**BRAVATO Module for Vaccine Structured Benefit-Risk Assessment**

**Version 1, April 1, 2023**

***Myocarditis following mRNA COVID-19 Vaccines in Males:  
A Case Study based on US data from June 2021***

This example case study is based on methods used by the CDC COVID-19 Benefits Risk Team to assess the benefit-risk of COVID-19 vaccines in the United States in early 20211,12, 20. Specifically, this example is a modified version of the analysis by Gargano et al from July 2021 of the benefit-risk of available mRNA vaccines in the US at the time myocarditis following mRNA vaccines was first identified. To that end, the age and sex specific incidences of COVID-19 hospitalization were those used by Gargano, based on US COVID-NET data from May 22, 2021. Assumptions for mRNA vaccine efficacy were from several sources and were slightly lower than those used by Gargano.  Risks and consequences of myocarditis following mRNA vaccines were compiled from several more recent sources and were somewhat higher than those used by Gargano.12

This is intended only as an example and does not represent a comprehensive compilation or analysis of all information on mRNA vaccine-associated myocarditis risks. When doing benefit-risk analyses, each user/country should carefully consider the key information to examine regarding each of the benefits and harms associated with COVID-19 vaccines in their specific situation.

|  |  |  |
| --- | --- | --- |
| **Section 1: Decision Context** | | |
| **1A. Authorship and Role** | | |
| **Question** | **Responses** | **Comments** |
| **Author(s) and affiliation(s)** |  |  |
| **Date completed/updated**[[1]](#footnote-1) | Completed November 2022  Based on US COVID-19 hospitalization data from June 2021; COVID vaccine efficacy data from 2021; and vaccine safety data (myocarditis) from 2021 and 2022 |  |
| **Module role:** Is this module currently being used to plan, report or review a B-R assessment? | Select one:   * Planning * **Reporting** * Reviewing |  |
| **1B. Vaccine of Interest Topics** | | |
| **Question** | **Responses** | **Comments** |
| **Vaccine of Interest:** | COVID-19 mRNA vaccines | Moderna and Pfizer original/ancestral COVID-19 vaccines only |
| **Formulation / Regimen / Schedule of the vaccine of interest:** | IM, 2 doses; 3-8 weeks (Pfizer) or 4-8 weeks (Moderna) between doses  Recommended storage conditions |  |
| **Vaccine Development/Lifecycle stage:** | Emergency Use Authorization (EUA) |  |
| **Objective of the vaccine of interest immunization program:** | Prevention of severe COVID- Disease, prevention of health system overload |  |
| **1C. Disease and Treatments Topics** | | |
| **Question** | **Responses** | **Comments** |
| **Disease of interest:** | COVID-19 (severe disease in particular) |  |
| **Population of interest:** | Adolescents and Adults > 16 years of age (Pfizer) and  > 18 older (Moderna)  Geographic location is US | Persons eligible for vaccine under EUA between Dec. 2020 and June 2021 |
| **Nature of condition:** | COVID-19 causes serious respiratory infection with high rates of hospitalization, treatment in ICU, need for ventilation, and death.  Rates of serious disease are highly age dependent, with most elderly at highest risk and children and young adults at 10-50-fold lower risk.  Disease is slightly more serious in men than women |  |
| **Existing vaccines and therapies**: | Other available COVID vaccines in US – Janssen (Ad26) under EUA  Monoclonal Ab, steroids have modest effectiveness | Note: Antivirals were not yet available in June 2021, the date used for this B-R assessment. |
| **Unmet medical need:** | Monoclonal Ab, steroids have modest effectiveness (~33%) in treatment of serious disease. Monoclonals had limited availability as of June 2021.  Antivirals ~33-90% effective if given within 5 days - not yet available in June 2021  Janssen (Ad26) vaccine 66.3% effective against COVID-19, 93% effective against COVID-19 associated hospitalization 100% against COVID-19 deaths. 13 cases TTS / million females 18 – 49 vaccinatedCS-1 |  |
| **1D. High-level Benefit-Risk Topics** | | |
| **Question** | **Responses** | **Comments** |
| **Purpose and drivers for the B-R assessment:** | Identification of myocarditis as an adverse outcome of COVID-19 mRNA vaccine, especially in young males |  |
| **Comparator(s)** | No vaccine |  |
| **Time horizon for B-R assessment:** | 120 days following 2nd dose of mRNA vaccine |  |
| **What is the justification for this time horizon?** | Expected minimum length of highest-level protection by COVID-19 mRNA vaccine against serious outcomes (hospitalization, ICU treatment, death)  Risk of myocarditis after 2nd dose vaccine, mainly in days 0-7 following vaccination | For period in question (Dec 2020-June 2021) vaccine effectiveness against hospitalization shown to persist for at least 120 daysCS-2 following 2nd dose.  Assume constant COVID-19 incidence during this period. Given varying incidence of COVID-19 at this time, a 120-day interval is considered a reasonable time frame to assume continuation of this specific COVID-19 incidence. |
| **Subgroups of special interest:** |  | Myocarditis risk observed to be highest in males ages 16-17 years and to decrease with increasing age; substantially lower risk in females in each age group |
| Subgroup 1 | | |
| Name | Males 16 – 17 years |  |
| Definition |  |  |
| Subgroup 2 | | |
| Name | Males 18 – 29 years |  |
| Definition |  |  |
| Subgroup 3 | | |
| Name | Males 30+ years |  |
| Definition |  |  |
| **Section 2: Identifying key endpoints for B- R (Developing a Value Tree)** | | |
| **Question** | **Responses** | **Comments** |
| **Benefit #1** | | |
| Name | Hospitalizations due to COVID-19 infection prevented |  |
| Definition and benefit window (per Statistical Analysis Plan). | Number of persons per 1,000,000 vaccinated for whom hospitalization due to COVID-19 would be prevented through 120 days after 2nd dose of COVID-19 vaccine |  |
| Key or not key for B-R and rationale | **Key** – most common serious outcome due to COVID-19 infection |  |
| Identified or potential benefit and rationale | **Identified** – self-evident |  |
| Clinical impact / severity | Median hospitalization 4-6 days in adults with COVID-19CS-3 |  |
| Rationale for inclusion | Key objectives of vaccination program are to reduce severe COVID-19 illness and to reduce use of public health /hospital resources |  |
| Limitations (cannot be avoided) and uncertainties (potentially mitigable) of this endpoint | Data sources may not be able to distinguish between hospitalizations due to COVID-19 vs COVID-19 incidentally discovered during hospitalizations for other causes.  Only considers deaths amongst those hospitalized (due to data source limitations). Consequences include that this endpoint will miss persons who die without being hospitalized, such as nursing home patients who die without hospitalization; also, this could artifactually undercount deaths in LMICs that have limited hospitalisation facilities (and who represent approximately ⅓ of COVID deaths (per CDC COVID trackerCS-4 | See references/ additional information below. |
| **Benefit #2** | | |
| Name | Intensive care unit (ICU) admissions due to COVID-19 prevented |  |
| Definition and benefit window | Number of persons per 1,000,000 vaccinated for whom hospitalization in ICU due to COVID-19 would be prevented through 120 days after 2nd dose of COVID-19 vaccine |  |
| Key or not key for B-R and rationale | **Key** |  |
| Identified or potential and rationale | **Identified** - Well defined benefit of COVID-19 prevention |  |
| Clinical impact / severity | Median length of ICU stays ranges from 5 to 19 daysCS-5 |  |
| Rationale for inclusion | Key objectives to reduce severe COVID-19 illness and to reduce use of public health /hospital resources |  |
| Limitations and uncertainties of this endpoint | Endpoint is based on proportion of those hospitalized due to COVID-19 who were admitted to ICU in one study. May not be representative of proportion in entire country. May be underestimated if insufficient number of ICU beds available in some hospitals. | Includes ICU admissions among those hospitalized (COVID-NET) |
| **Benefit #3** |  |  |
| Name | Deaths prevented among persons hospitalized with COVID-19 infection |  |
| Definition and benefit window | Number of persons per 1,000,000 vaccinated for whom death while hospitalization due to COVID-19 would be prevented through 120 days after 2nd dose of COVID-19 vaccine |  |
| Key or not key for B-R and rationale | **Key** |  |
| Identified or potential and rationale | **Identified** - Well defined benefit of COVID-19 prevention |  |
| Clinical impact / severity | Self-evident |  |
| Rationale for inclusion | Key objectives to reduce severe COVID-19 illness and to reduce use of public health/hospital resources |  |
| Limitations and uncertainties of this endpoint | May underestimate the overall risk of death from COVID-19, since this is based on proportion of those hospitalized due to COVID-19 who die while hospitalized and misses persons who die without being hospitalized (see limitations of Benefit #1: Hospitalizations due to COVID-19 infection prevented) |  |
| **Risk #1** | | |
| Name | Hospitalization due to Myocarditis within days 0-7 following COVID-19 mRNA vaccine 2nd dose |  |
| Definition and risk window, if relevant | Number of individuals hospitalized due to myocarditis within days 0- 7 following 2nd dose per one million persons receiving mRNA 2nd dose vaccination |  |
| Key or not key for B-R and rationale | **Key** |  |
| Identified or potential and rationale | **Identified** |  |
| Clinical impact / severity | 85% of persons with myocarditis (regardless of severity) following mRNA vaccination are hospitalized for at least one day (median hospitalization 1 dayCS-6  Risk of long-term sequelae low but not yet clearly definedCS-7 |  |
| Rationale for inclusion | Serious adverse event requiring hospitalization |  |
| Limitations (cannot be avoided) and uncertainties (potentially mitigable) of this endpoint | Uncertainties in exact count of events measured in different studies/countries. Different criteria used for case inclusion in different studies, with some studies not including expert review of cases. Some uncertainty as to whether myocarditis is attributable to mRNA vaccine in specific cases. Uncertainty in long-term clinical impact of myocarditis. To date, it appears to be short and self-limited. CS-7 |  |
| **Risk #2** |  |  |
| Name | ICU admission due to Myocarditis within days 0-7 after COVID-19 mRNA vaccine 2nd dose |  |
| Definition and risk window, if relevant | Number of individuals with ICU admission for myocarditis within days 0-7 following 2nd dose per million persons receiving 2nd dose mRNA vaccine |  |
| Key or not key for B-R and rationale | **Key** |  |
| Identified or potential and rationale | **Identified** |  |
| Clinical impact / severity | ICU/Cardiac unit admission for myocarditis post mRNA vaccines uncommon; if ICU admission occurs, it is generally short (median stay of 1 day (IQR, 1-2 days)) CS-8,9  Hospitalization mainly for monitoring of heart rhythmCS-7,8 |  |
| Rationale for inclusion | Serious adverse event following mRNA vaccination |  |
| Limitations and uncertainties of this endpoint | Limitations in reporting of need for ICU/CCU admission in different studies. Initial studies showed higher rates than later studies, as the clinical course of myocarditis became better understood. |  |
| **Risk #3** |  |  |
| Name | Death following Myocarditis on days 0-7 following COVID-19 mRNA vaccine 2nd dose |  |
| Definition and risk window, if relevant | Number of individuals who died due to myocarditis within days 0-7 days of 2nd dose per million persons receiving 2nd dose mRNA vaccine |  |
| Key or not key for B-R and rationale | **Key** |  |
| Identified or potential and rationale | **Potential**: Death due to myocarditis following mRNA vaccine not confirmed, likely extremely rare |  |
| Clinical impact / severity | Self-evident |  |
| Rationale for inclusion | Potential serious consequence of severe myocarditis following mRNA vaccine |  |
| Limitations and uncertainties of this endpoint | To date, no confirmed cases of death due to mRNA myocarditis in the U.S. Uncertainty in confirming mRNA vaccine as cause of myocarditis-related death |  |
|  | | |
| **Other risks considered** | | |
| **Question** | **Responses** |  |
| **Other risks considered** | None |  |
| **Which risks were considered?** |  |  |
| **Rationale for exclusion** |  |  |
| **Section 3: Data sources**: | | |
| **Source** | **Role in B-R assessment** | **Rationale and Limitations for B-R** |
| CDC COVID NET | Hospitalizations, ICU admissions, and deaths due to COVID-19 – age/sex and time specific (rates in May 2021 used in this analysis) | Population based data (hosp. in 14 states); provides age/sex/time specific rates.CS-10-12 Overall hospitalization rates were adjusted assuming all hospitalizations were in unvaccinated persons, consistent with available data at the time. Actual rates were from Gargano analysis.CS-12 Proportions unvaccinated and vaccinated were from CDC COVID Data Lake (May 22) and denominators from 2019 US Census projections.  Limitations: May slightly overestimate hospitalization rates due to COVID-19, as a COVID-19 diagnosis may be an incidental finding in some cases.CS-13  May not represent actual hospitalization rates throughout the US at this time. Proportion treated in ICU may have been limited by insufficient beds. Deaths that did not occur in hospital are not included (this limitation could particularly underestimate deaths among the nursing home population).CS-19 |
| FDA manuscript | Rates of myocarditis following 2nd dose COVID-19 mRNA vaccine - | Population based rates from nationwide health insurance claims database; slightly different age ranges for data than other studies (see below),  Limitations: Cases not reviewed or adjudicated for compatibility with standard case definition CS-13 |
| CDC Vaccine safety datalink | Rates of myocarditis following 2nd dose COVID-19 mRNA vaccine | Cases reviewed and adjudicated per standard case definition, population based; slightly different age cut-offs than other studies.  Limitations: based on 8 HMOs; limited number of cases (79) compared to other systemsCS-6,8 |
| Metanalysis of myocarditis | Rates of myocarditis following 2nd dose COVID-19 mRNA vaccine - | Metanalysis of 4 studies; different age cut-offsCS-14 |
| Risk of Myocarditis and pericarditis following BNT162b2 and mRNA 1293 COVID-19 vaccination | Risk and clinical severity and outcomes of myocarditis following mRNA vaccination | Analysis of cases in Vaccine Safety Datalink – prospective follow-up of persons receiving mRNA vaccines in 8 integrated healthcare-delivery systems (population based).CS-8 It is assumed that 85% of myocarditis cases are hospitalized, for a median of 1 day hospitalization, none were admitted to the ICU or died, and all were discharged home. Also US VAERS myocarditis dataCS-7 - large data set, cases reviewed and adjudicated; Limitation: passive reporting |
| Efficacy of mRNA vaccines | Efficacy of mRNA vaccines against hospitalization | Published Clinical trials of Pfizer and Moderna vaccinesCS-15,16  Post-licensure follow-up of vaccine effectiveness in the United StatesCS-2,17,18  Limitations: limited follow-up at time of the original analysis (June 2021); however, vaccine effectiveness for this period well validated in many subsequent studies. |
| **Section 4: Statistical methods**: | | |
| **Overview of approach used to give data in Sections 5 and 6:** Spreadsheet analysis modelled benefits and harms per 1 million vaccines, using US data on rates of COVID-19 hospitalizations, ICU, deaths from COVID-NET, May 2021 (base case)CS-12, and estimates of rates of myocarditis following vaccine from 3 different sourcesCS-6,8,13-14, as well as rates of outcomes of myocarditis.CS-6 Age and sex specific rates of hospitalizations for unvaccinated persons were from COVID-NETCS-12. ICU admissions and deaths were from same data, representing proportions of hospitalized cases treated in the ICU, and who died while in the hospital, respectively. Analyses includes 3 age strata (16-17, 18-29 and 30+ years), and calculated benefits/harms for males for each age group. mRNA vaccine efficacy against hospitalization was 90%, based on pre-licensure vaccine trials and early post-licensure effectiveness studies.CS-2,15-18  The analyses also include sensitivity analyses for each of these strata using COVID-19 hospitalization rates 3x higher, and 1/3 of base case.  Figures representing benefits and harms in males (aged 16-17, 18-29 and 30+ years) were designed using the base case estimates provided in the tables. COVID-19 vaccine effectiveness against severe outcomes (hospitalization, ICU admission and death) is assumed to be 90% over the full 120-day benefit interval. | | |
| **Question** | **Responses** |  |
| **Date range for data used in analysis:** | December 2020 through June 2021 |  |
| **Vaccine Effectiveness** | mRNA vaccines have 90% effectiveness for at least 120 days following vaccination in preventing hospitalization, ICU admission and death due to prevailing COVID-19 variants in the U.S. (mainly alpha). CS-2,17,18 |  |
| **Type of measurements:** | Cases prevented or caused during a 120-day time horizon per 1,000,000 vaccinated |  |
| **Population-level modelling:** | No |  |
| **Population-level model summary** (if included) |  |  |
| **Adjustment for strata, pooling of data sources, approach for 95% CI assessment)** | None |  |
| **Alternative incidence rates (due to varying transmission intensities):** | | |
| Transmission rate 1 | | |
| Name | Base rate |  |
| Definition | Based on US hospitalization rate in week of May 22, 2020CS-12 |  |
| Transmission rate 2 | | |
| Name | 1/3 base rate |  |
| Definition |  |  |
| Transmission rate 3 | | |
| Name | 3x base rate |  |
| Definition |  |  |
|  | | |
| **Scenarios of special interest**. | | |
| Scenario 1 |  |  |
| Name | None used |  |

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| **Section 5: Benefit Data**: |

**Table 1 Benefits: COVID-19 vaccine vs no vaccine, 16–17-year-old Male, Base case (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 23 | 227 | 204 |  |  | 4902 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 8 | 77 | 69 |  |  | 14493 |  |
| **COVID-19 Deaths** | 0 | 3 | 3 |  |  | 333333 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 2 Benefits – COVID-19 vaccine vs no vaccine, 18–29-year-old Male, Base case (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 71 | 707 | 636 |  |  | 1572 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 18 | 176 | 158 |  |  | 6329 |  |
| **COVID-19 Deaths** | 1 | 11 | 10 |  |  | 100000 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 3 Benefits: COVID-19 vaccine vs no vaccine, 30+ year-old Male, Base case (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 305 | 3053 | 2748 |  |  | 364 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 94 | 937 | 843 |  |  | 1186 |  |
| **COVID-19 Deaths** | 38 | 379 | 341 |  |  | 2933 |  |

**Table 4 Benefits: COVID-19 vaccine vs no vaccine, 16–17-year-old Male, Low COVID-19 incidence (⅓ base case) (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion or Rate (/1,000,000) | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 8 | 76 | 68 |  |  | 14706 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 3 | 26 | 23 |  |  | 43478 |  |
| **COVID-19 Deaths** | 0 | 1 | 1 |  |  | 1000000 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 5 Benefits: COVID-19 vaccine vs no vaccine, 18–29-year-old Male, Low COVID-19 incidence (⅓ base case) (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion or Rate (/1,000,000) | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 24 | 236 | 212 |  |  | 4717 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 6 | 59 | 53 |  |  | 18868 |  |
| **COVID-19 Deaths** | 0 | 3 | 3 |  |  | 333333 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 6 Benefits: COVID-19 vaccine vs no vaccine, 30+ year-old Male, Low COVID-19 incidence (⅓ base case) (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion or Rate (/1,000,000) | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 102 | 1018 | 916 |  |  | 1092 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 31 | 312 | 281 |  |  | 3559 |  |
| **COVID-19 Deaths** | 13 | 127 | 114 |  |  | 8772 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 7 Benefits: COVID-19 vaccine vs no vaccine, 16–17-year-old Male, High COVID-19 incidence (3x base case) (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion or Rate (/1,000,000) | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 68 | 680 | 612 |  |  | 1634 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 23 | 229 | 206 |  |  | 4854 |  |
| **COVID-19 Deaths** | 1 | 11 | 10 |  |  | 100000 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 8 Benefits: COVID-19 vaccine vs no vaccine, 18–29-year-old Male, High COVID-19 incidence (3x base case) (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion or Rate (/1,000,000) | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 212 | 2121 | 1909 |  |  | 524 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 53 | 526 | 473 |  |  | 2114 |  |
| **COVID-19 Deaths** | 3 | 32 | 29 |  |  | 34483 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 9 Benefits: COVID-19 vaccine vs no vaccine, 30+ year-old Male, High COVID-19 incidence (3x base case) (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion or Rate (/1,000,000) | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI low** | **95% CI high** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
| **COVID-19 Hospitalization** | 916 | 9159 | 8243 |  |  | 121 | See Endpoints and Data Sources sections |
| **COVID-19 ICU admission** | 281 | 2811 | 2530 |  |  | 395 |  |
| **COVID-19 Deaths** | 114 | 1138 | 1024 |  |  | 977 |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

|  |
| --- |
| **Section 6: Risk Data and mitigations**: |

**Table 1 Risks: Myocarditis following COVID-19 vaccine; comparator no vaccine, 16-17-year-old Male, Base case (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine** | **Comparator** | **Cases caused** | **95% CI low** | **95% CI high** | **NNH\*** | **Notes, Uncertainty and Strength of Evidence** |
| **Hospitalization due to myocarditis** | 128 | 1.3 | 127 |  |  | 7874 | Background rate myocarditis in 7-day period is 0.2-2.2 per million |
| **ICU admission due to myocarditis** | 42 | <1 | 42 |  |  | 23810 |  |
| **Deaths due to myocarditis** | 0 | 0 | 0 |  |  | --- | No deaths confirmed due to vaccine associated myocarditis |

\*NNH = number needed to harm

Transmission rate definition, Scenario definition

**Table 2 Risks: Myocarditis following COVID-19 vaccine; comparator no vaccine, 18-29-year-old Male, Base case (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine** | **Comparator** | **Cases caused** | **95% CI low** | **95% CI high** | **NNH\*** | **Notes, Uncertainty and Strength of Evidence** |
| **Hospitalization due to myocarditis** | 77 | 1 | 76 |  |  | 13158 | Background rate myocarditis in 7-day period is 0.2-2.2 per million |
| **ICU admission due to myocarditis** | 25 | <1 | 25 |  |  | 40000 |  |
| **Deaths due to myocarditis** | 0 |  | 0 |  |  | ---- | No deaths confirmed due to vaccine associated myocarditis |

\*NNH = number needed to harm

Transmission rate definition, Scenario definition

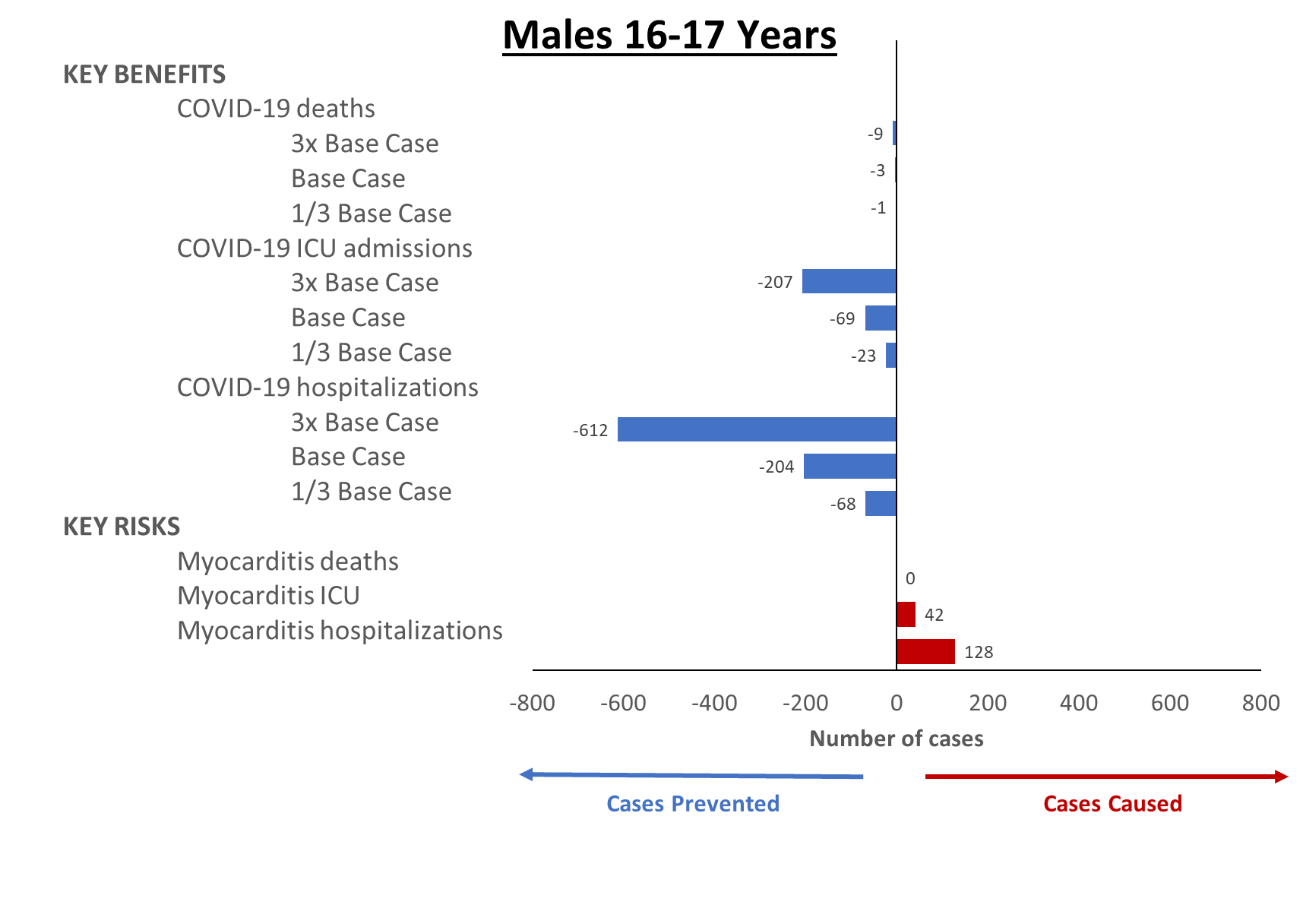
**Table 3 Risks – Myocarditis following COVID-19 vaccine; comparator no vaccine, 30+ year-old Male, Base case (June 2021 US), per million vaccinated**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine** | **Comparator** | **Cases caused** | **95% CI low** | **95% CI high** | **NNH\*** | **Notes, Uncertainty and Strength of Evidence** |
| **Hospitalization due to myocarditis** | 3 | ~1 | 2 |  |  | 500000 | Background rate myocarditis in 7-day period is 0.2-2.2 per million |
| **ICU admission due to myocarditis** | 1 | <1 | 1 |  |  | 1000000 |  |
| **Deaths due to myocarditis** | 0 |  | 0 |  |  | --- | No deaths confirmed due to vaccine associated myocarditis |

|  |  |  |
| --- | --- | --- |
| **Mitigation** | **Endpoints Affected** | **Notes, Uncertainty and Strength of Evidence** |
| None considered |  |  |

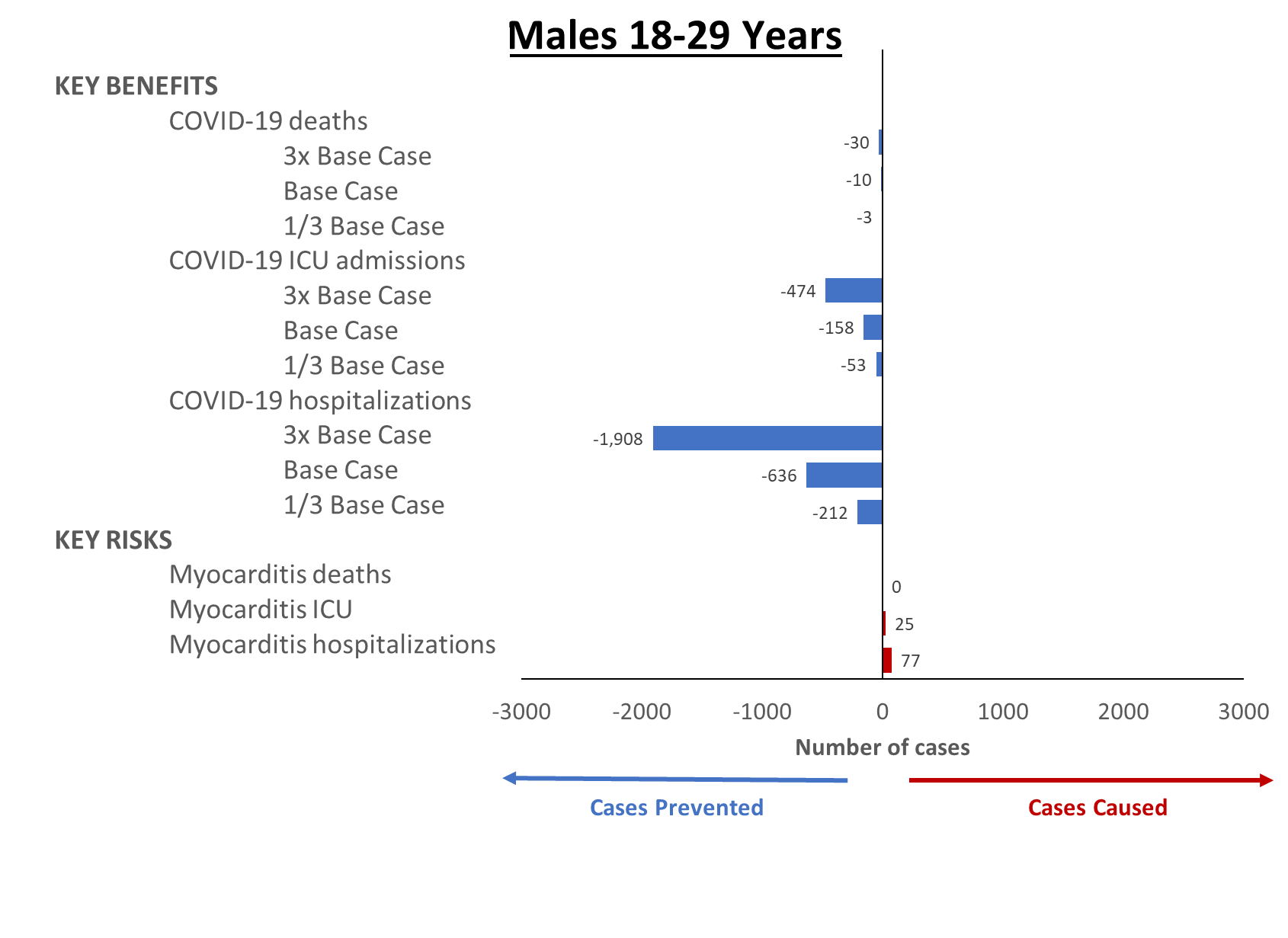
**Mitigations for Risks**

**Figure 1. Cases caused and prevented for key benefits and risks\*: COVID-19 vaccine vs no vaccine, Males 16-17-years-old, Base case (June 2021 US), per million vaccinated**

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**\* Benefits:** events prevented by vaccination, **Risks:** events expected following vaccination

**Figure 2. Cases caused and prevented for key benefits and risks\*: COVID-19 vaccine vs no vaccine, Males 18-29-years-old, Base case (June 2021 US), per million vaccinated**

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**\* Benefits:** events prevented by vaccination, **Risks:** events expected following vaccination

**Figure 3. Cases caused and prevented for key benefits and risks\*: COVID-19 vaccine vs no vaccine, Males 30+ years-old, Base case (June 2021 US), per million vaccinated**

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**\* Benefits:** events prevented by vaccination, **Risks:** events expected following vaccination

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| --- | --- |
| **Section 7: Clinical impact / weighting**: **(optional)** | |
| **Question** | **Responses** |
| Is (or will) a preference study being used to support the B-R assessment | Yes / **no** |

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| --- |
| **Section 8: Integrated B-R Assessment** |
| For the base case analysis, during a period of moderately low COVID-19 incidence in the US, the benefits of mRNA COVID-19 vaccination outweigh the harms for all age groups of males. The balance of benefits and harms is strongest for males > 30 years of age (e.g. per 1,000,000 vaccinated individuals, expected prevention of 2,748 COVID-19 related hospitalizations, and 843 COVID-19 related ICU admissions and 341 COVID-19 related deaths, compared to an expected 3 myocarditis hospitalizations, 1 ICU admission and no deaths). Additionally, the median length of COVID-19 hospitalizations prevented is 4-6 days, while that for myocarditis hospitalizations caused is 1 day. For the youngest age males (16-17-year-old), the balance is less strong, but still favors benefits (e.g. 204 COVID-19 related hospitalizations, 69 ICU admissions, and 3 deaths expected to be prevented per million vaccinations, vs. 128 myocarditis hospitalizations, 42 ICU admissions, and no deaths following vaccination). For males 18-29-years-old, benefits also strongly outweigh the risks of mRNA vaccination.  In sensitivity analyses, when COVID-19 incidence is 3-fold higher (moderately high incidence), benefits even more strongly outweigh risks for all age groups.  When COVID-19 incidence is low (⅓ that of the base case, the benefits still outweigh the risks for both males over 30 years-old and 18-29 years-old (for 18-29 years, expected benefits of 212 hospitalizations, 53 ICU admissions and 3 deaths prevented, vs. risks of 77 hospitalizations, 25 ICU admissions and no deaths due to mRNA myocarditis). However, for 16–17-year-old males, the assessment is more complex. The expected risks for hospitalization and ICU admission are greater in number than the benefits - e.g. 128 hospitalizations and 42 ICU admissions expected due to mRNA myocarditis, vs expected benefits of 68 fewer hospitalizations, 23 fewer ICU admissions and 1 fewer death due to COVID-19, all per 1,000,000 vaccinated individuals. Given that hospitalization and ICU admissions for myocarditis are mainly for heart monitoring while COVID-19 hospitalization is considerably longer than and much more clinically impactful than for myocarditis, we judge benefits to outweigh risks for the low incidence scenario in the 16-17-year-old males as well.  Based on these analyses with US data, overall, benefits outweigh risks for mRNA vaccines vs. no vaccines in males ages 16 and older.  Limitations of this analysis include the use of US data only. For example, other countries may have different COVID-19 incidence rates, different qualities and uses of medical care, ability to receive second doses, etc.). These expected risks and benefits may also need to consider additional factors, including not just the length of hospitalization (longer for COVID-19 than mRNA myocarditis) but the nature of the hospitalization as well as risks of long COVID (post-acute sequelae of COVID-19) following COVID-19 infection on one hand, versus the long-term impact of mRNA myocarditis, still not clearly defined, on the other. |

**Case Study References**

1. S. Oliver, “Risk/Benefit assessment of thrombotic thrombocytopenic events after Janssen COVID-19 vaccines: Applying Evidence to Recommendation Framework,” 23 April 2021. [Online]. Available: https://stacks.cdc.gov/view/cdc/107511. [Accessed 1 December 2022].
2. Tenforde MW et al., “Effectiveness of Severe Acute Respiratory Syndrome Coronavirus 2 Messenger RNA Vaccines for Preventing Coronavirus Disease 2019 Hospitalizations in the United States,” *Clinical Infectious Diseases,* vol. 74, no. 9, p. 1515–1524, 2022.
3. Garg S. et al., “Clinical Trends Among U.S. Adults Hospitalized With COVID-19, March to December 2020: A Cross-Sectional Study,” *Annals of Internal Medicine,* vol. 174, no. 10, 2021.
4. CDC, “NVSS - Provisional Death Counts for COVID-19 - Executive Summary,” [Online]. Available: https://www.cdc.gov/nchs/covid19/mortality-overview.htm. [Accessed 9 November 2022].
5. Rees EM et al., “COVID-19 length of hospital stay: a systematic review and data synthesis,” *BMC Med,* vol. 18, no. 1, p. 270, 2020.
6. Goddard K et al., “Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States,” *Ann Intern Med,* 2022.
7. Oster ME et al., “Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021,” *JAMA,* vol. 327, no. 4, p. 331–340, 2022.
8. Goddard K et al., “Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination,” Vaccine, vol. 40, no. 35, p. 5153–5159, 2022.
9. Diaz GA et al., “Myocarditis and Pericarditis After Vaccination for COVID-19,” JAMA, vol. 326, no. 12, pp. 1210-1212, 2021.
10. Garg S. et al., “Clinical Trends Among U.S. Adults Hospitalized With COVID-19, March to December 2020: A Cross-Sectional Study,” Annals of Internal Medicine, vol. 174, no. 10, 2021.
11. Taylor CA et al., “Severity of Disease Among Adults Hospitalized with Laboratory-Confirmed COVID-19 Before and During the Period of SARS-CoV-2 B.1.617.2 (Delta) Predominance — COVID-NET, 14 States, January–August 2021,” CDC MMWR, vol. 70, no. 43, p. 1513, 2021.
12. Gargano J et al., “Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021,” CD MMWR, vol. 70, no. 27, p. 977–982, 2021.
13. Funk PR et al., “Benefit-risk assessment of COVID-19 vaccine, mRNA (Comirnaty) for age 16-29 years,” *Vaccine,* vol. 40, no. 19, pp. 2781-89, 2022.
14. Ling RR et al., “Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis,” *Lancet Respir Med,* vol. 10, no. 7, p. 679–688, 2022.
15. Baden LR et al., “Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine,” nejm, vol. 384, pp. 403-416, 2020.
16. Polack F et al., “Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine,” NEJM, vol. 383, pp. 2603-2615, 2020.
17. Pawlowski C et al., “FDA-authorized mRNA COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system,” Med (N Y), vol. 2, no. 8, pp. 979-992, 2021.
18. Young-Xu Y et al., “Coverage and Estimated Effectiveness of mRNA COVID-19 Vaccines Among US Veterans,” JAMA, vol. 4, no. 10, p. e2128391, 2021.
19. Lu Y et al. Pre-vaccine period COVID-19 natural history: Risk factors for COVID-19 deaths among elderly nursing home Medicare beneficiaries. The Journal of Infectious Diseases, 2021.
20. MacNeil JR et al. Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients - United States, April 2021. MMWR Morb Mortal Wkly Rep. 2021 Apr 30;70(17):651-656.

1. A completed module may have blanks for unknown or missing data. [↑](#footnote-ref-1)