injection site, total recovery of radioactivity was greatest in the liver and much lower in the spleen, with very little recovery in the adrenal glands and ovaries. The metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans.

The in vivo metabolism was examined in rat plasma, urine, faeces, and liver samples from the PK study. ALC-0315 and ALC-0159 are metabolised by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

In GLP toxicity studies, two variants of the COVID-19 mRNA vaccine candidate were tested, designated "variant 8" and "variant 9" (V8 and V9, respectively). The variants differ only in their codon optimisation sequences which are designed to improve antigen expression, otherwise the amino acid sequences of the encoded antigens are identical. COVID-19 mRNA vaccine (V9) was evaluated clinically and submitted for application. Two GLP-compliant repeat-dose toxicity studies were performed in Wistar Han rats; one with each variant. Both studies were 17 days in duration with a 3-week recovery period. A DART study in Wistar Han rats has been completed. Safety pharmacology, genotoxicity and carcinogenicity studies have not been conducted, in accordance with the 2005 WHO vaccine guideline.[165]

The IM route of exposure was selected for nonclinical investigation as it is the clinical route of administration. Rats were selected as the toxicology test species as they demonstrated an antigen-specific immune response to the vaccine and are routinely used for regulatory toxicity studies with an extensive historical safety database.

Administration of up to 100 μg COVID-19 mRNA vaccine by IM injection to male and female Wistar Han rats once every week, for a total of 3 doses, was tolerated without evidence of systemic toxicity. Expected inflammatory responses to the vaccine were evident such as oedema and erythema at the injection sites, transient elevation in body temperature, elevations in WBC count and acute phase reactants, and lower A:G ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunisations. Changes secondary to inflammation included slight and transient reduction in body weights and transient reduction in reticulocytes, platelets, and RBC mass parameters. Decreased reticulocytes were reported in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922) but have not been observed in humans treated with this biotherapeutic[166] suggesting this is a species-specific effect. Decreased platelet counts were noted after repeat administration, but were small in magnitude of change, likely related to inflammation-related platelet activation and consumption, and unassociated with other alterations in haemostasis. Elevated levels of gamma-glutamyl transferase were observed in the first repeat-dose toxicity study with COVID-19 mRNA vaccine (V8) without evidence of cholestasis or hepatobiliary injury but was not recapitulated in the second repeat dose-toxicity study with COVID-19 mRNA vaccine (V9), the final clinical candidate. All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase for COVID-19 mRNA vaccine, with the exception of low magnitude higher red cell distribution width (consistent with a regenerative erythroid response) and lower A:G ratios (resulting from acute phase response) in animals administered COVID-19 mRNA vaccine. Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size and/or weight of draining iliac lymph nodes and spleen.

Vaccine-related microscopic findings at the end of the dosing phase consisted of oedema and inflammation in injection sites and surrounding tissues, increased cellularity in the draining iliac lymph nodes, bone marrow and spleen and hepatocyte vacuolation in the liver. Vacuolation of portal hepatocytes, the only test article-related liver microscopic finding, was not associated with any microscopic evidence of hepatic injury or hepatic functional effects (i.e., liver functional enzymes were not elevated) and may be associated with hepatocyte uptake of the LNP lipids.[167] Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the 3-week recovery period for COVID-19 mRNA vaccine. A robust immune response was elicited to the COVID-19 mRNA vaccine antigen.

Administration of COVID-19 mRNA vaccine to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 μg) was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of COVID-19 mRNA vaccine administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (foetuses and pups).

In summary, the nonclinical safety findings related to COVID-19 mRNA vaccine administration primarily represent an expected immune reaction to vaccine administration and are clinically manageable or acceptable risks in the intended population. The key safety findings regarding COVID-19 mRNA vaccine from nonclinical studies and their relevance to human usage are presented in Table 13. There was no evidence of vaccine-elicited disease enhancement.

## Table 13. Key Safety Findings and Relevance to Human Usage

| Key Safety findings from Nonclinical Studies[a] | Relevance to Human Usage |
|---|---|
| **Pharmacology** | |
| **NHP Challenge Model**<br>No evidence of vaccine-elicited disease enhancement. | Suggests low risk of vaccine-enhanced disease in humans. |
| **Toxicity** | |
| **Injection site reactions:**<br>Injection site reactions were common and reversible or showed signs of reversibility at the end of the 3-week recovery period in nonclinical studies. | In common with other vaccines, COVID-19 mRNA vaccine administration has the potential to generate injection site reactions such as oedema and erythema at the injection sites. |
| **Inflammation and immune activation:**<br>Evidence of inflammation or immune activation was common, reversible, and included transiently higher body temperature, higher circulating WBCs, and higher acute phase reactants. Secondarily, transiently lower body weights, reticulocytes, platelets, and RBC mass parameters were observed. | In common with all vaccines, COVID-19 mRNA vaccine administration has the potential to generate inflammation which can lead to increased body temperature, higher circulating WBCs and higher acute phase proteins.<br><br>Decreased reticulocytes have not been observed in humans treated with the LNPsiRNA pharmaceutical Onpattro[166], suggesting this finding in rats is a species-specific effect.<br><br>COVID-19 mRNA vaccine administration has the potential to transiently decrease platelets and RBC mass parameters. These transient decreases are anticipated to be slight and are not likely to be clinically meaningful. |
| **Developmental and Reproductive Toxicity**<br>No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a DART study of COVID-19 mRNA vaccine in rats. | No effects are anticipated in WOCBP, pregnant women or their offspring. |

a. Safety pharmacology, genotoxicity, and carcinogenicity studies were not conducted, in accordance with 2005 WHO vaccine guideline, as they are generally not considered necessary to support development and licensure of vaccines for infectious diseases. In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.

## Module SIII. Clinical Trial Exposure

Four vaccine candidates were evaluated in Study BNT162-01. Based on safety and immunogenicity results from this study, 2 vaccine candidates, BNT162b1 and BNT162b2, were selected for evaluation in Study C4591001, which was a Phase 1/2/3 randomised, placebo-controlled, observer-blind, dose-finding, vaccine candidate -selection, and efficacy study in healthy adults.

Phase 1 of Study C4591001 comprised dose-level–finding evaluations of the 2 selected vaccine candidates; multiple dose levels (some corresponding to those evaluated in Study BNT162-01) were evaluated. Study vaccine was administered using the same 2-dose schedule as in Study BNT162-01 (21 days apart). Dose levels were administered first to an 18- to 55-year age cohort, then to a 56- to 85-year age cohort.

Both vaccine candidate constructs were safe and well tolerated. BNT162b2 at the 30-µg dose level was selected and advanced to the Phase 2/3 expanded cohort and efficacy evaluation primarily because:

- the reactogenicity profile for BNT162b2 was more favourable than BNT162b1 in both younger and older adults with similar immunogenicity results.
- in the NHP challenge study (VR-VTR-10671 – see Module SII), a trend toward earlier clearance of BNT162b2 was observed in the nose.

Phase 2 of the study C4591001 comprised the evaluation of safety and immunogenicity data for the first 360 participants (180 from the active vaccine group and 180 from the placebo group, with each group divided between the younger and older age cohorts) entering the study after completion of Phase 1.

The Phase 3 part of the study C4591001 evaluated the efficacy and safety in all participants (including the first 360 participants from Phase 2). Phase 3 introduced enrolment of participants 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort, as well as enrolment of a 12- to 15-year-old cohort, and immunogenicity data from participants 12- to 15-year-old cohort are anticipated to bridge to the 16- to 25-year-old cohort.

Booster groups were subsequently added to evaluate boostability and protection against variant virus strains.

The pivotal study was initially planned to enrol approximately 30,000 participants, which would have a probability of 78% of detecting an AE with a frequency of 0.01% (1/10000) and a probability of 95% of detecting an AE with a frequency of 0.02% (1/5000).

The protocol was amended to enrol approximately 46,000 participants, which slightly enhanced the ability to detect AEs. However, rarer events might not be detected.

Participants in the pivotal study were initially planned to be followed for up to 24 months in order to assess the potential for late-occurring adverse reactions, such as the theoretical risk of VAED including VAERD. After completing the final efficacy analysis with vaccine efficacy shown to be 95%, and obtaining regulatory authorisation to vaccinate in many countries, MAH started to unblind all participants to determine those participants randomised to placebo so that they could be offered vaccine in accordance with local authorisation. In study C4591001, the total follow-up time from Dose 1 to unblinding for the 21,926 participants in the vaccine group was 83.4 person-year and for the 21,921 participants in the placebo group was 82.2 person-years.

The efficacy analysis in the 12 years and older population for the primary series, the analysis of 6-month post dose 2 data in the 16 years and older population and the evaluation of booster effects and/or protection against emerging SARS-CoV-2 variants of concern, in participants 18 to 55 years of age have been reported out in previous RMPs. Refer to Annex 7 for CT exposure.

Analysis of 6-month post Dose-3 data was conducted on 12 to 15 years of age who received the BNT162b2 booster at the cut-off on 03 November 2022. Clinical trial exposure tables are provided in Annex 7 (Table 28 to Table 30).

Further evaluation for the paediatric population (5-<12 years of age) has been conducted in study C4591007 (see Annex 7 from Table 31 to Table 38).

Phase 1 is the dose finding portion of the study. Dose levels were tested in sentinel cohorts of children by age de-escalation, starting with the lowest dose level in the oldest age group. For each age group, the dose level identified as safe and tolerable and immunogenic in C4591007. Phase 1 was advanced for further evaluation in Phase 2/3.

Phase 2/3 was planned to evaluate BNT162b2 2-doses separated by 21 days at the selected dose levels for each age group for safety and tolerability, immunogenicity, and efficacy (depending on meeting success criteria for immunobridging and accrual of a sufficient number of COVID-19 cases). An immunobridging analysis was designed to compare SARS-CoV-2 neutralizing antibody responses in paediatric participants within each age group in Study C4591007 to a group of young adult participants 16 to 25 years of age in the C4591001 efficacy study.

The study design was modified (Amendment 6) to provide the necessary safety and immunogenicity data to support an EUA and future licensure of a 3rd dose of BNT162b2 to maximize the protection against variants of concern including Delta and Omicron as seen in real-world vaccine effectiveness in older age groups.

Exposure to the 3rd dose of BNT162b2 for participants aged 5 to <12 years of age by demographic characteristics is shown in Annex 7 (Table 39 and Table 40). In addition, exposure in special population for participants 5 to <12 years of age who received a 3rd dose is shown in Annex 7 (Table 41).

Further evaluation for the paediatric population (from the 2 to <5 years and 6 months to <2 years of age) has been conducted in study C4591007 (which remains ongoing).

As of the cut-off date of 16 July 2021, a total of 48 participants (6 months to < 2 years [16], 2 years to <5 years [32]) in Phase 1 were vaccinated in the BNT162b2 clinical development program.

Exposure to BNT162b2 for participants aged 6 months to < 2 years of age and 2 years to <5 years of age by number of doses and demographic characteristics for Phase 1 are shown in Annex 7 (Table 42 to Table 47). Exposure in special populations for participants aged 2 years to <5 years of age is shown in Table 48.

As of the cut-off date of 29 April 2022, a total of 3013 Phase 2/3 participants (6 months to < 2 years [1178], 2 years to <5 years [1835]) were vaccinated in the BNT162b2 clinical development program in the blinded placebo controlled follow up period.

Exposure for Phase 2/3 Blinded Placebo-Controlled Follow-up Period are shown in Annex 7 Table 49 to Table 53. In addition, Phase 2/3 exposure in special populations for participants aged 6 months to < 2 years of age and 2 years to <5 years of age are shown in Table 54 and Table 55.

A total of 650 participants received BNT162b2 vaccine in the open-label follow-up period after the unblinding in participants who originally received placebo and then received BNT162b2.

A total of 76 participants who turned 5 years of age then received BNT162b2 at the age-appropriate dose level of 10 µg.

As regards exposure for the Open-Label Follow-up Period – Participants who originally received Placebo and then received BNT162b2 after unblinding are shown in Annex 7 from Table 56 to Table 60. In addition, Phase 2/3 exposure in special populations for participants aged 6 months to < 2 years of age and 2 years to <5 years of age are shown in Table 61 and Table 62.

A total of 687 participants received BNT162b2 in the open-label follow-up period who originally received BNT162b2. A total of 121 participants who turned 5 years of age then received BNT162b2 at the age-appropriate dose level of 10 µg.

As regards to exposure for the Open-Label Follow-up Period – Participants who originally received BNT162b2 are shown in Annex 7 from Table 63 to Table 67. In addition, Phase 2/3 exposure in special populations for participants aged 6 months to < 2 years of age and 2 years to <5 years of age are shown in Table 68 and Table 69.

Combined exposure for Phase 2/3, 6 months post dose 3, for participants aged 6 months to < 12 years who received original BNT162b2 and participants who were randomized to placebo and received BNT162b2 after unblinding is reported in Annex 7, from Table 70 to Table 81.

*Evaluation of boosting dose(s) - Study C4591031*

Clinical data in approximately 1840 participants >55 years of age from ongoing C4591031 Substudy E (BNT162b2-experienced participants), including safety and immunogenicity data up to 1 month after receipt of a single dose (Dose 4) of BNT162b2 (30 or 60 µg), monovalent BNT162b2 OMI (30 or 60 µg), or bivalent BNT162b2 + BNT162b2 OMI (30 or 60 µg) are provided.

Exposure specific for BNT162b2 (30 µg), monovalent BNT162b2 OMI (30 µg), and bivalent BNT162b2 + BNT162b2 OMI at 30 µg (15 µg each) from substudy E is shown in Annex 7 from Table 82 to Table 87.

In addition, clinical data from approximately 640 participants ≥18 to ≤55 years of age from ongoing Study C4591031, Substudy D (Cohort 2: BNT162b2-experienced participants), including safety and immunogenicity to 1 month after receipt of an additional booster (fourth) dose of an Omicron variant specific vaccine, BNT162b2 OMI 30 µg are provided. These data are derived from participants who were originally randomized to the active vaccine group in Phase 3 of registrational Study C4591001 and completed the original BNT162b2 30-µg two-dose primary series, then enrolled into Study C4591031, Substudy A, and were randomized to receive a third (booster dose) of BNT162b2 30 µg or placebo ≥6 months after receiving Dose 2.

Exposure for BNT162b2 30-µg and the Omicron variant specific BNT162b2 OMI 30 µg from Substudy D is shown in Annex 7 from Table 88 to Table 91.

Study C4591031, Substudy C (SSC) evaluated booster dosing at BNT162b2 at 30 µg and 10 µg dose levels in healthy individuals 12 through 17 years of age who completed a 2-dose primary series of BNT162b2 (30 µg) at least 5 months prior to study randomization. The 1-month post dose 3 results are provided in Annex 7 from Table 92 to Table 95.

*Exposure to bivalent BNT162b2 (original/Omi BA.4/BA.5)- Study C4591044 (12 years of age and older)*

Study C4591044 evaluated a dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 30 µg and 60 µg in individuals 12 through 17 years (30 µg only) and individuals 18 years of age and older who completed 3 doses of BNT162b2 (30 µg) at least 150 to 365 days prior to study randomization. The results are provided in Annex 7 from Table 96 to Table 101.

*Exposure to bivalent BNT162b2 (original/Omi BA.4/BA.5) - Study C4591048 (6 months -11 years of age)*

Study C4591048 evaluated a dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg in individuals 6 months to <5 years of age (sub-study B, Group 2) and at 10 µg in individuals 5 to <12 years of age (sub-study D Group 2) who completed 3-doses of BNT162b2 (3 or 10 µg) at least 60 to 240 days prior to study randomization.

The results are provided in Annex 7 from Table 102 to Table 106 (SSB) and from Table 107 to Table 110 (SSD).

Ongoing[5] Pfizer-BioNTech COVID-19 mRNA vaccine interventional clinical studies also include:

- B7471026: A phase 3, randomized, double blind trial to describe the safety and immunogenicity of 20 valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older.

- BNT162-21: An exploratory phase 1, randomized, observer-blind, active-controlled, dose escalation trial evaluating the safety, tolerability, and immunogenicity of an investigational RNA-based SARS-CoV-2 vaccine in COVID-19 vaccine experienced healthy adults.

Population for analysis of CT data in this RMP includes the following 6 trials:

- C4591001: Phase 1/2/3, placebo-controlled, randomised, observer-blind, dose finding-, study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.

- BNT162-01: A multi-site, phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults.

- C4591007: Phase 1/2/3, Phase 1 - open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3- placebo-controlled, observer- blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and young adults.

- C4591031: Phase 3 master study to evaluate BNT162b2 boosting strategies in healthy individuals previously vaccinated with BNT162b2. Each substudy design is detailed separately and these substudies may be conducted in parallel, as required by the clinical plan, within the framework of this master protocol.

- C4591044: An interventional, randomized, active-controlled, phase 2/3 study to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b RNA based vaccine candidates as a booster dose in COVID 19 vaccine experienced healthy individuals.

- C4591048: A master phase 1/2/3 protocol to investigate the safety, tolerability, and immunogenicity of bivalent BNT162b2 RNA based vaccine candidate(s) in healthy children.

[5] Studies C4591005, C4591015, C4591017, C4591020, C4591024, C4591030, C4591054 and BNT162-03, BNT162-04, BNT162-06, BNT162-14, BNT162-17 were completed and therefore are removed from this list.

## Module SIV. Populations Not Studied in Clinical Trials

### SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Detailed descriptions of all inclusion and exclusion criteria for clinical studies are provided in the individual CSRs.

**Inclusion criteria**

- Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, can be included. For the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable infection with HIV, HCV, or HBV was permitted as the study progressed. Specific criteria for these Phase 3 participants can be found in the Section 10.8 of C4591001 protocol.

- Study C4591001 Phase 2/3 only: Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, front-line essential workers and others).

- The participants enrolled in Study C4591001 were 12 years of age and older; with the 12- to 15-year-old cohort included in the protocol starting from October 2020.

- The participants enrolled in Study C4591007 were 5 to <12 years, 2 to <5 years, and 6 months to <2 years of age.

- The participants enrolled in C4591031 Substudy E and Substudy D were 18 years of age and older.

- The participants enrolled in C4591048 Substudy D were 5 to <12 years and in Substudy B were 2 to <5 years, and 6 months to <2 years of age.

**Exclusion criteria**

Phase 1 exclusion criteria were stricter than criteria in Phases 2 and 3 of the study. Participants were excluded from the studies according to the general criteria listed below:

**Previous vaccination with any coronavirus vaccine**

Reason for exclusion: To avoid confounding the assessment of serological or clinical immune response in the study population.

Is it considered to be included as missing information? No.

Rationale: Minimal potential clinical impact on the target population.

**Previous clinical or microbiological diagnosis of COVID-19**

Reason for exclusion: Phase 1 excluded participants with a previous clinical or microbiological diagnosis of COVID-19 because these participants may have some degree of protection from subsequent infection by SARS-CoV-2 and therefore would confound the pivotal efficacy endpoint.

During Phase 2/3, participants with prior undiagnosed infection were allowed to be enrolled. Screening for SARS-CoV-2 with nucleic acid amplification test by nasal swab or antibodies to non-vaccine SARS-CoV-2 antigen by serology was not conducted before vaccine administration in Phase 2/3, but samples were taken to run these assays after vaccination, thus identifying participants with unidentified prior infection. This group will be assessed to identify whether prior infection affects safety.

Is it considered to be included as missing information? No.

Rationale: Safety in study participants with prior infection was assessed in the pivotal study.

**Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination**

Reason for exclusion: Immunocompromised participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate efficacy, which is the primary pivotal endpoint.

Is it considered to be included as missing information? Yes.

Rationale: Participants with potential immunodeficient status were not specifically included in the study population. However, since the study population is intended to be as representative as possible of the vulnerable population to COVID-19 illness, sub-analyses of immunogenicity data in future studies may provide further understanding of immune responses in this population.

**Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study**

Reason for exclusion: To avoid confounding the assessment of serological or clinical immune response in the study population.

Is it considered to be included as missing information? No.

Rationale: No impact on the safety of the target population.

**Women who are pregnant or breastfeeding**

Reason for exclusion: To avoid use in a vulnerable population.

Is it considered to be included as missing information? Yes.

Rationale: Maternal vaccination with COVID-19 mRNA vaccine has been studied in C4591015 to explore unexpected negative consequences to the embryo or foetus.

**Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study**

Reason for exclusion: To avoid misleading results deriving from non-compliance to study procedures.

Is it considered to be included as missing information? No.

Rationale: Safety profile of COVID-19 mRNA vaccine is not expected to differ in these subjects when properly administered.

### SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical studies are limited in size and, therefore, unlikely to detect very rare adverse reactions, or adverse reactions with a long latency.

### SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

There has been limited exposure to COVID-19 mRNA vaccine in some special populations such as pregnant/breastfeeding women and specific subpopulations. Epidemiologic studies are currently ongoing.

**Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | There is limited experience with use of COVID-19 mRNA vaccine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of COVID-19 mRNA vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants >12 years of age**<br>Through the cut-off date of 12 October 2022 (cohort 2) and through 31 October 2022 (cohort 3) there were no CT cases of pregnancy from C4591044. |

## Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| | **Booster dose Participants >55 years of age**<br>Through the cut-off date of, 05 April 2022 (Sentinel cohort) and through 16 May 2022 (expanded cohort) there were no CT cases of pregnancy from C4591031 sub study E.<br>**Booster dose Participants ≥18 years to ≤55 years of age**<br>Through the cut-off date of 11 March 2022, there were no CT cases of pregnancy from C4591031 sub study D, cohort 2.<br><br>*Original (monovalent)*<br><br>**Participants 6 months to <5 years of age**<br>Not applicable.<br>**Participants 5 to <12 years of age**<br>Through the cut-off date of 06 September 2021, there were no CT cases of pregnancy from study C4591007.<br>**Participants 12 to 15 years of age**<br>Through the cut-off date of 13 March 2021, there were no cases of pregnancies from Study C4591001.<br>**Participants 16 years of age and older**<br>Through the cut-off date of 13 March 2021, there were 50 cases (52 events) originating from Study C4591001, and all were unique pregnancies.<br><br>**(3rd dose) Participants 16 years of age and older**<br>Through the cut-off date of 17 June 2021, there were no cases indicative of exposure during pregnancy originating from Study C4591001 in participants enrolled in the booster group.<br>**(3rd dose) Participants 12 to 15 years of age**<br>Through the cut-off date of 03 November 2022, there were no cases indicative of exposure during pregnancy originating from Study C4591001 in participants enrolled in the booster group.<br>**(3rd dose) Participants 5 to <12 years of age**<br>Through the cut-off date of 22 March 2022, there were no cases of pregnancy from study C4591007. |
| Breastfeeding women | Breastfeeding women were not initially included in the COVID-19 mRNA vaccine clinical development program.<br>It is unknown whether COVID-19 mRNA vaccine is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COVID-19 mRNA vaccine and any potential adverse effects on the breastfed newborn/infant/toddler from COVID-19 mRNA vaccine or from the underlying maternal condition. For preventive vaccines, the underlying |

## Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| | maternal condition, complicated by underlying risks, is susceptible to disease prevented by the vaccine.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants >12 years of age**<br>Through the cut-off date of 12 October 2022 (cohort 2) and through 31 October 2022 (cohort 3) there were no CT cases of breastfeeding from C4591044.<br><br>**Booster dose Participants >55 years of age**<br>Through the cut-off date of 05 April 2022 (Sentinel cohort) and through 16 May 2022 (expanded cohort) there were no CT cases reporting breastfeeding from C4591031 sub study E.<br>**Booster dose Participants ≥18 years to ≤55 years of age**<br>Through the cut-off date of 11 March 2022, there were no CT cases reporting breastfeeding from C4591031 sub study D, cohort 2.<br><br>*Original (monovalent)*<br><br>**Participants 16 years of age and older**<br>Through the cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding from Study C4591001.<br>**Participants 12 to 15 years of age**<br>Through the cut-off date of 13 March 2021, there were no CT cases indicative of exposure during breastfeeding from Study C4591001.<br>**Participants 5 to <12 years of age**<br>Through the cut-off date of 06 September 2021, there were no cases indicative of exposure during breastfeeding from study C4591007.<br>**Participants 6 months to <5 years of age**<br>Not applicable.<br><br>**(3rd dose) Participants 16 years of age and older**<br>Through the cut-off date of 17 June 2021, there were no cases indicative of exposure during breastfeeding originating from Study C4591001 in participants enrolled in the booster group.<br>**(3rd dose) Participants 12 to 15 years of age**<br>Through the cut-off date of 03 November 2022, there were no cases indicative of exposure during breast feeding originating from Study C4591001 in participants enrolled in the booster group.<br>**(3rd dose) Participants 5 to <12 years of age**<br>Not applicable. |
| Participants with relevant comorbidities: | Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included. This allowed enrolment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, BMI >30 |

## Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| • Participants with hepatic impairment<br>• Participants with renal impairment<br>• Participants with cardiovascular disease<br>• Immunocompromised participants<br>• Participants with a disease severity different from inclusion criteria in CTs | kg/m$^2$, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity.<br>Participants with potential immunodeficient status were not specifically included in the study population.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants >12 years of age**<br>Please refer to the exposure of special populations from study C4591044 in Annex 7.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 6 months to <2 years and ≥ 2 to < 5 years**<br>Please refer to the exposure of special populations from C4591048 Substudy B, group 2 in Annex 7.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 5 years to <12 years**<br>Please refer to the exposure of special populations from C4591048 Substudy D group 2 in Annex 7.<br><br>**Booster dose Participants >55 years of age**<br>Please refer to the exposure of special populations in from C4591031 sub study E in Annex 7.<br><br>**Booster dose Participants ≥18 years to ≤55 years of age**<br>Please refer to the exposure of special populations i from C4591031 sub study D, cohort 2 in Annex 7.<br><br>*Original (monovalent)*<br><br>**Participants 16 years of age and older**<br>Please refer to the exposure of special populations in Annex 7.<br>**Participants 12 to 15 years of age**<br>Please refer to the exposure of special populations in Annex 7.<br>**Participants 5 to < 12 years of age**<br>Please refer to the exposure of special populations in Annex 7.<br>**Participants 6 months to <5 years of age**<br>Please refer to the exposure of special populations in in Annex 7.<br><br>**(3rd dose) Participants (16 years of age and older)**<br>Please refer to the exposure of special populations from C4591001 in Annex 7.<br>**(3rd dose) Participants 12 to 15 years of age**<br>Please refer to the exposure of special populations from C4591001 in Annex 7.<br>**(3rd dose) Participants (5 to <12 years of age)**<br>Please refer to the exposure of special populations from C4591007 in Annex 7. |

## Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| Population with relevant different ethnic origin/race | Please refer to exposure information by ethnic origin/race from the studies. |
| Subpopulations carrying relevant genetic polymorphisms | No data available. |
| Paediatric participants | The safety and efficacy of COVID-19 mRNA vaccine in children aged less than 6 months of age have not yet been established. Limited data are available.<br><br>The safety and efficacy of bivalent BNT162b2 (original/Omi BA.1) in children aged less than 12 years of age has not yet been established.<br><br>The safety and efficacy of bivalent BNT162b2 (original/Omi BA.4/BA.5) in children aged less than 6 months of age has not yet been established.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 6 months to <2 years and ≥ 2 to < 5 years**<br>A total of 60 participants ≥6 months to <5 years of age received a fourth dose with bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg through the cut-off date of 25 November 2022 in the C4591048 Substudy B Group 2.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants aged 5 years to <12 years**<br>A total of 113 participants ≥5 years to <12 years of age received a fourth dose with bivalent BNT162b2 (original/Omi BA.4/BA.5) at 10 µg through the cut-off date of 25 November 2022 in the C4591048 Substudy D Group 2.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants 12 to 17 years of age**<br>A total of 107 participants received bivalent BNT162b2 (original/Omi BA.4/BA.5) after 3 doses of BNT162b2 30 µg, through the cut-off date of 12 October 2022 in study C4591044.<br><br>*Original (monovalent)*<br><br>**Participants 6 months to <5 years of age**<br>As of the cut-off date of 29 April 2022:<br>• 3013 participants in the blinded-placebo controlled follow-up period received the Pfizer-BioNTech COVID-19 vaccine.<br>• 650 participants in the open-label follow-up period after the unblinding in participants who originally received placebo and then received the Pfizer-BioNTech COVID-19 vaccine. Moreover, 76 participants turned 5 years of age, then received Pfizer-BioNTech COVID-19 vaccine at the age-appropriate dose level of 10 µg.<br>• 687 participants in the open-label follow-up period who originally received Pfizer-BioNTech COVID-19 vaccine. Moreover, 121 |

## Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| | participants who turned 5 years of age, then received Pfizer-BioNTech COVID-19 vaccine at the age-appropriate dose level of 10 µg.<br><br>**Participants 5 to < 12 years of age**<br>A total of 48 participants in Phase 1, 5 to < 12 years of age and of 1518 participants in Phase 2/3 study C4591007 received Pfizer BioNTech COVID-19 Vaccine through the cut-off date of 06 September 2021.<br>**Participants 12 to 15 years of age**<br><br>One thousand a hundred eighty (1180) paediatric participants 12 to 15 years of age received COVID-19 mRNA vaccine through the cut-off date of 13 March 2021 in study C4591001.<br><br>**Participants 16 years of age and older**<br>Six hundred and seventy-one (671) paediatric participants 16 to 17 years of age received COVID19 mRNA vaccine through the DLP of 13 March 2021 in study C4591001.<br><br>**Booster (3rd dose) Participants 12 to 15 years of age**<br>A total of 825 participants in Phase 3 of study C4591001 received a booster (3rd) dose 30 µg of Pfizer-BioNTech COVID-19 Vaccine through the cut-off date of 03 November 2022.<br><br>**Booster (3rd dose) Participants 5 <12 years of age**<br>A total of 401 participants in Phase 2/3 of study C4591007 received a booster (3rd) dose 10 µg of Pfizer-BioNTech COVID-19 Vaccine through the cut-off date of 22 March 2022; a total of 24 participants, who were 5 to <12 years of age at the time of the study enrollment, turned 12 years of age during the study or after the BNT162b2 10-µg two-dose primary series vaccination period, then received BNT162b2 Dose 3 at the age-appropriate dose level of 30 µg. |
| Elderly (≥65 years old) | Clinical studies of COVID-19 mRNA vaccine included a total of 8846 participants 65 years of age and over; of these, 8827 were from study C4591001, through the cut-off date of 13 March 2021:<br>4590 participants in the blinded placebo-controlled follow-up period.<br>4237 participants in the open-label follow-up period after unblinding<br>Nineteen (19) participants 65 years of age and over were from study BNT162-01 study through the cut-off date of 23 October 2020.<br><br>**bivalent BNT162b2 (original/Omi BA.4/BA.5) Participants 65 years of age and older**<br>Please refer to the exposure Tables from study C4591044.<br><br>**Booster dose Participants 65 years of age and older**<br>Please refer to the exposure Tables from C4591031 sub study E.<br><br>*Original (monovalent)*<br><br>**Booster (Participants 65 years of age and older**<br>Through the cut-off date of 17 June 2021, there were no elderly |

## Table 14. Exposure of Special Populations included or not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| | participants (≥65 years old) from Study C4591001 enrolled in the booster group. |

Abbreviations: BMI = body mass index; CT = clinical trial; DLP = data lock point.

## Module SV. Post-Authorisation Experience

### SV.1. Post-Authorisation Exposure

### MAH and License Partner Data – Cumulative Exposure

The post-marketing exposure is based on the worldwide estimated cumulative number of shipped doses, which is detailed below and also presented in the COVID-19 mRNA vaccine Periodic Safety Update Report (PSUR) , with reporting period 19 December 2024 through 18 June 2025.

**MAH Data**

The worldwide estimated cumulative number of shipped doses by vaccine presentation, region and countries and by age group reported in the shipment tracker (Order Book)[6] from 01 December 2020 through 18 June 2025 is showed in the table below.

Approximately a total of 5,067,503,570[7] doses of BNT162b2 monovalent and bivalent presentations were shipped worldwide.

[6] The Order Book is the most accurate tracker of shipment used as data source for the majority of Regions and Countries; US shipment data not available in the Order Book were taken from the Order Management Dashboard and data for Germany, Hong Kong, Macau and Taiwan were provided by BioNTech.

[7] The total includes doses shipped for COVAX, USG Donation and EC Donation programs; it does not include CP data.

## Table 15. Cumulative Estimated Number of Shipped Doses by Vaccine Presentation, Region and Age Group

| Age Group | Paediatrics | | | | Adults | | | |
|---|---|---|---|---|---|---|---|---|
| **Vaccine Presentation →** | **Monovalent Presentations** | | **Bivalent Presentations** | **Total** | **Monovalent Presentations** | **Bivalent Presentations** | | **Total** |
| **Region/ Country ↓** | Original | Omicron XBB.1.5 Omicron JN.1 Omicron KP.2 | Bivalent BA.4/BA.5 Bivalent BA.1 | | Original | Omicron XBB.1.5 Omicron JN.1 Omicron KP.2 | Bivalent BA.4/BA.5 Bivalent BA.1 | |
| Europe, US, Japan | 166,965,500 | 21,606,900 | 12,557,480 | 201,129,880 | 1,519,322,120 | 478,411,740 | 254,445,895 | 2,252,179,755 |
| ROW | 276,122,200 | 2,424,400 | 11,960,040 | 290,506,640 | 1,983,645,705 | 215,259,060 | 124,782,530 | 2,323,687,295 |
| Total | 443,087,700 | 24,031,300 | 24,517,520 | 491,636,520 | 3,502,967,825 | 693,670,800 | 379,228,425 | 4,575,867,050 |

## CP Data

Cumulative Contractual Party (Fosun) data on the number of original, bivalent and monovalent doses administered in Hong Kong, Macau and Taiwan are provided below.

**Table 16. Cumulative Administered Doses of Original, Bivalent BA.4/BA.5 and Monovalent Vaccine Presentations – Contractual Party Data**

| Region<br>Country<br>-Vaccine Presentation | Number of Administered Doses |
|---|---|
| **Asia** | **32,594,807** |
| **Hong Kong** | **12,273,015** |
| Original[a] | 11,451,700 |
| *- Original 30 mcg PBS and Tris* | 11,407,900 |
| *- Original 10 mcg Tris* | 19,900 |
| *- Original 3 mcg Tris* | 23,900 |
| Bivalent BA.4/BA.5 15/15 mcg[b] | 615,883 |
| Monovalent XBB.1.5[c] | 174,400 |
| *- Monovalent XBB.1.5 30 mcg[d]* | 166,090 |
| *- Monovalent XBB.1.5 10 mcg[e]* | 2630 |
| *- Monovalent XBB.1.5 3 mcg[e]* | 5680 |
| Monovalent JN.1 | 31,032 |
| - Monovalent JN.1 30 mcg[f] | 28,434 |
| - Monovalent JN.1 10 mcg[g] | 858 |
| - Monovalent JN.1 3 mcg[f] | 1740 |
| **Macau** | **428,092** |
| Original + Bivalent BA.4/BA.5[h] | 399,319 |
| Monovalent XBB.1.5 30 mcg[i] | 24,318 |
| Monovalent JN.1 | 4455 |
| *- Monovalent JN.1 30 mcg* | *4372* |
| *- Monovalent JN.1 3 and 10 mcg* | *83* |
| **Taiwan** | **19,893,700** |
| Original | 19,893,700 |
| *- Original 30 mcg PBS and Tris[j]* | *17,622,400* |
| *- Original 10 mcg Tris* | *1,931,300* |
| *- Original 3 mcg Tris* | *340,000* |

a. Cumulative period: through 18 June 2024.
b. Cumulative period: through 20 April 2024.
c. Because of the differences of calculation methods, Hong Kong Government do not publish vaccination data after end of November 2024, so statistics on the number of vaccinations were used until the end of November 2024, and statistics on sales volume were used from 15 April 2025.
d. Cumulative period: through 19 November 2024.
e. Cumulative period: through 15 April 2025.
f. Cumulative period: through 18 June 2025.
g. Cumulative period: through 23 June 2025.
h. Cumulative period: through 24 February 2024.
i. Cumulative period: through 26 November 2024.
j. Cumulative period: through 30 August 2023.

### SV.1.1. Method Used to Calculate Exposure

Not applicable.

### SV.1.2. Exposure

Not applicable.

## Module SVI. Additional EU Requirements for the Safety Specification

### Potential for misuse for illegal purposes

COVID-19 mRNA vaccine does not have characteristics that would make it attractive for use for illegal purposes; therefore, there is only a low potential for COVID-19 mRNA vaccine misuse for illegal purposes.

## Module SVII. Identified and Potential Risks

In accordance with EMA RMP guidance for COVID-19 vaccines, the below factors were taken into consideration for the generation of the safety specification and are not determined to be identified or potential risks.

- **The vaccine construct and the formulation.**

The COVID-19 mRNA vaccine consists of non-infectious, non-replicating RNA in a lipid-based formulation, which delivers the RNA to cells in the immunized person. Protein expression from the RNA is transient, and as is RNA itself. There is no systemic toxicity associated with the LNP or its metabolism (Study reports 38166 and 20GR142). Vacuolation of hepatocytes was observed in rat toxicity studies and believed to be associated with the uptake of the LNP and was without evidence of any effect on liver function. The liver vacuolation was reversed approximately 3-weeks after the last administration.

- **The degradation of the active substance / antigen and potential impact on safety related to this; (e.g., for mRNA-based vaccines).**

Like endogenous mRNA in the cytosol, vaccine RNA in cytosol is degraded. The COVID-19 mRNA contains no known toxic products of the degradation of the RNA or the lipids in the formulation.

- **The vaccine does not contain an adjuvant.**

### SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns of COVID-19 mRNA vaccine in the initial RMP are in Table 17.

**Table 17. Summary of Safety Concerns**

| | |
|---|---|
| Important Identified Risks | Anaphylaxis |
| Important Potential Risks | Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) |
| Missing Information | Use in pregnancy and while breast feeding |
| | Use in immunocompromised patients |
| | Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) |
| | Use in patients with autoimmune or inflammatory disorders |
| | Interaction with other vaccines |
| | Long term safety data |

### SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the RMP list of safety concerns.

**Reasons for not including an identified or potential risk in the list of safety concerns in this RMP include:**

Risks with minimal and/or temporary clinical impact in relation to the severity of the disease prevented, such as reactogenicity events. The following reactogenicity events are identified risks not included in the RMP safety concerns: Injection site pain, Injection site swelling and Injection site redness, Pyrexia, Chills, Fatigue, Headache, Myalgia, and Arthralgia.

Very rare potential risks for any medicinal treatment, including vaccines, which are well known to healthcare professionals (e.g. anaphylaxis) are not included in the list of safety concerns.

In acknowledgment of the EMA coreRMP19 guidance, the reactogenicity profile of COVID-19 mRNA vaccine is discussed below with respect to observed differences in solicited reactogenicity systemic events between Dose 1, Dose 2, and Dose 3. The observed differences do not impact the safety profile of the vaccine and are not proposed to be included in the list of safety concerns, rather they are discussed for completeness in the presentation of the safety profile.

**Reactogenicity**

- C4591048 Substudy A (Phase 1: 3-Dose Bivalent BNT162b2 (Original/Omi BA.4/BA.5) Primary Series + Fourth Dose of BNT162b2 (Omi XBB.1.5) and Phase 2/3: 2-dose series BNT162b2 (Omi XBB.1.5) at 10 µg in Participants 6 Months to <2 Years and Single-Dose BNT162b2 (Omi XBB.1.5) at 10 µg in Participants 2 to <5 Years of Age

Across Phase 1 and Phase 2/3, the variant-adapted BNT162b2 vaccines demonstrated a favourable safety profile in paediatric participants 6 months to <5 years of age. Overall, reactogenicity events within 7 days after vaccinations were mostly mild or moderate in severity with no apparent dose dependency.

- C4591048 Substudy B Group 2 Subset (≥6 Months to <5 Years of Age: Fourth Dose With bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg

In this initial subset of 60 participants, the frequencies of local and systemic reactions reported within 7 days after administration of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 3 µg were lower than the frequencies previously observed in association with BNT162b2 within the respective age group.

- C4591048 Substudy D Group 2 (≥5 to <12 Years of Age): Fourth Dose With bivalent BNT162b2 (original/Omi BA.4/BA.5) at 10 µg

The reactogenicity profile within 7 days after bivalent BNT162b2 (original/Omi BA.4/BA.5) was generally similar to that previously observed in association with BNT162b2 within the respective age group.

- C4591044 Cohorts 2 (≥12 Years of Age) and 3 (≥18 Years of Age): Fourth Dose of bivalent BNT162b2 (original/Omi BA.4/BA.5) at 30 or 60 µg

The reactogenicity profile within 7 days after bivalent BNT162b2 (original/Omi BA.4/BA.5) vaccine was generally similar to that previously observed in association with booster doses of an omicron BA.1-modified BNT162b2 bivalent vaccine and to BNT162b2 within the respective age groups at the same dose.

- C4591031 Substudy E (Expanded Cohort >55 years of age)

Overall, for participants in 18-55 and >55 yrs of age groups (expanded and sentinel) the reactogenicity profile (local reactogenicity and systemic events) was similar to that previously observed following BNT162b2 and BNT162b2 (B.1.1.529 BA.1) in preceding studies.

- C4591031 Substudy D (18 to 54 years of age)

Overall, for all 3 cohorts the reactogenicity profile (local reactogenicity and systemic events) was similar to that previously observed following BNT162b2 in preceding studies.

- Participants 12 years of age and older

The reactogenicity data were collected by participants' e-diary for reporting prompted local reactions and systemic events for 7 days after each dose.

- Phase 1, Study BNT162-01

Local reactions generally increased in frequency and/or severity with increasing dose level and number of doses of COVID-19 mRNA vaccine. Most local reactions were mild or moderate in severity and resolved within several days of onset. For COVID-19 mRNA vaccine, incidence of local reactions was generally less after each dose in the older group (56-85 years) compared with the younger group (18-55 years), and severity of reactions was similar between both age groups.

- Phase 3, Study C4591001

Most local reactions reported after the first and second dose and in both the 16-55 and >55-year-old age groups, were mild or moderate in severity, and no Grade 4 local reactions were reported. Pain at the injection site was the most commonly reported local reaction, more frequently in the younger adult age group (83.7% vs 78.3%) than in the older adult age group (70.1% vs 66.1%); the frequency was similar after dose 1 compared with after dose 2. Redness and swelling at the injection site were less frequently reported and were similar between age groups after any dose.

The frequency and severity of local reactions in the adolescent group (12-15 years) after either dose, was similar to that observed in the adult population aged 16 years and above). Most local reactions were mild or moderate in severity, with pain at the injection site being the most frequently reported in the BNT162b2 group. No Grade 4 reactions were noted.

Overall, the pattern of local reactions reported in a subset of participants who received Dose 3 at least 6 months following Dose 2 was generally similar to that observed in prior analyses of Phase 2/3 participants after Dose 2.

***Systemic Events***

- Phase 1, Study BNT162-01

Systemic events generally increased in frequency and/or severity with increasing dose level and number of doses of COVID-19 mRNA vaccine. Most systemic events were mild or moderate, arose within the first 1 to 2 days after dosing, and were short-lived. For COVID-19 mRNA vaccine, the incidence of systemic events after each dose was similar in the older group (56-85 years) compared with the younger group (18-55 years). Reports of severe systemic events were similar between the younger and older COVID-19 mRNA vaccine groups.

- Phase 3, Study C4591001

Systemic events were generally increased in frequency in the younger adult group compared with the older group, with frequencies and severity increasing with number of doses (dose 1 vs dose 2), except for vomiting and diarrhoea (reported similarly infrequently in both age groups and at similar incidences after each dose).

Systemic events in the younger group compared with the older group were:

| Systemic Event | 16-55 y-o (Dose 1 vs Dose 2) | >55 y-o (Dose 1 vs Dose 2) |
|---|---|---|
| Fatigue | 49.4% vs 61.5% | 33.7% vs 51.0% |
| Headache | 43.5% vs 54.0% | 25.0% vs 39.4% |
| Muscle Pain | 22.9% vs 39.3% | 13.6% vs 28.9% |
| Chills | 16.5% vs 37.8% | 6.5% vs 23.4% |
| Joint Pain | 11.8% vs 23.8% | 8.7% vs 19.0% |
| Fever | 4.1% vs 16.4% | 1.3% vs 11.8% |
| Vomiting | 1.2% vs 2.2% | 0.5% vs 0.7% |
| Diarrhea | 10.7% vs 10.0% | 8.4% vs 8.2% |

For the young adult group (16-55-year), after both doses, most systemic events were mild or moderate in severity. Fever >38.9 °C to 40.0 °C was reported in the BNT162b2 group after Dose 1 for 0.3% and after Dose 2 for 1.5% of participants, and in the placebo group after Dose 1 for 0.1% and after Dose 2 for 0.1% of participants. Fever >40 °C was reported for 1 participant in the BNT162b2 group. Fever >40 °C was not reported in the older BNT162b2 group or in any placebo participants.

The frequency and severity of systemic events in the adolescent group (12-15 years) after either dose, was similar to that observed in the adult population (aged 16 years and above). The most frequently reported systemic events were fatigue, headache, chills and muscle pain. One adolescent participant who received BNT162b2 had fever of 40.4°C on Day 2 after Dose 1, with temperature returning to normal on Day 4. Severe systemic events were reported infrequently and at lower incidence in adolescents (≤3.5%) compared with young adults (≤6.0%) after any dose.

Overall, the pattern of systemic events reported in a subset of participants who received Dose 3 at least 6 months following Dose 2 was generally similar to that observed in prior analyses of Phase 2/3 participants after Dose 2.

Study C4591007

- Participants 5 to <12 years of age

Overall, the pattern of local reactions reported in children 5 to <12 years of age after each dose was generally similar to that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001 with regard to pain at the injection site, but children had slightly higher frequencies of swelling and redness at the injection site (still within tolerable limits).

Overall, the pattern of systemic events reported in children 5 to <12 years of age after each dose was generally comparable to, or less than, that observed in prior analyses of Phase 2/3 participants ≥12 years of age in Study C4591001.

- Participants 2 to <5 years of age

Pain/tenderness at the injection site was the most frequently reported local reaction within 7 days after each dose, with swelling and redness at the injection site reported much less frequently.

Fatigue was the most frequently reported systemic event reported within 7 days after each dose, at similar frequencies in the BNT162b2 and placebo groups.

- Participants 6 Months to <2 Years of Age

Tenderness at the injection site was the most frequently reported local reaction within 7 days after each dose, with swelling and redness at the injection site reported much less frequently.

***Systemic Events***

Irritability was the most frequently reported systemic event reported within 7 days after each dose, followed by drowsiness and decreased appetite.

Overall, reactogenicity to three doses of vaccine was mostly mild to moderate and short-lived, with most events occurring at similar or lower frequencies after the third dose compared with the first or second dose of BNT162b2 3-µg in infants and children 6 months to <5 years of age. The median onset of reactogenicity events was typically 1 to 2 days after each dose and most events resolved within 1 to 2 days after onset.

**Adverse Events of Special Interest (AESI)**

For safety surveillance of clinical study and post-authorization safety data, Pfizer utilizes a dynamic list of TME (MedDRA terms) to highlight conditions of special interest. The conditions and their associated MedDRA terms took into consideration the AESI lists from the following expert groups and regulatory authorities:

- Brighton Collaboration (SPEAC)[168]
- ACCESS protocol[169]
- US CDC (preliminary list of AESI for VAERS surveillance)[170]
- MHRA (unpublished guideline).

The AESI list and associated MedDRA terms are expected to change as the vaccine safety profile evolves.

## SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

### Important Identified Risk: Myocarditis and Pericarditis

Risk-benefit impact

Myocarditis and pericarditis are serious conditions that may range in clinical importance from mild to life-threatening.

Since their identification as important risks, myocarditis and pericarditis have been included as protocol-specified AESIs in COVID-19 vaccine interventional clinical studies.

### Missing Information: Use in Pregnancy and while breast feeding

Risk-benefit impact

The safety profile of the vaccine in pregnant or breastfeeding women was not fully known at first authorization of the vaccine due to their initial exclusion from the pivotal clinical study. However, post-marketing experience in pregnant women is available. [171] Additionally 2 pregnant women studies, C4591015 (the maternal immunization interventional clinical study) and C4591022 (the pregnancy registry study) are completed and ongoing, respectively. Other ongoing non-interventional studies are also open to pregnant women (e.g. C4591009, C4591052).

According to C4591015 CSR, COVID-19 vaccine was safe and well-tolerated in maternal and infant participants. Among maternal participants who received BNT162b2, local reactions and systemic events following vaccination were predominantly mild to moderate in severity and short lived (median duration 1.0 to 3.0 days). Reactogenicity after each dose was generally higher among participants in the COVID-19 vaccine group compared to what was observed in the placebo group. Numerical differences between infant participants with reported congenital anomalies were observed between groups, with anomalies reported in 8/156 participants in the BNT162b2 group and 2/159 in the placebo group. For each anomaly observed, the frequency difference between the BNT162b2 and placebo groups was low with 95% confidence intervals that encompassed zero. Apart from atrial septal defect, all anomalies were single occurrences. The clinical data were reviewed in the context of the available data on background rates of the observed congenital anomalies. Taking this and the low number of events reported in this study into consideration, the findings were not determined to be indicative of a safety risk for infants.

A large amount of observational data from studies in pregnant women vaccinated with the initially approved Comirnaty vaccine have not shown an increase in adverse pregnancy outcomes. In addition, observational studies in breastfeeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants.

**Missing Information: Use in immunocompromised patients**

Risk-benefit impact

The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19.

The safety profile of the vaccine in immunocompromised individuals was not fully known at first authorization of the vaccine due to their exclusion from the pivotal clinical study. Interventional study C4591024 in immunocompromised participants ≥2 years of age is completed. An ongoing non-interventional study is open to immunocompromised participants (C4591052).

**Missing Information: Use in frail patients with co-morbidities (eg. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)**

Risk-benefit impact

There is limited information on the safety of the vaccine in frail patients with co-morbidities who are potentially at higher risk of severe COVID-19.

**Missing Information: Use in patients with autoimmune or inflammatory disorders**

Risk-benefit impact

There is limited information on the safety of the vaccine in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

**Missing Information: Long term safety data**

Risk-benefit impact

The long-term safety of COVID-19 mRNA vaccine was not fully known at first authorization, however further safety data has been collected in interventional Study C4591001 (completed) for up to 2 years following administration of dose 2 of COVID-19 mRNA vaccine and multiple longer-term non-interventional studies are ongoing (C4591036, C4591052).

## SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

- In accordance with CHMP positive opinion (EMEA/H/C/005735/II/0087) received on 10 March 2022 and based on the accumulation of post-authorization safety information, anaphylaxis has been removed as an IIR in the list of safety concerns because anaphylaxis is a known risk of vaccines that is understood by HCPs who administer vaccines and patients and does not considerably impact the benefit/risk

profile of the vaccine. Product labeling and standards of medical care during the vaccination procedure provide adequate risk mitigation.

- In accordance with the preliminary PSUR assessment report (EMEA/H/C/PSUSA/00010898/202212) received on 12 May 2023, the important potential risk VAED/VAERD is removed from the list of safety concerns of the RMP, as the available cumulative data (clinical trial and post-marketing data) showed no safety information that substantiates retaining VAED/VAERD as an important potential risk. VAED/VAERD will continue to be monitored through routine pharmacovigilance.

- The MAH removed the missing information "Interaction with other vaccines" on the basis of the C4591030 final study report and the non-interventional effectiveness data from a large retrospective cohort study of commercially insured US adults conducted by Pfizer and supported by the results from 15 prospective study publications describing the effect of coadministration of COVID-19 vaccine dose(s) with an influenza vaccine on immune responses and safety.

## SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

#### SVII.3.1.1. Important Identified Risk: Myocarditis and Pericarditis

**Table 18. Myocarditis and Pericarditis[a]**

| Potential mechanisms, evidence source and strength of evidence |
|---|
| A mechanism of action (MOA) by which the vaccine could cause myocarditis and pericarditis has not been established. Nonclinical studies, protein sequence analyses and animal studies in rats and non-human primates have not identified a MOA. Hypotheses for MOA include an immune stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination or a hypersensitivity response.<br><br>**Participants 5 to < 12 years of age**<br>The MMWR[172] issued on 01 April 2022, estimated the incidence of myocarditis and pericarditis after infection, MIS and vaccination using EHR data from 40 US health care systems participating in PCORnet, the National Patient-Centered Clinical Research Network (7) for the period January 1, 2021–January 31, 2022. In this study, 27% of persons received mRNA-1273 (Moderna) vaccine and 73% received BNT162b2 (Pfizer-BioNTech) vaccine. In the unspecified dose cohort, 36% received Moderna and 64% Pfizer-BioNTech. In the any dose cohort, 29% received Moderna and 71% Pfizer-BioNTech. Doses specified as booster doses were excluded.<br>Among males aged 5–11 years, the incidences of myocarditis and myocarditis or pericarditis using a 7 and 21-day window were 0–4 after the first vaccine dose, 0 after the second dose, and 12.6–17.6 cases per 100,000 after infection. Among females aged 5-11 years, there were no cases of myocarditis or pericarditis after vaccination; incidences of myocarditis and myocarditis or pericarditis were 5.4–10.8 cases per 100,000 after infection. Because there were no or few cases of myocarditis or pericarditis after vaccination, the RRs for several comparisons could not be calculated or were not statistically significant.<br><br>The US Centers for Disease Control and Prevention (CDC) presented data at a VRBPAC meeting on 14 June 2022 on the number of myocarditis cases within 7 days and 8-21 days of vaccination per million doses from spontaneous reports through 26 May 2022 in the Vaccine Adverse Event Reporting System (VAERS)[173]. In children 5-17 years of age, 54.8 million Pfizer-BioNTech doses were administered (including 3.8 million |

## Table 18. Myocarditis and Pericarditis[a]

booster [third] doses). In general, the reporting rates were higher 0-7 days after vaccination than after 8-21 days across age groups and sexes. In the 0-7-day risk interval post dose 2, the crude reporting rates were highest in ages 16-17 years followed by 12-15 years and lowest for 5-11 years. For persons 5-11 years of age, the reporting rates in the 0-7-day risk interval were (per 1 million doses administered): 0.2 post dose 1, 2.6 post dose 2, and 0 post booster in males; 0.2 post dose 1, 0.7 post dose 2, and 0 post booster in females. The reporting rates were slightly elevated post dose 2 in males, compared with the estimated background rates (0.2-2.2 per 1-million-person days in the 0–7-day interval). No excess cases were numerically estimated by authors in this analysis.

Data from the Vaccine Safety Datalink (VSD) active surveillance network shared publicly by the CDC on 14 June 2022 showed the incidence rates of chart confirmed myocarditis or pericarditis treated in emergency department or inpatient settings within 0-7 days post mRNA COVID-19 primary series and booster through 28 May 2022. The occurrence of myocarditis and pericarditis was rare (n=3 post dose 2) based on approximately 800,000 doses administered in children 5-11 years of age, and lowest of the other reported age groups (12-15 and 16-17 years). The reported incidence rates per million doses administered 0-7 days post vaccination had wide reported confidence intervals (males, 15.2 [95% CI 3.1-44.5]; females, 0 [95% CI 0-15.6]), suggesting instability and low precision.

Hause et al provided an analysis of safety of BNT162b2 vaccination among US children 5-11 years of age using 3 vaccine safety monitoring systems: v-safe (a voluntary smartphone-based system that monitors reactions and health effects), VAERS (the national spontaneous reporting system co-managed by CDC and Food and Drug Administration [FDA]), and VSD (an active surveillance system that monitors electronic health records for prespecified events, including myocarditis). [174] The estimated exposure in this age group at the date of the report was >16 million vaccine doses. In VAERS, the reporting rate of verified myocarditis during days 0–7 after dose 2 was substantially lower among males ages 5–11 years (2.2 per 1 million doses administered) than males ages 12–15 years (45.7 per 1 million doses administered). In weekly sequential analyses of VSD data, no signal for an increased risk of myocarditis after vaccination was found.

**Participants 12 to 15 years of age**
As per MMWR[172] (01 April 2022), among males aged 12–17 years, the incidences of myocarditis and myocarditis or pericarditis were 2.2–3.3 after the first vaccine dose, 22.0–35.9 after the second dose, and 50.1–64.9 cases per 100,000 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 4.9–69.0, and with second dose recipients, were 1.8–5.6; all RRs were statistically significant. Among females aged 12-17 years, incidences of myocarditis or pericarditis were 2.0 after the first vaccine dose, 2.1-5.4 after the second vaccine dose, and 24.7-35.7 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 25.7-19.8, and with second dose recipients, were 2.5-2.2; all RRs were statistically significant.

In a prospective nationwide multicenter study from Denmark[175] among individuals 12–17 years of age, the study revealed an incidence of 97 males and 16 females with myocarditis following COVID-19 vaccination per million. During the first 12 months of the COVID-19 era, the incidence of MIS-C and elevated troponin was 355 and 187 per million male and female adolescents (12-17 years) infected with SARS-CoV-2 (1 in 2800 males and 1 in 5300 females), significantly higher than the incidence of myopericarditis after COVID-19 vaccination in both males and females (Fisher's exact test; $P < 0.01$). In another Danish population-based cohort study[176], vaccination with BNT162b2 was associated with a significantly increased rate of myocarditis or myopericarditis among women only - in the 12-39 years age group, the absolute rate was 1.6 (95% CI 1.0 - 2.6) per 100 000 female individuals aged 12-39 years within 28 days of vaccination. In the overall BNT162b2 cohort, the absolute rate was 1.4 (1.0-1.8) per 100,000 vaccinated individuals within 28 days, and among individuals aged 12-17 years, the rate was 1.0 (0.2 to 3.0) per 100 000 individuals within 28 days of BNT162b2 vaccination. In this study, clinical outcomes of myocarditis or myopericarditis were predominantly mild and generally similar between vaccinated and unvaccinated individuals, although precision in describing clinical outcomes was limited owing to few events.

## Table 18. Myocarditis and Pericarditis[a]

In evaluation of 404,407 adolescents vaccinated with BNT162b2 in Israel, Mevorach et al[177] estimated the risk of myocarditis among male recipients in the 21 days after the first and second doses of 0.56 cases per 100,000 after the first dose and 8.09 cases per 100,000 after the second dose; the risk estimates among female recipients were 0 cases per 100,000 after the first dose and 0.69 cases per 100,000 after the second dose. The risk of myocarditis after receipt of the second vaccine dose among male adolescents 12 to 15 years of age was estimated to be 1 case per 12,361; the corresponding risk among female adolescents was estimated to be 1 case per 144,439. In this study, all the cases were clinically mild, involving a mean duration of hospitalization of 3.1 days (range, 1 to 6) and no readmissions during 30 days of follow-up.

**Booster Dose (Participants 12 to 15 years of age)**
The most recent estimates for myocarditis and pericarditis following booster dose administration and with inclusion of paediatric age groups were presented publicly by the US CDC on 7 June 2022 and 14 June 2022 at VRBPAC meetings and concerned data from VAERS and VSD. [173]
The VAERS analyses concerned data as of 26 May 2022 and included an estimated 93.4 million booster (third) doses of mRNA vaccines in people 18 years of age or older, and 3.8 million booster (third) doses of BNT162b2 in children 12-17 years of age. The reporting rates of myocarditis at 0-7 days were 15.3, 24.1, 9.9, and 4.8 per million booster doses in males 12-15, 16-17, 18-24, and 25-29 years of age, respectively, with rates being lower than those reported post dose 2 in the same age groups and risk period (46.4, 75.9, 38.9, and 15.2, respectively). The reporting rates of myocarditis 0-7 days post-booster dose did not exceed estimated background incidence for the period in males 30 years of age or older, and in females of any age presented.

The analysis of US VSD[173] reported the incidence rates of chart confirmed myocarditis or pericarditis treated in emergency department or inpatient settings within 0-7 days post mRNA COVID-19 primary series and booster through 28 May 2022 for paediatric age groups. The exposure (ie, doses administered) in the VSD dataset was substantially lower than the overall national exposure utilized for the VAERS estimates above (ie, for children 12-17 years of age, there were 249,775 booster doses in VSD compared to 3.8 million booster doses in VAERS estimates). The number of verified myocarditis and/or pericarditis events in the 0–7-day risk interval following boosters in 12-17 years was <10 in males or females, rendering wide reported confidence intervals and therefore a degree of uncertainty in the reported incidences; the data will be surveilled as it accumulates and is disclosed publicly.

In a 20 April 2022[178] presentation of VDS data through 12 April 2022 of people 12-39 years of age, the incidence rates of chart confirmed myocarditis or pericarditis treated in emergency department or inpatient settings within 0-7 days post mRNA COVID-19 primary series and booster were compared to 22 to 42 days after the corresponding vaccine exposure. Myocarditis rates were approximately halved following the booster (third) dose of mRNA COVID-19 vaccine than those following the primary series (with overlapping confidence intervals) for ages 12-39 years: 41.4 per million doses (33.1- 51.1) after BNT162b2 primary series vs 21.4 per million dose (12.7- 33.8) after BNT162b2 booster.

Similarly, in the US publication by Kuehn et al, myocarditis occurrence after booster doses administered to adolescents was estimated by analysing VAERS system and v-safe reports received between 09 December 2021 and 20 February 2022.[179] During the study period, roughly 2.8 million US adolescents received a BNT162b2 booster dose. The confirmed myocarditis rate after a booster dose was 11.4 per 1 million administered doses among adolescent boys 12-17 years of age. By comparison, the myocarditis rate after the second dose in the primary vaccine series was 70.7 per 1 million among individuals 12-15 years of age and 105.9 per 1 million doses among individuals 16-17 years of age.

**Participants 16 years of age and older**
As per MMWR[172] (01 April 2022), among males aged 18-29 years, the incidences of myocarditis and myocarditis or pericarditis were 2.7-8.1 after the first vaccine dose, 12.1-15.0 after the second dose, and 85.5-100.6 cases per 100,000 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 31.8-12.5, and with second dose recipients, were 7.0-6.7; all RRs were statistically

## Table 18. Myocarditis and Pericarditis[a]

significant. Among males aged 30 years or older, the incidences of myocarditis and myocarditis or pericarditis were 3.8-7.3 after the first vaccine dose, 3.1-7.3 after the second dose, and 100.2-114.0 cases per 100,000 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 26.6-15.6, and with second dose recipients, were 32.3-15.6. Among females aged 18-29 years, incidences of myocarditis or pericarditis were 2.5-4.6 after the first vaccine dose, 3.1-5.2 after the second vaccine dose, and 23.8-33.6 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 9.4-7.4, and with second dose recipients, were 7.6-6.4. Among females aged 30 years or older, incidences of myocarditis or pericarditis were 3.1-6.2 after the first vaccine dose, 1.7-4.1 after the second vaccine dose, and 53.8-61.7 after infection. RRs for cardiac outcomes comparing infected persons with first dose recipients were 17.1-10.0, and with second dose recipients, were 31.2-14.9. The estimates in this study are similar to previous reports by CDC.

An HCO study from Israel[180] found a RR for myocarditis after vaccination of 3.24 (95% CI, 1.55 -12.44; RD 2.7 events per 100,000 persons [95% CI 1.0 to 4.6]) compared with unvaccinated group. The study did not provide age and gender specific stratifications, but it reports that in the vaccinated group with myocarditis, the median age was 25 years (interquartile range, 20 to 34), and 90.9% were male. The same study found an excess risk of myocarditis of 11 events per 100,000 persons after SARS-COV-2 infection. Two further studies from Israel reported similar results. Witberg et al.[181] observed a small excess in events 3–5 days following the second dose of BNT162b2 vaccine, but most were mild presentations and just one classified as fulminant. Mevorach et al.[177] observed an incidence ratio of 5.34 for myocarditis in 5,442,696 persons following BNT162b2, although this was attenuated when restricted to the definite and probable cases of myocarditis. Risk of myocarditis was restricted to males under the age of 40 years and only observed following the second dose.

In a self-controlled case series study of over 38 million people aged 16 or older vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021[182], authors estimated an extra one (95% CI 0, 2) myocarditis event per 1 million people vaccinated with BNT162b2 in the 28 days following a first dose and with an extra 40 (95% CI 38, 41) myocarditis events per 1 million patients in the 28 days following a SARS-CoV-2 positive test. The association with the second dose was not significant for BNT162b2 (IRR 1.3 [95% CI 0.98-1.72]). The risk was higher in participants aged under 40 years, with an estimated 2 (95% CI 1, 3) and 3 (95% CI 2, 4) excess cases of myocarditis per 1 million people receiving a first or second dose of BNT162b2; and 10 (95% CI 7, 11) extra cases of myocarditis following a SARS-CoV-2 positive test in the same age group.

**Booster Dose (Participants 16 years of age and older)**
Using US VAERS data of adults aged ≥18 years who have met the myocarditis case definition following administration of 81.2 million COVID-19 mRNA booster doses in the United States between 22 September 2021 through 6 February 2022, the US CDC found the rate of myocarditis following BNT162b2 to be highest in males aged 18-24 years (4.1 per 1 million booster doses). The rates for other age groups and females were low (or null).[174]

Two studies from Israel report incidence of myocarditis and pericarditis after booster dose. Aviram et al [183] report that 11,905 recipients >18 years who have received a booster dose throughout August 2021, there were 4 cases of myocarditis: all male and young (21-38 years).
Three out of 4 patients presented a notable medical history, of which 1 had prior myocarditis episodes (2014-2015 presumably associated with a viral infection), and one patient had a history of childhood long QT and genetic mutation in keratin 16 gene; the clinical course was uneventful in all 4 patients. The second study evaluated military personnel in Israel[184] vaccinated with a third dose of BNT162b2 until September 30, 2021, and diagnosed with myocarditis up to October 14, 2021, found the incidence rates of myocarditis in the week and 2 weeks following a third vaccine dose were 3.17 (95% CI, 0.64-6.28) and 5.55 (95% CI, 1.44-9.67) per 100 000 vaccines given, respectively. Because all myocarditis cases were in young men (18-24 years old), authors estimated the incidence for this specific population to be 6.43 (95% CI, 0.13-12.73) and 11.25 (95% CI, 2.92-19.59) per 100,000 vaccines given in the week and 2 weeks after a third vaccine dose, respectively.

## Table 18. Myocarditis and Pericarditis[a]

**Characterisation of the risk**

**LP.8.1 administration**

**Data from the safety database (non-CT) cumulative as of 18 June 2025**

There were no cases reported as of the data lock point.

**JN.1 administration**

**Data from the safety database (non-CT) cumulative as of 18 June 2025**

*Individuals 6 month to <5 years of age*
Of a total of 8 reported cases in this age group, there were no cases of myocarditis or pericarditis

*Individuals 5 to 11 years of age*
Of a total of 20 reported cases in this age group, there were no cases of myocarditis or pericarditis

*Individuals 12 years of age and older*
Of a total of 3,986 reported cases in this age group, there were 31 cases (0.8%), reporting events of myocarditis (17) and of pericarditis (16). In 2 of these 31 cases, more than 1 relevant PT was coded.

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved/ Resolving | Not Resolved | Resolved with sequelae | Unknown |
|---|---|---|---|---|---|---|---|
| PT all | 33 | 19 | 0 | 15 | 9 | 3 | 6 |
| Myocarditis | 13 | 8 | 0 | 2 | 5 | 1 | 3 |
| Myopericarditis | 4 | 3 | 0 | 2 | 0 | 2 | 0 |
| Pericarditis | 16 | 8 | 0 | 9 | 4 | 0 | 3 |

**KP.2 administration**

**Data from the safety database (non-CT) cumulative as of 18 June 2025**

*Individuals 6 month to <5 years of age*
Of a total of 225 reported cases in this age group, there were no cases of myocarditis or pericarditis

*Individuals 5 to 11 years of age*
Of a total of 361 reported cases in this age group, there were no cases of myocarditis or pericarditis

*Individuals 12 years of age and older*
Of a total of 1203 reported cases in this age group, there were 9 cases (1.0%) reporting events of myocarditis (5) and of pericarditis (4).

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved/ Resolving | Not Resolved | Resolved with sequelae | Unknown |
|---|---|---|---|---|---|---|---|
| PT all | 9 | 3 | 1 | 3 | 0 | 0 | 5 |
| Myocarditis | 5 | 1 | 1 | 0 | 0 | 0 | 4 |
| Pericarditis | 4 | 2 | 0 | 3 | 0 | 0 | 1 |

**XBB 1.5 administration**

**Data from the safety database (non-CT) cumulative as of 18 June 2025**

## Table 18. Myocarditis and Pericarditis[a]

*Individuals 6 month to <5 years of age*
Of a total of 423 reported cases in this age group, there were no cases of myocarditis or pericarditis.

*Individuals 5 to 11 years of age*
Of a total of 524 reported cases in this age group, there was 1 case (0.2%) of myocarditis and no cases of pericarditis.

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved / Resolving | Not Resolved | Unknown |
|---|---|---|---|---|---|---|
| Myocarditis | 1 | 1 | 0 | 1 | 0 | 0 |

*Individuals 12 years of age and older*
Of a total of 11,11,895 reported cases in this age group, there were 113 cases (0.9%) reporting events of myocarditis (66) or pericarditis (58), all serious. In 9 of these 113 cases, more than 1 relevant PT was coded (e.g, Myocarditis and Myopericarditis or Pericarditis and Pleuropericarditis).

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved with sequelae | Resolved / Resolving | Not Resolved | Unknown |
|---|---|---|---|---|---|---|---|
| All PT-events | 124 | 72 | 3 | 4 | 62 | 30 | 25 |
| Giant cell myocarditis | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| Myocarditis | 57 | 34 | 3 | 3 | 27 | 10 | 14 |
| Myopericarditis | 8 | 6 | 0 | 1 | 3 | 3 | 1 |
| Pericarditis | 54 | 27 | 0 | 0 | 28 | 16 | 10 |
| Pericarditis constrictive | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| Pleuropericarditis | 3 | 3 | 0 | 0 | 3 | 0 | 0 |

**bivalent BNT162b2 (original/Omi BA.1 and BA.4/BA.5) administration**

**Data from the safety database (non-CT) cumulative as of 18 June 2025**

*Individuals 6 month to <5 years of age*
Of a total of 280 reported cases in this age group, there were no cases of myocarditis or pericarditis.

*Individuals 5 to 11 years of age*
Of a total of 911 reported cases in this age group, there were no cases of myocarditis or pericarditis.

*Individuals 12 years of age and older*
Of a total of 30,908 reported cases in this age group, there were 259 cases (0.8%) reporting myocarditis/myopericarditis (176) or pericarditis/pleuropericarditis (119), all serious. In 31 of these 259 cases, more than 1 relevant PT was coded.

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown |
|---|---|---|---|---|---|---|---|
| All PT-events | 295 | 148 | 18 | 114 | 13 | 77 | 73 |
| Eosinophilic myocarditis | 2 | 1 | 0 | 1 | 0 | 0 | 1 |

## Table 18. Myocarditis and Pericarditis[a]

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Giant cell myocarditis | 2 | 1 | 1 | 0 | 0 | 0 | 1 |
| Immune-mediated myocarditis | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| Myocarditis | 142 | 65 | 12 | 44 | 6 | 43 | 37 |
| Myopericarditis | 29 | 21 | 1 | 15 | 3 | 5 | 5 |
| Pericarditis | 117 | 57 | 4 | 52 | 4 | 28 | 29 |
| Pleuropericarditis | 2 | 2 | 0 | 1 | 0 | 1 | 0 |

**Original (Monovalent) Administration**

**Data from the safety database (non-CT) cumulative as of 18 June 2025**

*Individuals 6 month to <5 years of age*

Of a total of 1,356 reported cases in this age group, there were 3 cases (0.2%) reporting myocarditis (1) or pericarditis events (2), all serious.

| PT | No. of Events | Events with Criterion of Hospitalization | Not Resolved |
|---|---|---|---|
| All PT-events | 3 | 1 | 3 |
| Pericarditis | 2 | 0 | 2 |
| Myocarditis | 1 | 1 | 1 |

*Individuals 5 to 11 years of age*

Of a total of 18,172 reported cases in this age group, there were 125 cases (0.7%) reporting myocarditis/myopericarditis (90) or pericarditis events (45), all serious. In 10 of these 120 cases, the participant developed both myocarditis and pericarditis.

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved / Resolving | Not Resolved | Unknown |
|---|---|---|---|---|---|---|
| All PT-events | 137 | 41 | 6 | 71 | 23 | 36 |
| Carditis | 3 | 0 | 0 | 1 | 1 | 1 |
| Myocarditis | 67 | 26 | 5 | 34 | 5 | 23 |
| Myopericarditis | 22 | 7 | 0 | 13 | 8 | 1 |
| Pericarditis | 45 | 8 | 1 | 23 | 9 | 12 |

*Individuals 12 years of age and older*

Of a total of 1,738,415 reported cases in this age group, there were 22,874 cases (1.3%) reporting myocarditis/myopericarditis (13,879) or pericarditis/pleuropericarditis events (10,969), all serious. In 2,080 of these 22,874 cases, more than 1 relevant PT was coded.

| PT | No. of Events | Events with Criterion of Hospitalization | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown |
|---|---|---|---|---|---|---|---|
| All PT-events | 25169 | 10457 | 323 | 9688 | 697 | 7919 | 6542 |
| Autoimmune myocarditis | 7 | 5 | 0 | 2 | 0 | 1 | 4 |
| Carditis | 188 | 41 | 3 | 34 | 1 | 64 | 86 |
| Chronic myocarditis | 4 | 1 | 0 | 1 | 0 | 2 | 1 |

## Table 18. Myocarditis and Pericarditis[a]

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Eosinophilic myocarditis | 21 | 15 | 6 | 11 | 1 | 1 | 2 |
| Giant cell myocarditis | 7 | 7 | 0 | 3 | 0 | 1 | 3 |
| Hypersensitivity myocarditis | 9 | 7 | 1 | 6 | 0 | 2 | 0 |
| Immune-mediated myocarditis | 5 | 1 | 1 | 1 | 0 | 0 | 3 |
| Myocarditis | 11,638 | 5,638 | 247 | 4424 | 414 | 3,354 | 3260 |
| Myopericarditis | 2192 | 1,580 | 14 | 1,059 | 64 | 642 | 413 |
| Autoimmune pericarditis | 2 | 1 | 0 | 0 | 0 | 1 | 1 |
| Pericarditis | 10917 | 3090 | 49 | 4082 | 214 | 3828 | 2744 |
| Pericarditis adhesive | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Pericarditis constrictive | 33 | 17 | 2 | 15 | 2 | 6 | 8 |
| Pleuropericarditis | 84 | 54 | 0 | 50 | 1 | 16 | 17 |

**bivalent BNT162b2 (original/Omi BA.4/BA.5) administration**

- *Participants 6 month to <5 years of age*

**Data from the CT dataset C4591048 Substudy B**
Myocarditis and Pericarditis were not observed in any participant through the cut-off date of 25 November 2022.

- *Participants 5 to 11 years of age*

**Data from the CT dataset C4591048 Substudy D**
Myocarditis and Pericarditis were not observed in any participant through the cut-off date of 25 November 2022.

- *Participants 12 years of age and older*

**Data from the CT dataset C4591044** Myocarditis and Pericarditis were not observed in any vaccine group through the cut-off date of 12 October 2022 (cohort 2) and 31 October 2022 (cohort 3).

**Original (Monovalent) + bivalent BNT162b2 (original/Omi BA.1)**

- *Booster Dose Participants >55 years of age*

**Data from the CT dataset C4591031 Substudy E**
Myocarditis and Pericarditis were not observed in any vaccine group through the cut-off date of 05 April 2022 (Sentinel cohort) and through 16 May 2022 (Expanded cohort).

- *Booster Dose Participants ≥18 years to ≤55 years of age*

**Data from the CT dataset C4591031 Substudy D, cohort 2**
Myocarditis and Pericarditis were not observed in any vaccine group through the cut-off date of 11 March 2022.

**Original (Monovalent) Administration**

- *Participants 6 month to <5 years of age*

**Data from the CT dataset (study C4591007)**
Through 29 April 2022, there were no cases of myocarditis/pericarditis in this age group.

- *Participants 5 to <12 years of age*

**Data from the CT dataset (study C4591007)**
Myocarditis and Pericarditis were not observed through the cut-off date of 06 September 2021. In the 6-month post dose 3 data with cut off 23 February 2023, myocarditis and pericarditis were not observed.

- *(3rd) Dose Participants 5 to <12 years of age*

**Data from the CT database (study C4591007)**
Through 22 March 2022, no cases were retrieved reporting myocarditis and pericarditis in the participants who received a booster dose.

- *Participants 12 to 15 years of age*

**Data from the CT dataset[b]:**
There were no cases reporting Myocarditis or Pericarditis as SAE in the clinical trial dataset through the cut-off date of 30 September 2021.

- *(3rd) Dose Participants 12 to 15 years of age*

**Data from the CT database (Study C4591001)**
Through 03 November 2022, no cases were retrieved reporting myocarditis and pericarditis in the participants who received a booster dose.

- *Participants 16 years of age and older*

**Data from the CT dataset (Study C4591001)**
There were 3 cases reporting myocarditis and pericarditis as SAEs in the clinical trial dataset through the cut-off date of 30 September 2021. These cases originated from Phase 3 clinical study C4591001 and are summarized below:

Myocarditis: 1 case of myocarditis reported as resolved and deemed not related to study treatment by the Investigator.
Pericarditis (2 cases): Two (2) serious adverse events [PT Pericarditis] were reported as resolved/resolving, both deemed not related to study treatment by the Investigator.

- *(3rd) Dose Participants 16 years of age and older*

**Data from the CT database (Study C4591001)**
Through 17 June 2021, no cases were retrieved reporting myocarditis and pericarditis in the participants who received booster dose.

Conclusion: the product labels include information about myocarditis and pericarditis following vaccine administration; a Direct Healthcare Professional Communication (DHPC) to address these findings was distributed. Surveillance will continue.

**Risk factors and risk groups**

Post-authorization reports have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the EU and US CDC has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine.

The disease course is self-limiting in a vast majority of cases: 95% of patients show a rapid resolution of symptoms and normalization of cardiac biomarkers, electro- and echocardiographic findings within days.[185] Cardiac arrhythmias, cardiac arrest or death were not found significantly associated with the vaccine.[180,186] Importantly, the available data suggest that the incidence rate of myocarditis in the context of COVID-19 is much greater than the risk of myocarditis following vaccination.

**Preventability**

Healthcare professional should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.

**Impact on the risk-benefit balance of the biologic product**

The vaccine continues to have a favourable risk benefit balance.

**Public health impact**

Considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.

a. **Search criteria**: the following PTs were used to retrieve cases of Myocarditis and Pericarditis:
Autoimmune myocarditis; Carditis; Chronic myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Myocarditis-myositis-myasthenia gravis overlap syndrome; Myopericarditis.
Autoimmune pericarditis; Immune-mediated pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

*Individuals 6 month to <5 years of age:* includes cases where age in years was provided or where age was not provided, and age group was equal to infant.
*Individuals 5 to 11 years of age*: includes cases where age in years was provided or where age was not provided, and age group was equal to child.
*Individuals 12 years of age and older:* includes cases where age in years was provided or where age was not provided, and age group was equal to adolescent, adult and elderly.

**Note**: BC criteria is no longer applied; please refer to vaccine specific summary safety reports and periodic aggregate reports for further information on the characteristics of the post-marketing cases.
b. Please note that CT dataset from the safety database includes only cases reporting SAEs.

### SVII.3.1.2. Important Potential Risk:

There are no important potential risks.

### SVII.3.2. Presentation of the Missing Information

**Table 19. Use in Pregnancy and while Breast Feeding**

| |
|---|
| Evidence source:<br>The safety profile of the vaccine in pregnant or breastfeeding women was not fully known at initial vaccine authorization due to their exclusion from the pivotal clinical study. During the pandemic, based on emerging data on the clinical consequences of SARS-CoV-2 infection in pregnant women and their foetuses and the recommendations of various medical advisory bodies, many pregnant women chose to be vaccinated.<br><br>The available safety information on COVID-19 vaccination during pregnancy, the clinical consequences of COVID-19 during pregnancy and the evolving epidemiology on the virulence of SARS-CoV-2 should be considered in the benefit-risk consideration for vaccination during pregnancy and while breastfeeding.<br><br>Population in need of further characterization:<br>Limited data is communicated in product labelling; for clinical study of the safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women and while breast feeding, (see PART III.2 and PART III.3). |

**Table 20. Use in Immunocompromised Patients**

| |
|---|
| Evidence source:<br>The safety profile of the vaccine in individuals with overt immunocompromised conditions was not fully known at initial vaccine authorization. During the pandemic, based on emerging data on the clinical consequences of SARS-CoV-2 infection in immunocompromised patients and the recommendations of various medical advisory bodies, many immunocompromised patients were vaccinated.<br><br>The available safety information on COVID-19 vaccination in immunocompromised patients, the clinical consequences of COVID-19 in immunocompromised patients, and the evolving epidemiology on the virulence of SARS-CoV-2 should be considered in the benefit-risk consideration for vaccination in this population.<br><br>Population in need of further characterisation:<br>Safety data will be collected in individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants as this population of individuals in the active surveillance studies and the clinical studies proposed by the MAH (see PART III.2 and PART III.3). |

### Table 21. Use in Frail Patients with Co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Evidence source:
The vaccine has been studied in individuals with stable chronic diseases (e.g., hypertension, obesity) however, it has not been studied in frail individuals with severe co-morbidities that may compromise the immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population.

Population in need of further characterisation:
Safety data will be collected in individuals who are frail due to age or debilitating disease in the active surveillance studies and through routine pharmacovigilance (see PART III.2 and PART III.3).

### Table 22. Use in Patients with Autoimmune or Inflammatory Disorders

Evidence source:
There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.

Population in need of further characterisation:
Safety data will be collected in individuals with autoimmune or chronic inflammatory diseases, including those who may be on immunosuppressants in the active surveillance studies (see PART III.2 and PART III.3).

### Table 23. Long Term Safety Data

Evidence source:
At this time, 6-month post dose 2 safety data are available for all patients who have received COVID-19 mRNA vaccine in Study C4591001.

Anticipated risk/consequence of missing information:
At the time of first authorization of the vaccine, the long-term safety of COVID-19 mRNA vaccine is not fully known, however there remain no known risks with a potentially late onset. Data have been collected from participants in study C4591001 for up to 2 years following the 2nd dose of vaccine. Additionally, non-interventional surveillance studies are ongoing to follow long-term safety in vaccine recipients.

## Module SVIII. Summary of the Safety Concerns

### Table 24. Summary of Safety Concerns

| | |
|---|---|
| Important Identified Risks | Myocarditis and Pericarditis |
| Important Potential Risks | None |
| Missing Information | Use in pregnancy and while breast feeding |
| | Use in immunocompromised patients |
| | Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) |
| | Use in patients with autoimmune or inflammatory disorders |
| | Long term safety data |

## PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

### III.1. Routine Pharmacovigilance Activities

Pfizer, on behalf of the MAH, monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations. Pfizer, on behalf of the MAH, gathers data for signal detection and evaluation commensurate with product characteristics.

Routine pharmacovigilance activities for signal detection occur on a regular basis and include review of individual and aggregated AE reports, use of observed versus expected analyses when feasible and appropriate, use of data capture aides to facilitate the capture of clinical details on potential cases of multisystem inflammatory syndrome in children and adults (MIS-C/A) experienced by individuals following administration of Pfizer-BioNTech COVID-19 Vaccine (an updated DCA[8] is provided in Annex 4) and regulatory authority safety alerts monitoring.

### Potential Medication Errors

This section is applicable to all formulations of the vaccine in the RMP.

Potential medication errors are mitigated through the information in the SmPC and available resources and referenced materials for healthcare providers and individuals receiving vaccination.

- The EU SmPC (section 6.6) contains instructions for vaccine dilution and administration, vaccination dosing, and storage conditions for the formulations of the COVID-19 mRNA vaccine.

- Formulation Guide which provides information for vaccine storage, vial differentiation, dose planning, and administration is available, for healthcare provider reference.

- Patient Traceability and Vaccination Reminder card (Annex 7) will be provided with the pre-printed manufacturer name, placeholder spaces for dates of vaccinations and batch/lot numbers as a mitigation effort for potential confusion between vaccines. (See Traceability for additional details).

These available resources will inform healthcare providers on the proper preparation and administration of various formulations of the vaccine and reduce the potential for medication error.

[8] The Multisystem inflammatory syndrome (MIS) data capture aid in Annex 4 of the RMP has been streamlined and simplified in order to improve the response rate.

*Vial Differentiation*

All vials have specific colour flip off plastic cap and label differentiation factors:

Potential medication errors are mitigated through the information in the label (colour of label boarder, product name on the label) and available resources and referenced materials for healthcare providers.

Various resources and referenced resources to inform HCPs on the proper preparation and differentiation will be available.

| **Age Group**<br><br>**Formulation** | **12 years of age and older**<br><br>**Ready to use** | | | **6 months to 11 years old**<br><br>**Dilute to use** | **6 months to 11 years old**<br><br>**Ready to use** |
|---|---|---|---|---|---|
| **Vial cap color/ Syringe** | Grey<br><br>Frozen | Grey<br><br>Refrigerated only | Single dose pre-filled syringe (PFS) | Orange | Blue |
| **Dosage and INN name for each vaccine** | Comirnaty JN.1<br>30 mcg/dose<br>(Bretovameran)<br><br>Comirnaty KP.2<br>30 mcg/dose<br>(Cemivameran)<br><br>Comirnaty Omicron LP.8.1<br>30 mcg/dose<br>(mRNA encoding LP.8.1) | Comirnaty JN.1<br>30 mcg/dose (Bretovameran)<br><br>Comirnaty KP.2<br>30 mcg/dose (Cemivameran)<br><br>Comirnaty Omicron LP.8.1<br>30 mcg/dose<br>(mRNA encoding LP.8.1) | Comirnaty JN.1<br>PFS (Refrigerated, Glass)<br>(Bretovameran)<br><br>Comirnaty KP.2<br>PFS (Refrigerated, Glass)<br>(Cemivameran)<br><br>Comirnaty Omicron LP.8.1<br>PFS (Refrigerated, Glass)<br>(mRNA encoding LP.8.1) | Comirnaty JN.1<br>10 mcg/dose (Bretovameran) | Comirnaty JN.1<br>10 mcg/dose<br>(Bretovameran)<br><br>Comirnaty KP.2<br>10 mcg/dose<br>(Cemivameran)<br><br>Comirnaty Omicron LP.8.1<br>10 mcg/dose (mRNA encoding LP.8.1) |
| **Injection volume per dose** | 0.3 mL | | 0.3 mL | 0.2 mL | 0.3 mL |
| **Amount of diluent per vial** | No dilution | | No dilution | 1.3 mL | No dilution |
| **Doses per vial/syringe** | Single dose frozen vial contains 1 dose<br>Multi dose frozen vial contains 6 doses | Multi dose refrigerated only vial contains 6 doses | 1 dose per syringe | Multi dose vial contains 10 doses after dilution | Single dose vial contains 1 dose<br><br>Multi dose vial contains 6 doses |
| **Fill volume per vial/syringe** | 0.48 mL for single dose<br><br>2.25 mL for multidose vial vial | 2.25 mL for multi dose refrigerated only vial | 0.418 mL (PFS Refrigerated, Glass) | 1.3 mL | 0.48 ml for single dose vial<br><br>2.25 mL for multidose vial |
| **Formulation** | Tris sucrose | | Tris sucrose | Tris sucrose | Tris sucrose |

| | |
|---|---|
| **Grey Caps (no dilution)** | Multi dose: If an attempt is made to dilute the 30 mcg/dose dispersion for injection vial, the user would immediately feel resistance to the addition of any further volume, because the vial fill volume is 2.25 mL and there is little remaining physical space to add diluent to the vial.<br><br>Single dose: The filled volume is 0.48 mL because it contains 1 dose for extraction. If diluted with sodium chloride 9 mg/mL (0.9%) solution by mistake, more than 1 dose of over diluted vaccine may be erroneously extracted. |
| **Single dose pre-filled syringe (PFS)** | The filled volume for the Refrigerated, Glass PFS is 0.418 mL because it contains 1 dose for IM administration. *Note*: carton for glass PFS has "Do not freeze." |
| **Orange caps (requires dilution)** | Vial with orange cap needs to be diluted with 1.3 mL of sodium chloride 9 mg/mL (0.9%) solution. Using less than 1.3 mL of diluent (such as 1.1 mL which is the dilution volume for the 3 mcg/dose diluted product [yellow cap amount]), will lead to incorrect dosing and the user would not be able to correctly extract 10 doses.<br><br>If excess diluent such as 2.2 mL which is the dilution volume for the 3 mcg/dose diluted product (maroon cap amount), is used to dilute the 10 mcg/dose vial, it would be difficult to add the entire volume of diluent into the vial, and the preparer will likely feel resistance. |
| **Blue caps (no dilution)** | Multi dose: If an attempt is made to dilute the 10 mcg/dose dispersion for injection vial, the user would immediately feel resistance to the addition of any further volume, because the filled volume is 2.25 mL and therefore, there is little remaining physical space to add additional diluent to the vial.<br><br>Single dose: The filled volume is 0.48 mL because it contains 1 dose for extraction. If diluted with sodium chloride 9 mg/mL (0.9%) solution by mistake, the user would be able to extract multiple doses, and the product would be over diluted and not achieve the appropriate dose level if administered. |

**Traceability**

The SmPC, includes instructions for healthcare professionals:

- to clearly record the name and batch number of the administered vaccine to improve traceability (section 4.4).

- to report any suspected adverse reactions including batch/Lot number if available (section 4.8).

Traceability is available for every shipping container of COVID mRNA vaccine, which are outfitted with a unique device that provides real-time monitoring of geographic location and temperature 24 hours per day, 7 days per week. Each device will also trace the batch/lot of the associated shipment. The device is activated prior to shipment and information is transmitted wirelessly to Pfizer at a predefined cadence, on behalf of the MAH, until delivery to the vaccinator's practice site. A shipment quality report that indicates if the product is acceptable for immediate use is generated by Pfizer on behalf of the MAH and transmitted to the vaccinator's practice site upon pressing of the stop button on the data logger, or arrival notification from the carrier in combination with the data loggers location and/or light signal.

Additionally, alarms and escalation/notification for excursions (per pre-defined specifications) are programmed into the device. These data may be used for the assessment of a safety signal.

The vaccine carton labelling also contains a 2-D barcode which has the batch/lot and expiry embedded within, should there be capability at a vaccination site to utilize this as an information source.

Further, Pfizer on behalf of the MAH, provides Traceability and Vaccination Reminder cards (Annex 7) to vaccinators that may be completed at the time of vaccination. The Traceability and Vaccination Reminder cards contain the following elements:

- Placeholder space for name of vaccinee;

- Vaccine brand name and manufacturer name;

- Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;

- Reminder to retain the card and bring to the appointment for the second dose of the vaccine;

- QR code that links to additional information; and

- Adverse event reporting information.

In addition, to the Traceability and Vaccination Reminder cards, two stickers per dose, containing printed batch/lot information and a coloured border corresponding to the associated vials for the dose, were made available to support documentation of the batch/lot on the Traceability and Vaccination Reminder card and vaccinee medical records. We also acknowledge that some EU member states may require utilisation of nationally mandated vaccination cards or electronic systems to document batch/lot number; therefore, the available Traceability and Vaccination Reminder cards and stickers with printed lot/batch information may not be utilized in all member states.

The following milestones are proposed for the availability of the stickers with printed lot/batch information:

- Initial vaccine availability: Sufficient quantities of blank "Traceability and Vaccination Reminder cards" were made available to vaccinators in the member states where utilisation of a nationally mandated vaccination card is not required.

- 29 January 2021: In addition to the blank "Traceability and Vaccination Reminder cards", stickers with printed lot/batch information were made available to vaccinators at large scale (1000 subjects/day), mass vaccination sites in the member states where the national authority has not mandated another mechanism for documenting the lot/batch information.

- The MAH will continue to provide the separate sticker deliveries as per current process for those markets requiring it.

**Cold-Chain Handling and Storage**

Multiple modalities will be utilised for quality assurance throughout shipment due to the required ultra-cold storage for COVID-19 mRNA vaccine.

- Each shipment of the vaccine is outfitted with a unique device that provides real-time monitoring of geographic location and temperature 24 hours per day, 7 days per week until delivery to a vaccinator's practice site. Alarms and escalation/notification to Pfizer on behalf of the MAH and/or to the recipient for excursions (per pre-defined specifications) are programmed into the device. Additionally, a shipment quality report that indicates if the product is acceptable for immediate use is generated by Pfizer and transmitted to the vaccinator's practice site.

- Joint adverse event and product complaint (including available batch/lot information) trending reviews occur routinely with Global Product Quality.

- Additionally, available resources and referenced materials for vaccinators will include information regarding proper handling of the shipment container as temporary storage, and handling/disposal of dry ice until the received shipment is either placed into an ultra-low temperature freezer or is maintained in accord with pre-defined specifications in the shipment container as temporary storage (i.e., upon receipt of the shipment quality report noted above), as appropriate.

## III.2. Additional Pharmacovigilance Activities

The MAH proposes the following 4 studies, of which 1 in Europe only, 1 in US only, and 2 in US and Canada. There is 1 low-interventional study (C4591036) and 3 non-interventional studies, summarised in the table below and further detailed in Table 25 and Table 26.

| Study Number | Country | Interventional/ non-Interventional/ Low-Interventional | Purpose |
|---|---|---|---|
| C4591009 | US | Non-Interventional | Safety |
| C4591022 | US/CA | Non-Interventional | Safety |
| C4591036 (former Pediatric Heart Network) | US/CA | Low-Interventional | Safety |
| C4591052 | EU | Non-Interventional | Safety |

*Non-Interventional Post Approval Safety Studies (*1*)*

The MAH proposes 1-complementary study of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs.

- Study C4591052 is a bivalent BNT162b2 (original/Omi BA.1) and bivalent BNT162b2 (original/Omi BA.4/BA.5) safety surveillance study conducted in collaboration with University Medical Center Utrecht on behalf of Vaccine Monitoring Collaboration for Europe Consortium research team VAC4EU and based on the master surveillance protocol.

In addition to the EU study, Pfizer is conducting 1 US study and 2 US/CA for safety surveillance of COVID 19 mRNA. These studies include:

- 1 study using secondary data from administrative claims and electronic health records from data research partners participating in the US Sentinel System (C4591009).

- 1 low-interventional study using primary data from the Pediatric Heart Network (PHN), a NIH-funded consortium of leading research hospitals across the US, Canada, and other countries that conducts research in cardiovascular disease, to characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis over a 5-year period (C4591036).

- 1 study will monitor rates of pregnancy and infant outcomes in planned and unplanned pregnancies exposed to BNT162b2 using an established pregnancy registry. Women receiving BNT162b2 during pregnancy will be followed from exposure to one-year post-partum. Analyses will be conducted to evaluate if the pregnant women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with pregnant women who are unvaccinated (C4591022).

The protocols for the safety studies in the US (C4591009, and in US/CA C4591022) were added in Annex 3 Part C.

*Non-Interventional Post-Approval Safety Studies Assessing Myocarditis/Pericarditis*

Studies, C4591009 (US), and C4591052 (EU) will describe the incidence of myocarditis/pericarditis following Comirnaty vaccination overall, and stratified by age group, gender, race/ethnicity (if feasible), dose, and risk interval using structured information and following case confirmation via medical record review where feasible. To assess the magnitude of risk, these studies include comparative methods (self-controlled analyses, and analyses involving a separate comparator group).

Relative risk (RR) estimates from comparative analyses will be obtained overall and stratified by the same factors as described above when supported by sufficient cell counts.

To evaluate long-term outcomes, myocarditis/pericarditis-specific analytic endpoints the ongoing study C4591009, will assess the natural history of post-vaccination myo-/pericarditis, e.g., recovery status (medical record review) and/or identification of serious cardiovascular outcomes (structured data) within 1 year of myo-/pericarditis diagnosis among individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine.

A long-term primary data collection low-interventional study is C4591036 (former Pediatric Heart Network (PHN), to evaluate the clinical course, risk factors, long-term sequelae, and quality of life of post-vaccine myocarditis/pericarditis over a 5-year period.

In addition, the protocol of study C4591036 has been amended to include evaluation of individuals receiving additional approved doses, including the bivalent Omicron-modified vaccine.

Additionally, the MAH has committed to conduct a standalone post-authorization observational safety study (C4591052) to evaluate the bivalent omicron-modified vaccine.

*Non-Interventional Post-Approval Safety Studies that include paediatric subjects aged 5 to < 12 years old*

Studies C4591009 (US) and C4591036 (US and Canada) will assess the use of vaccine for the occurrence of safety events of interest, including myocarditis and pericarditis. Each of these studies includes individuals of all ages, including ages 5 to <12, except for low-interventional study C4591036, which only includes individuals <21 years of age.

*Non-Interventional Post-Approval Safety Studies in Pregnancy*

It is anticipated that initial use in pregnancy will be subject to local health authority recommendations regarding which individuals should be vaccinated and likely very limited intentional vaccination of pregnant women; therefore, initially this information will derive from 3 of the real-world safety studies (C4591009, C4591022 and C4591052), described in Table 25.

The MAH will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In preGNancy) when developing any pregnancy related study objectives (currently not listed in Table 25 and Table 26).

The MAH agrees that monitoring vaccine safety in pregnant women is critical. Given that a pregnancy registry based on primary data collection is susceptible to non-participation, attrition, small sample size and limited or lack of comparator data, Pfizer, on behalf of the MAH, would like to propose monitoring vaccine safety in pregnancy using electronic health care data, which could be conducted in a representative pregnant woman population exposed to the vaccine and minimize selection bias, follow-up bias, and reporting bias. In addition, internal comparison groups, such as contemporaneous unvaccinated pregnant women or women receiving other vaccine(s) to prevent COVID-19 (if available) could be included.

## Table 25. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| C4591009<br>US | A non-interventional post approval safety study Pfizer-BioNTech COVID-19 vaccine in the United States.<br><br>Non-Interventional<br>*Ongoing* | To capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the Pfizer-BioNTech COVID-19 vaccine since its availability under an EUA using electronic health records and claims data from data partners participating in the Sentinel System. | Post-approval observational study using real-world data. | The general US population (all ages), pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System.<br>This study will include an analysis of individuals who receive a booster dose of the Pfizer-BioNTech COVID-19 vaccine. | Protocol submission: | 31-Aug-2021 |
| | | | | | Protocol amendment submission: | 11-Jul-2022 |
| | | | | | Monitoring report 1 submission: | 31-Oct-2022 |
| | | | | | Interim Analysis submission: | 30-Apr-2024[9] |
| | | | | | Final CSR submission: | 31-Mar-2026[10] |
| C4591022<br><br>US/Canada | Pfizer-BioNTech COVID-19 Vaccine exposure during pregnancy: A non-interventional | To assess whether pregnant women receiving BNT162b2 experience increased risk of | Analyses will be conducted to evaluate if the pregnant | Pregnant women and infant outcomes. | Interim reports submission: | 12-Apr-2022 |

[9] As per approval of PAM-MEA-037.5 (dated 09 Nov 2023) the ISR for C4591009 will be delayed to 30 Apr 2024 due to cybersecurity breach.

[10] FDA requested a protocol amendment to incorporate analyses in the 6 months- 4 years group. As part of the amendment, there were changes to the end of data collection and final study report milestone dates. Removal of the milestone for the second monitoring report is proposed due to the anticipated diminished value of the report relative to the planned interim study report to be submitted to both the EMA and US FDA by 30 April 2024.

## Table 25. Additional Pharmacovigilance Activities

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>***Study Status*** | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | post-approval safety study of pregnancy and infant outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry.<br><br>Non-Interventional<br>Ongoing | pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age, relative to pregnant women who received no COVID-19 vaccines during pregnancy. | women receiving the vaccine during pregnancy experience increased risk of pregnancy and infant outcomes compared with pregnant women who are unvaccinated. | | | 31-Jan-2023 |
| | | | | | | 31-Jan-2024 |
| | | | | | Final CSR submission: | 28-Feb-2026[11] |
| C4591036 (former Pediatric Heart Network Study)<br>US/Canada | Low-Interventional Cohort Study of Myocarditis/Pericarditis Associated With COMIRNATY in Persons Less Than 21 Years of Age<br><br>Low-Interventional<br>*Ongoing* | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron-modified vaccine. | Prospective cohort study. This study will include an analysis of individuals who receive booster dose of the Pfizer-BioNTech COVID-19 vaccine including the bivalent Omicron-modified vaccine, if feasible. | Patients <21 years presenting to PHN sites after receiving any dose of BNT162b2 including the bivalent Omicron-modified vaccine, if feasible and who were diagnosed with myocarditis / pericarditis as well as individuals not vaccinated with myocarditis/pericarditis. | Protocol submission: | 30-Nov-2021 |
| | | | | | 6-monthly interim study report[12] | 30-June-2023 |
| | | | | | Protocol amendment submission: | 15-Dec-2022 |

[11] C4591022 milestone changed due to additional follow-up time needed to capture newly recruited subjects due to FDA 16 Sep 2021 request to increase sample size. Justification submitted via EMEA/H/C/005735/IB/0204 procedure.

[12] The 5th interim report for Study C4591036 was submitted on 30 June 2025 under procedure PAM-MEA-041.8, currently under evaluation; next interim report (6th) should be submitted by 30 June 2026, covering a period of 12 months according to the outcome of PAM-MEA-041.7 procedure. Subsequent progress reports will be submitted every 12 months, instead of every 6 months, until the final report submission.

**Table 25. Additional Pharmacovigilance Activities**

| Study Number<br>*Country (ies)* | Study Title<br><br>Study Type<br>*Study Status* | Rationale and Study Objectives | Study design | Study populations | Milestones | |
|---|---|---|---|---|---|---|
| | | | | | 12-monthly interim study report[12] | 30-June-2025 |
| | | | | | Final CSR submission: | 28-Feb-2031[13] |
| C4591052<br>EU | Post-Authorisation Safety Study of Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 in Europe<br><br>Non-Interventional<br>*Ongoing* | To ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general EU populations. | This observational study will capture safety events (based on AESI) including myocarditis and pericarditis, in individuals of any age who received the COVID-19 bivalent Omicron-modified vaccine since its availability. | General population | Protocol synopsis submission: | 04-Jan-2023 |
| | | | | | Protocol submission | 30-Apr-2023 |
| | | | | | Final CSR submission | 30-Apr-2026 |

[13] The date of the final report has been extended based on the FDA's requirement to increase the sample size for Cohort 1 to 300 participants; this was also endorsed by EMA on 16 May 2022; PAM-MEA-041.1 was submitted on 31 July 2023 to provide protocol amendment #3, PAM-MEA-041.3 outcome (dated 12 October 2023) with reference to submitted PA #3 (PAM-MEA-041.4) endorsed C4591036 final CSR delay from 14 Nov 2029 to 28 February 2031.

## III.3. Summary Table of Additional Pharmacovigilance Activities

### III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

**Table 26. On-going and Planned Additional Pharmacovigilance Activities**

| **Study (*study short name, and title*)**<br>**Status (*planned/on-going*)** | **Country** | **Summary of Objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|---|
| **Category 3** | | | | | |
| C4591009<br>*Ongoing* | US | To assess the occurrence of pre-specified safety events of interest among individuals in the general US population and in subcohorts of interest within selected data sources participating in the US Sentinel System. | Myocarditis and pericarditis<br>AESI-based safety events of interest<br>Use in pregnancy<br>Use in immunocompromised patients<br>Long term safety data | Protocol submission: | 31-Aug-2021 |
| | | | | Protocol amendment submission: | 11-Jul- 2022 |
| | | | | Monitoring report 1 submission: | 31-Oct-2022 |
| | | | | Interim Analysis submission: | 30-Apr-2024[9] |
| | | | | Final CSR submission: | 31-Mar-2026[10] |
| C4591022<br>*Ongoing* | US/CA | To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age, relative to pregnant women who received no COVID-19 vaccines during pregnancy. | Use in pregnancy. | Interim reports submission: | 12-Apr-2022 |
| | | | | | 31-Jan-2023 |
| | | | | | 31-Jan-2024 |
| | | | | Final CSR submission: | 28-Feb-2026[11] |

## Table 26. On-going and Planned Additional Pharmacovigilance Activities

| Study (*study short name, and title*)<br>Status (*planned/on-going*) | Country | Summary of Objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|---|
| C4591036 (former Pediatric Heart Network Study)<br>*Ongoing* | US/CA | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron modified vaccine. | Myocarditis/pericarditis<br>Long term safety data. | Protocol submission: | 30-Nov-2021 |
| | | | | 6-monthly interim study report[12]: | 30-June-2023 |
| | | | | Protocol amendment submission: | 15-Dec-2022 |
| | | | | 12-monthly interim study report[12]: | 30-June-2025 |
| | | | | Final CSR submission: | 28-Feb-2031[13] |
| C4591052<br>*Ongoing* | EU | Post-approval observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 bivalent Omicron-modified Vaccine and pre-specified safety events of interest among persons administered the vaccine in the overall EU population. | Myocarditis/pericarditis<br>Use in pregnancy<br>AESI-based safety events of interest including vaccine associated enhanced disease in immunocompromised patients<br>Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)<br>Use in patients with autoimmune or inflammatory disorders<br>Long term safety | Protocol synopsis submission: | 04-Jan-2023 |
| | | | | Protocol submission | 30-Apr-2023 |
| | | | | Final CSR submission | 30-Apr-2026 |

## PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

None.

## PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

### V.1. Routine Risk Minimisation Measures

The product information is sufficient to mitigate the current identified and potential risks of COVID-19 mRNA vaccine. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC. No additional measures for risk minimisation are considered necessary by the MAH at this time. The proposed minimisation measures are summarised in the table below for each safety concern.

**Table 27. Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine risk minimisation activities |
|---|---|
| **Important Identified Risk** | |
| Myocarditis and Pericarditis | Routine risk communication:<br>SmPC section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |
| **Important Potential Risk** | |
| None | |
| **Missing Information** | |
| Use in pregnancy and while breast feeding | Routine risk communication:<br>SmPC section 4.6 Fertility, pregnancy and lactation<br>PL section 2. What you need to know before you receive Comirnaty<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |
| Use in immunocompromised patients | Routine risk communication:<br>SmPC section 4.4 Special warnings and precautions for use and section 5.1 Pharmacodynamic properties.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |

**Table 27. Description of Routine Risk Minimisation Measures by Safety Concern**

| | |
|---|---|
| Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) | Routine risk communication:<br>SmPC section 5.1 Pharmacodynamic properties.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |
| Use in patients with autoimmune or inflammatory disorders | Routine risk communication: None.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br>Other routine risk minimisation measures beyond the Product Information: None. |
| Long-term safety data | Routine risk communication: None.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: None.<br><br>Other routine risk minimisation measures beyond the Product Information: None. |

## V.2. Additional Risk Minimisation Measures

The additional risk minimisation measure to address myocarditis and pericarditis is a Direct Healthcare professional communication, as per below Table 28.

**Table 28. Additional Risk Minimisation Measures for the Important Identified Risk of Myocarditis and Pericarditis**

| **Direct Healthcare Professional Communication (DHPC)** | |
|---|---|
| Objectives | To ensure that healthcare providers (HCPs) are aware of the potential for myocarditis and pericarditis associated with COVID-19 mRNA vaccine use. |
| Rationale for the additional risk minimisation activity: | The DHCP communication is to inform HCPs about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alerted about the signs and symptoms and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations. |
| Target audience and planned distribution path: | The target audience includes general practitioners, cardiologists, specialists in emergency medicine and vaccination centres, HCPs who vaccinate patients and who provide medical care to patients who receive the vaccine. Target groups should be further defined at national level, depending on national health care systems. |
| Plans to evaluate the effectiveness of the interventions and criteria for success: | Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.<br><br>The one-time DHPC distribution started on 19 July 2021 in all EEA countries as per the EMA's communication plan. |

**Removal of additional risk minimisation activities**

On 19 July 2021, a Direct Healthcare Professional Communication (DHPC) was issued to inform healthcare practitioners about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccination.

The effectiveness of the additional risk minimization measure (aRMM) was evaluated by estimating the time trend, in relation to the dissemination of the DHPC letter, of the proportion of individuals who received real-world clinical assessment for myocarditis/pericarditis following Comirnaty vaccination as an outcome[14] of PASS C4591021.

While the rates of cardiac imaging were higher prior to the issuance of the DHPC letter, the rationale to inform healthcare practitioners about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alert to the signs and symptoms, and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations, was still effective. The unprecedented attention given to all signals and risks associated with the COVID-19 vaccine campaign caused heightened awareness of risks at timepoints that were before the typical notification processes for healthcare practitioners, such as with a DHPC. However, the overall intention of the DHPC was met between the notifications from regulators regarding their evaluation of said signals and actions to undertake in the interim, as well as the media attention given to the risks, as outlined in the data output from C4591021.

Therefore, the MAH proposes to remove the DHPC from the RMP at this time.

## V.3. Summary of Risk Minimisation Measures

**Table 29. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Myocarditis and pericarditis | Routine risk minimisation measures:<br><br>SmPC sections 4.4. and 4.8.<br><br>Additional risk minimisation measures: | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>*Studies (Final CSR Due Date)*<br>C4591036 [former Pediatric Heart Network study] (28-February 2031) is the key study for |

[14] "To assess the effectiveness of the DHPC communication about the risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine use and describe the rate of cardiac imaging use for vaccinated and unvaccinated individuals in this study population each calendar month during the study period, before and after distribution of the DHPC".

**Table 29. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | None | this safety concern however other ongoing noninterventional studies may also contribute safety information.<br>C4591009 (31-Mar-2026)<br>C4591052 (30-Apr-2026) |
| Use in pregnancy and while breast feeding | Routine risk minimisation measures:<br><br>SmPC section 4.6; PL section 2.<br><br>Additional risk minimisation measures:<br><br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>*Studies (Final CSR Due Date)*<br>C4591022 is the key study for this safety concern, however other ongoing non-interventional studies may also contribute safety information to this cohort.<br>C4591009[a] (31-Mar-2026)<br>C4591052[a] (30-Apr-2026) |
| Use in immunocompromised patients | Routine risk minimisation measures:<br><br>SmPC sections 4.4 and 5.1.<br><br>Additional risk minimisation measures:<br><br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>*Studies (Final CSR Due Date)*<br>C4591009 (31-Mar-2026)<br>C4591052 (30-Apr-2026) |
| Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) | Routine risk minimisation measures:<br><br>SmPC section 5.1.<br><br>Additional risk minimisation measures:<br><br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>*Studies (Final CSR Due Date)*<br>C4591052 (30-Apr-2026) |
| Use in patients with autoimmune or inflammatory disorders | Routine risk minimisation measures: | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None. |

## Table 29. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | None.<br><br>Additional risk minimisation measures:<br><br>None | Additional pharmacovigilance activities:<br><br>*Studies (Final CSR Due Date)*<br>C4591052 (30-Apr-2026) |
| Long term safety data | Routine risk minimisation measures:<br><br>None.<br><br>Additional risk minimisation measures:<br><br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None.<br><br>Additional pharmacovigilance activities:<br><br>*Studies (Final CSR Due Date)*<br>C4591009 (31-Mar-2026)<br>C4591036 (former PHN) (28-Feb-2031)<br>C4591052 (30-Apr-2026) |

a. Please note that studies C4591009, C4591022 and C4591052 address only "Use in pregnancy" and not "Breast feeding".

## PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

### Summary of risk management plan for Comirnaty

This is a summary of the risk management plan (RMP) for Comirnaty. The RMP details important risks of Comirnaty, how these risks can be minimised, and how more information will be obtained about Comirnaty's, risks and uncertainties (missing information).

Comirnaty summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Comirnaty should be used.

This summary of the RMP for Comirnaty, should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Comirnaty's RMP.

### I. The Medicine and What It Is Used For

Comirnaty is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people from the age of 6 months.

The originally authorised Comirnaty contained tozinameran, a messenger RNA (mRNA) molecule with instructions for producing a protein from the original strain of SARS-CoV-2, the virus that causes COVID-19.

Comirnaty is currently available as 3 adapted vaccines:

- Comirnaty JN.1 contains bretovameran, an mRNA molecule with instructions for producing a protein from the JN.1 subvariant of SARS-CoV-2.
- Comirnaty KP.2 contains cemivameran an mRNA molecule with instructions for producing a protein from the KP.2 subvariant of SARS-CoV-2.
- Comirnaty LP.8.1 contains an mRNA molecule with instructions for producing a protein from the Omicron LP.8.1 subvariant of SARS-CoV-2.

Comirnaty does not contain the virus itself and cannot cause COVID-19.

Further information about the evaluation of Comirnaty’s, benefits can be found in Comirnaty’s, EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage www.ema.europa.eu/en/medicines/human/EPAR/comirnaty.

### II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Comirnaty, together with measures to minimise such risks and the proposed studies for learning more about Comirnaty's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Comirnaty, is not yet available, it is listed under 'missing information' below.

## II.A List of Important Risks and Missing Information

Important risks of Comirnaty are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Comirnaty. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

**Table 30. List of Important Risks and Missing Information**

| | |
|---|---|
| Important identified risks | Myocarditis and Pericarditis |
| Important potential risks | None |
| Missing information | Use in pregnancy and while breast feeding |
| | Use in immunocompromised patients |
| | Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) |
| | Use in patients with autoimmune or inflammatory disorders |
| | Long term safety data |

## II.B Summary of Important Risks

The safety information in the Product Information is aligned to the reference.

### Table 31. Important Identified Risk: Myocarditis and Pericarditis

| | |
|---|---|
| Evidence for linking the risk to the medicine | Events of Myocarditis and Pericarditis have been reported. |
| Risk factors and risk groups | Post-authorization reports have been reported more frequently in adolescent and young adult male patients following the second dose of vaccine; however, reports have been received for adult males and females of broader age range and following the first vaccination also. |
| Risk minimisation measures | Routine risk minimisation measures: SmPC sections 4.4. and 4.8.<br><br>Additional risk minimisation measures: None |
| Additional pharmacovigilance activities | C4591036 (former Pediatric Heart Network study)<br>C4591009<br>C4591052<br><br>See Section II.C this summary for an overview of the post-authorisation development plan. |

### Table 32. Missing Information: Use in Pregnancy and while Breast Feeding

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: SmPC section 4.6; PL section 2.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | C4591022[a]<br>C4591009[a]<br>C4591052[a]<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

a. Please note that studies C4591009, C4591022, and C4591052 address only "Use in pregnancy" and not "Breast feeding".

### Table 33. Missing Information: Use in Immunocompromised Patients

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: SmPC sections 4.4 and 5.1.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | C4591009<br>C4591052<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 34. Missing Information: Use in Frail Patients with Co-morbidities (eg. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: SmPC section 5.1.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | C4591052<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 35. Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: None.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | C4591052<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 36. Missing Information: Long Term Safety Data**

| | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: None.<br><br>Additional risk minimisation measures: None. |
| Additional pharmacovigilance activities | C4591009<br>C4591036 (former PHN)<br>C4591052<br><br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

## II.C Post-Authorisation Development Plan

### II.C.1 Studies which are Conditions of the Marketing Authorisation

None.

### II.C.2 Other Studies in Post-Authorisation Development Plan

| Study | Purpose of the study |
|---|---|
| C4591009 | To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population (all ages), pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System. |

| Study | Purpose of the study |
|---|---|
| C4591022 | To assess whether pregnant women receiving BNT162b2 experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age relative to pregnant women who received no COVID-19 vaccines during pregnancy. |
| C4591036 (former Pediatric Heart Network study) | To characterize the clinical course, risk factors, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis including myocarditis after the bivalent Omicron modified vaccine. |
| C4591052 | To ensure comprehensive understanding of real-world safety of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in large samples of general EU populations. |

## PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

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Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 – Specific Adverse Drug Reaction Follow- Up Forms

Annex 5 – Protocols for proposed and on-going studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 – Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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## ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Pfizer-BioNTech COVID-19 Vaccine Multisystem Inflammatory Syndrome in Pediatric and Adults (MIS-C/A) Data Capture Aid

# PFIZER-BIONTECH COVID-19 VACCINE
# MULTISYSTEM INFLAMMATORY SYNDROME DATA CAPTURE AID

The following questions are intended to capture the clinical details about potential multisystem inflammatory syndrome (MIS) experienced by an individual following administration of Pfizer-BioNTech COVID-19 Vaccine.

1. **Please specify if the patient presented with fever.**

   ☐ Fever (measured temperature ≥38.0°C) present for ≥3 consecutive days

   ☐ Fever (measured temperature ≥38.0°C or subjective) present for 1-2 consecutive days

   ☐ No fever (no measured values ≥38.0°C or no subjective report of fever lasting ≥1 day)

   ☐ Unknown if fever present

2. **Please specify signs or symptoms of the multisystem inflammatory syndrome.** Select all that apply.

   ☐ Rash
   ☐ Erythema/cracking of the lips, mouth, or pharynx
   ☐ Bilateral nonexudative conjunctivitis
   ☐ Erythema or edema of the hands and feet
   ☐ Shock/hypotension
   ☐ Abdominal pain
   ☐ Vomiting
   ☐ Diarrhea
   ☐ Altered mental status
   ☐ Headache
   ☐ Weakness
   ☐ Paresthesias
   ☐ Lethargy

3. **Were any of the following tests performed?**

| Test | Date Performed | Results with units | Reference Range |
|---|---|---|---|
| C-reactive protein (CRP) | | | |
| Procalcitonin (PCT) | | | |
| Ferritin | | | |
| Erythrocyte sedimentation rate (ESR) | | | |
| B-type natriuretic peptide (BNP) | | | |
| NT-proBNP | | | |
| Troponin | | | |
| Neutrophils | | | |
| Lymphocytes | | | |
| Platelets | | | |

4. **Was any other diagnostic evaluation performed?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please specify:

5. **Did the patient have a history of COVID-19 infection within 12 weeks prior to the onset of multisystem inflammatory syndrome?**

   ☐ Yes ☐ No ☐ Unknown

6. **Are there any factors that may have contributed to multisystem inflammatory syndrome?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please specify:

**Version History**

| Version | Version Date | Summary of Revisions |
|---|---|---|
| 3.0 | 27-Feb-2025 | Existing DCA modified to develop simplified version |
| 2.0 | 03-Oct-2022 | Updated to add question regarding hospital admission, correct typo under clinical manifestations, and add another line for “other” for the relevant labs question |
| 1.0 | 03-Oct-2022 | Existing DCA converted to latest DCA format. Version 1 was never effective |

## ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

The additional risk minimisation measure to address myocarditis and pericarditis is a Direct Healthcare professional communication, as below:

### COVID-19 mRNA Vaccines Comirnaty and Spikevax: risk of myocarditis and pericarditis

Dear Healthcare professional,

BIONTECH/PFIZER and MODERNA BIOTECH SPAIN, S.L. in agreement with the

European Medicines Agency and <National competent authority> would like to inform you

of the following:

**Summary**

- Cases of myocarditis and pericarditis have been reported very rarely following vaccination with the COVID-19 mRNA Vaccines Comirnaty and Spikevax.
- The cases primarily occurred within 14 days after vaccination, more often after the second dose and in younger men.
- Available data suggest that the course of myocarditis and pericarditis following vaccination is similar to the course of myocarditis and pericarditis in general.
- Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.
- Healthcare professionals should advise vaccinated individuals to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations.

**Background on the safety concern**

The COVID-19 mRNA vaccines, Comirnaty and Spikevax, have been approved in the EU under conditional marketing authorisation for active immunisation to prevent COVID-19 infection caused by SARS-CoV-2, in individuals 12 years of age and older (Comirnaty) and 18 years of age and older (Spikevax), respectively.

Myocarditis and pericarditis have been reported in association with the COVID-19 mRNA vaccines.

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has evaluated all available data and concluded that a causal association between

COVID-19 mRNA vaccines and myocarditis and pericarditis is at least a reasonable possibility. Accordingly, the Summary of Product Characteristics, sections 4.4 ('Special warnings and precautions for use') and 4.8 ('Undesirable effects') have been updated.

The benefits of vaccination continue to outweigh any risks.

**Call for reporting**

Healthcare professionals are asked to report any suspected adverse reactions via their national reporting system and include batch/Lot number if available.

These medicinal products are subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

**Marketing Authorisation Holders' contact points**

| | |
|---|---|
| MODERNA BIOTECH SPAIN, S.L.<br>Calle Monte Esquinza 30<br>28010 Madrid<br>Spain<br>medinfo@modernatx.com<br>https://www.modernacovid19global.com/ | BioNTech Manufacturing GmbH An der Goldgrube 12<br>55131 Mainz<br>Germany<br>medinfo@biontech.de<br>www.comirnatyglobal.com |

The one-time DHPC distribution started on 19 July 2021 in all EEA countries as per the EMA's communication plan.

**Removal of additional risk minimisation activities**

C4591021 was a post-authorisation safety study (PASS) that assessed the risk of 37 prespecified AESIs in individuals of all ages (including pregnant individuals) in the general European population who received >1 dose of Comirnaty. In addition this PASS which was a category 3 commitment in the risk management plan and a postmarketing requirement to the Food and Drug Administration (FDA), was used to assess the effectiveness of the DHPC (aRMM) about the important risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine use, describing the rate of cardiac imaging use for vaccinated and unvaccinated individuals in the study population each calendar month during the study period, before and after distribution of the DHPC.

The analysis of cardiac imaging before and after the introduction of the DHPC demonstrated that the incidence rates of recorded cardiac imaging were higher before the issuance of the DHPC than after in both the vaccinated and unvaccinated cohorts. Incidence rate ratios were consistently below 1 in both vaccinated and unvaccinated cohorts.

Some possible reasons for these results include:

1) Pre-existing heightened clinical vigilance: Before the DHPC issue date (19 July 2021), there may have already been increased awareness and clinical suspicion of myocarditis and pericarditis in the context of COVID-19 vaccinations, especially as early safety signals and case reports emerged as well as the publication of the study by Barda[1]. Healthcare providers may have been proactively ordering cardiac imaging based on initial reports which may have resulted in elevated imaging rates before official communications.

2) Public and media attention prior to DHPC: Media coverage and patient awareness of concerns about myocarditis and pericarditis in relation to vaccines may have prompted more individuals to seek medical evaluation even before the formal communication about safety was disseminated. EMA began its safety assessments of myocarditis events in April 2021 following cases reported in Israel. Public and social media attention increased from around spring 2021 and onward, especially as myocarditis cases were highlighted as a rare adverse event after mRNA COVID-19 vaccination, mainly in younger males after the second dose.

3) Decline in imaging post-DHPC due to clearer clinical guidance: Once the DHPC was released, healthcare professionals received specific criteria and guidance to identify and manage suspected myocarditis and pericarditis cases. This clarity may have led to more targeted and judicious use of cardiac imaging, avoiding unnecessary tests following the official advice.

4) During 2021 and 2022, the uptake of the first COVID-19 booster dose among young adults in Europe (specifically those aged 18-24) was relatively modest compared with older age groups. According to the European Centre for Disease Prevention and Control (ECDC) data reported as of August 21, 2022, the median booster dose uptake among adults aged over 18 years in EU/EEA countries was about 64.7%, but uptake among younger adults aged 18-24 was lower 11.

5) Lower numbers of susceptible individuals: by the summer of 2021, most adults had already received two doses of the Pfizer vaccine, and most cases of vaccine associated myocarditis may have already occurred.

Although this analysis does not provide evidence that any of these factors are causal, collectively they may explain the observed pattern of cardiac imaging demonstrated from this study.

## Conclusion

While the rates of cardiac imaging were higher prior to the issuance of the DHPC letter, the rationale to inform HCPs about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alerted about the signs and symptoms and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations still had uptake. The unprecedented attention given to all signals and risks associated with the COVID-19 vaccine campaign caused heightened awareness of risks at timepoints that were before the typical notification processes for HCPs, such as with a DHPC. However, the overall intention of the DHPC was met between the notifications from regulators regarding their evaluation of said signals and actions to undertake in the interim, as well as the media attention given to the risks, as outlined in the data output from C4591021.

Therefore the MAH proposes to remove the DHPC from the RMP at this time.

1. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90.