BRAVATO Module for Vaccine Structured Benefit-Risk Assessment

Version 1, August 20, 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 2021. [1, 2, 3] 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 effectiveness 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. [2] Per Gargano, myocarditis here refers to the composite of myocarditis, pericarditis and myopericarditis.

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. For simplicity, this example focuses only on benefit–risk of myocarditis in males, as risk of myocarditis is substantially lower in females. For detailed review of risk in females, see Gargano. [2] For a more in-depth review of experience with benefit-risk analysis for COVID-19 vaccines in the United States, see Wallace et al. [4]. 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. [4]

Section 1: Decision Context		
1A. Authorship and Role		
Question	**Responses**	**Comments**
Author(s) and affiliation(s)		
Date completed/updated[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, including to national regulatory authorities** ● Reviewing	
1B. Vaccine of Interest Topics		
Question	**Responses**	**Comments**
Vaccine of Interest:	COVID-19 mRNA vaccines	Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) original/ancestral COVID-19 vaccines only

[1] A completed module may have blanks for unknown or missing data.

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 (see package inserts for each vaccine)	
Vaccine Development/Lifecycle stage:	Emergency Use Authorization (EUA)	Vaccination of adults age 16 and older during first 7 months use under EUAs
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	Males ≥ 16 years who were 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 treatment effectiveness against COVID-19.	Note: Antivirals to treat COVID-19 were not yet available in June 2021, the date used for this B-R assessment.
Unmet medical need:	Effective treatment of severe COVID-19	Monoclonal antibodies (mAb) and steroids have modest effectiveness (~33%) in treatment of severe COVID-19. mAb 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 (adenovirus vector platform) 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 vaccinated [1]
1D. High-level Benefit-Risk Topics		
Question	**Responses**	**Comments**
Purpose and drivers for the B-R assessment:	Identification of myocarditis as a rare adverse outcome of COVID-19 mRNA vaccination, especially in young males	In this example, myocarditis refers to any of the following conditions – myocarditis, pericarditis and myopericarditis [2] [5]
Comparator(s)	No vaccine	

Time horizon for B-R assessment:	Risk of COVID-19 infection leading to hospitalization, ICU treatment or death during 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 has been shown to persist for at least 120 days [6] following the 2nd dose. Assuming 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	Prevention of hospitalizations due to COVID-19 infection	
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** – Well documented benefit of COVID-19 mRNA vaccines	
Clinical impact / severity	Median hospitalization 4-6 days in adults with COVID-19 [7]	Median hospitalization is for unvaccinated adults 18 years or older at the time covered in this analysis [7]
Rationale for inclusion	Key objectives of vaccination program are to reduce severe COVID-19 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	See references / additional information below.

	hospitalizations for other causes, and so could overestimate deaths. In contrast, this 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 tracker. [8]	
Benefit #2		
Name	Prevention of intensive care unit (ICU) admissions due to COVID-19	
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 days. [9]	Based on metanalysis of global data

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 are 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	Most serious outcome of COVID-19	
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 day [10] Risk of long-term sequelae low but not yet clearly defined [11]	
Rationale for inclusion	Serious adverse reaction that may require 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 to define myocarditis for 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. [11]	
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)) [12] [13]	

	Hospitalization mainly for monitoring of heart rhythm; also, for pain control, and rarely more intensive therapies [11] [12]	
Rationale for inclusion	Serious adverse reaction 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 due to 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 is likely to be 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. but deaths have been observed in one follow-up study. [14] Uncertainty in confirming mRNA vaccine as cause of myocarditis-related death	

Other risks considered		
Question	**Responses**	
Other risks considered	No	
Which risks were considered?	N/A	
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. [15] [7] [2] 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. [2] 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. [5] 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). [16]
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 of myocarditis [5]. Risk derived based on 15.1 million persons age 18-64 years receiving at least 1 dose of mRNA vaccine.
CDC Vaccine safety datalink	Rates of myocarditis following 2nd dose COVID-19 mRNA vaccine	Cases reviewed and adjudicated per CDC myocarditis case definition; population based; slightly different age cut-offs than other studies. Limitations: based on 8 HMOs, with risk based on 6.7 million persons receiving at least one dose of mRNA vaccine; limited number of cases (79) compared to other sources for this analysis [10] [12]
Metanalysis of myocarditis	Rates of myocarditis following 2nd dose COVID-19 mRNA vaccine -	Metanalysis of 4 studies; different age cut-offs [17]

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). [12] 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 data [11] - 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 vaccines. [18] [19] Post-licensure follow-up of vaccine effectiveness in the United States. [6] [20] [21] 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 persons receiving the 2nd dose of mRNA vaccine, using US data on rates of COVID-19 hospitalizations, ICU, deaths from COVID-NET, May 2021 (base case) [2], and estimates of rates of myocarditis in 2nd dose mRNA vaccine recipients from 3 different sources, [10] [12] [5] [17] as well as rates of outcomes of myocarditis. [12] VAERS data used to estimate relative distribution of myocarditis risk by age when studies used different age groupings. Age and sex specific rates of hospitalizations for unvaccinated persons were from COVID-NET [2]. 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 effectiveness against hospitalization was 90%, based on pre-licensure vaccine trials and early post-licensure effectiveness studies. [6] [18] [19] [20] [21]

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). [6] [20] [21]	
Type of measurements:	Cases prevented or occurring 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, 2021 [2]	
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	

Section 5: Benefit Data

Table 1 Benefits: COVID-19 mRNA vaccine vs no vaccine, 16–17-year-old Male, Base case (June 2021 US), per million persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

Table 2 Benefits – COVID-19 vaccine vs no vaccine, 18–29-year-old Male, Base case (June 2021 US), per million persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

Table 3 Benefits: COVID-19 vaccine vs no vaccine, 30+ year-old Male, Base case (June 2021 US), per million persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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 persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

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 persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

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 persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

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 persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

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 persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

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 persons receiving 2nd dose mRNA vaccine. Benefits interval 120 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine of interest (mRNA vaccine)**	**Comparator (No vaccine)**	**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

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 persons receiving 2nd dose mRNA vaccine. Risk interval 0-7 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine (mRNA vaccine)**	**Comparator (No vaccine)**	**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

Note: Risks are not dependent on COVID-19 transmission rate

Table 2 Risks: Myocarditis following COVID-19 vaccine; comparator no vaccine, 18-29-year-old Male, Base case (June 2021 US), per million persons receiving 2nd dose mRNA vaccine. Risk interval 0-7 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine (mRNA vaccine)**	**Comparator (No vaccine)**	**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

Note: Risks are not dependent on COVID-19 transmission rate

Table 3 Risks – Myocarditis following COVID-19 vaccine; comparator no vaccine, 30+ year-old Male, Base case (June 2021 US), per million persons receiving 2nd dose mRNA vaccine. Risk interval 0-7 days after 2nd dose.

	Cases per 1,000,000						
Endpoint	**Vaccine (mRNA vaccine)**	**Comparator (No vaccine)**	**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

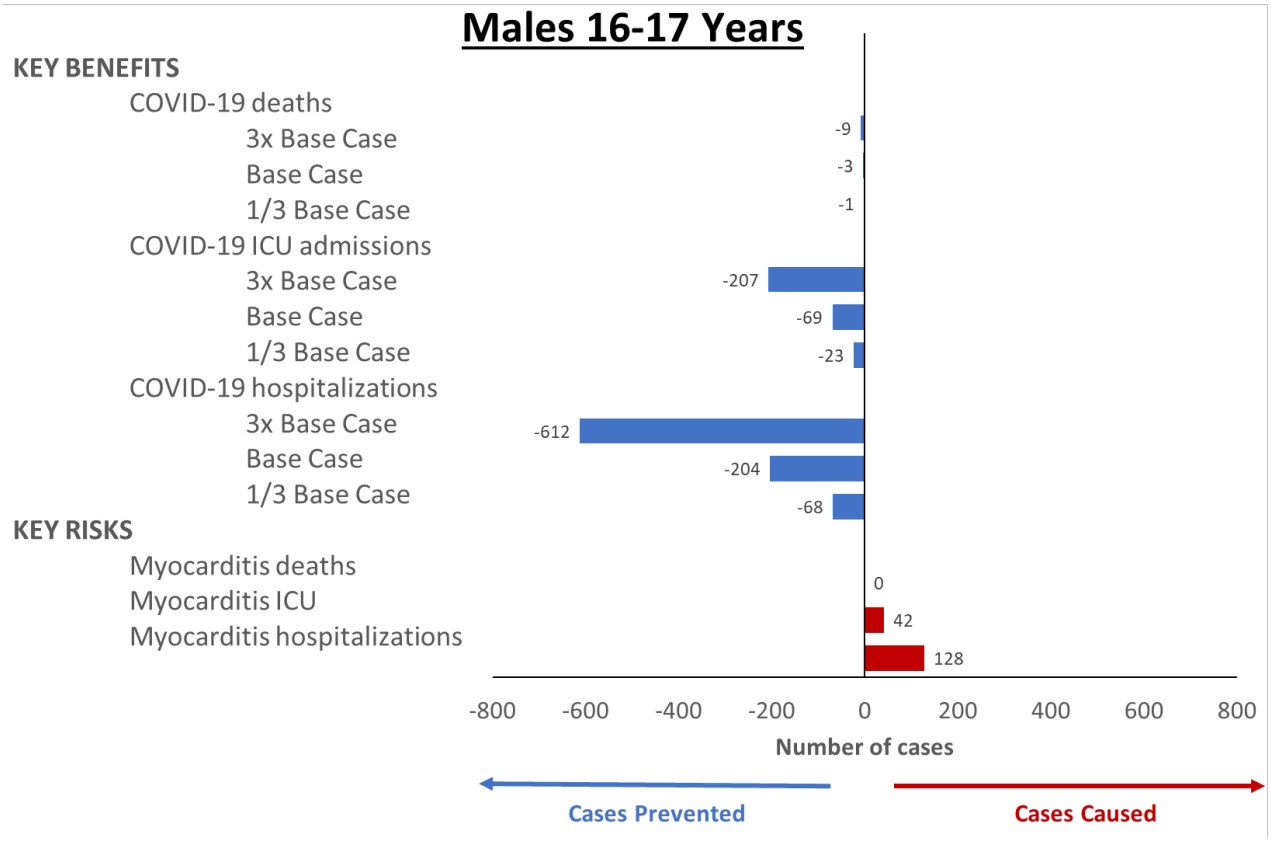
*NNH = number needed to harm

Note: Risks are not dependent on COVID-19 transmission rate

Mitigations for Risks

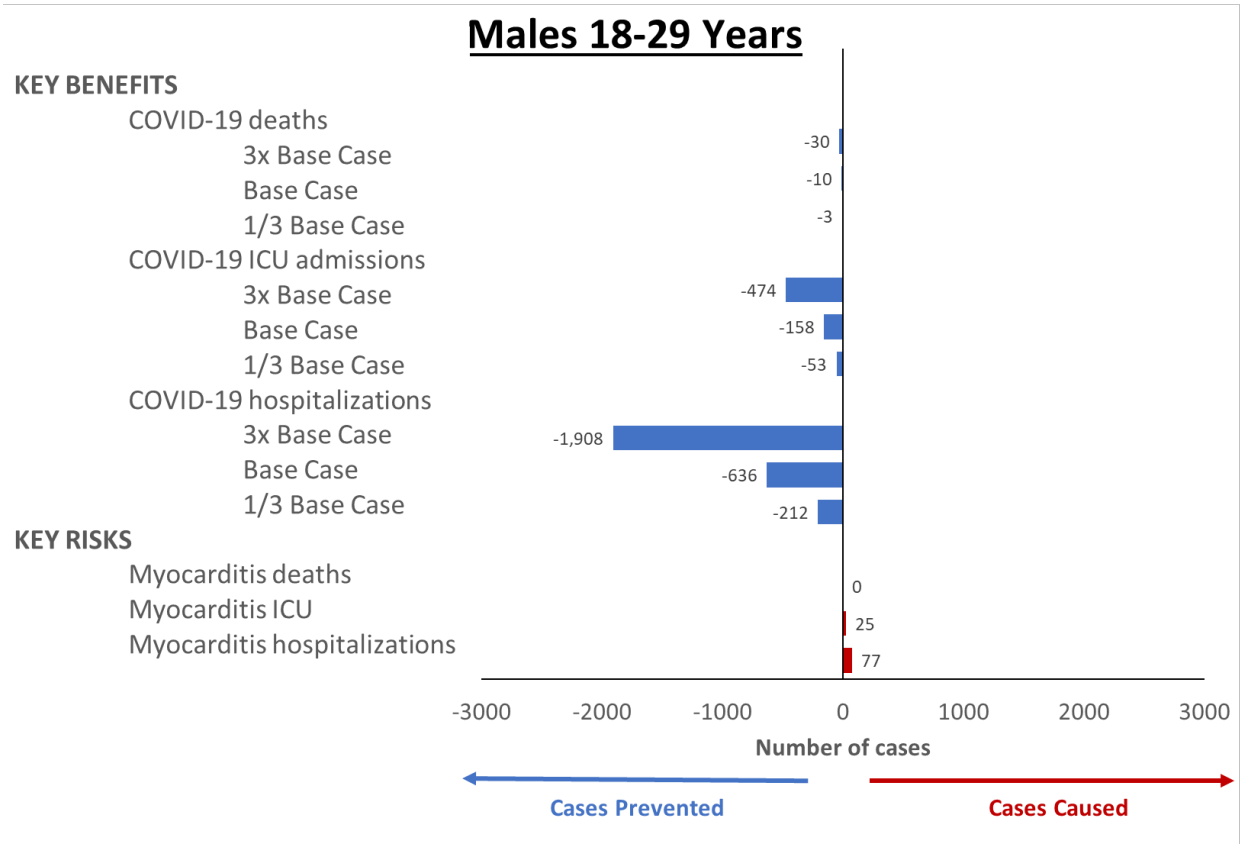
Mitigation	**Endpoints Affected**	**Notes, Uncertainty and Strength of Evidence**
None considered		

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



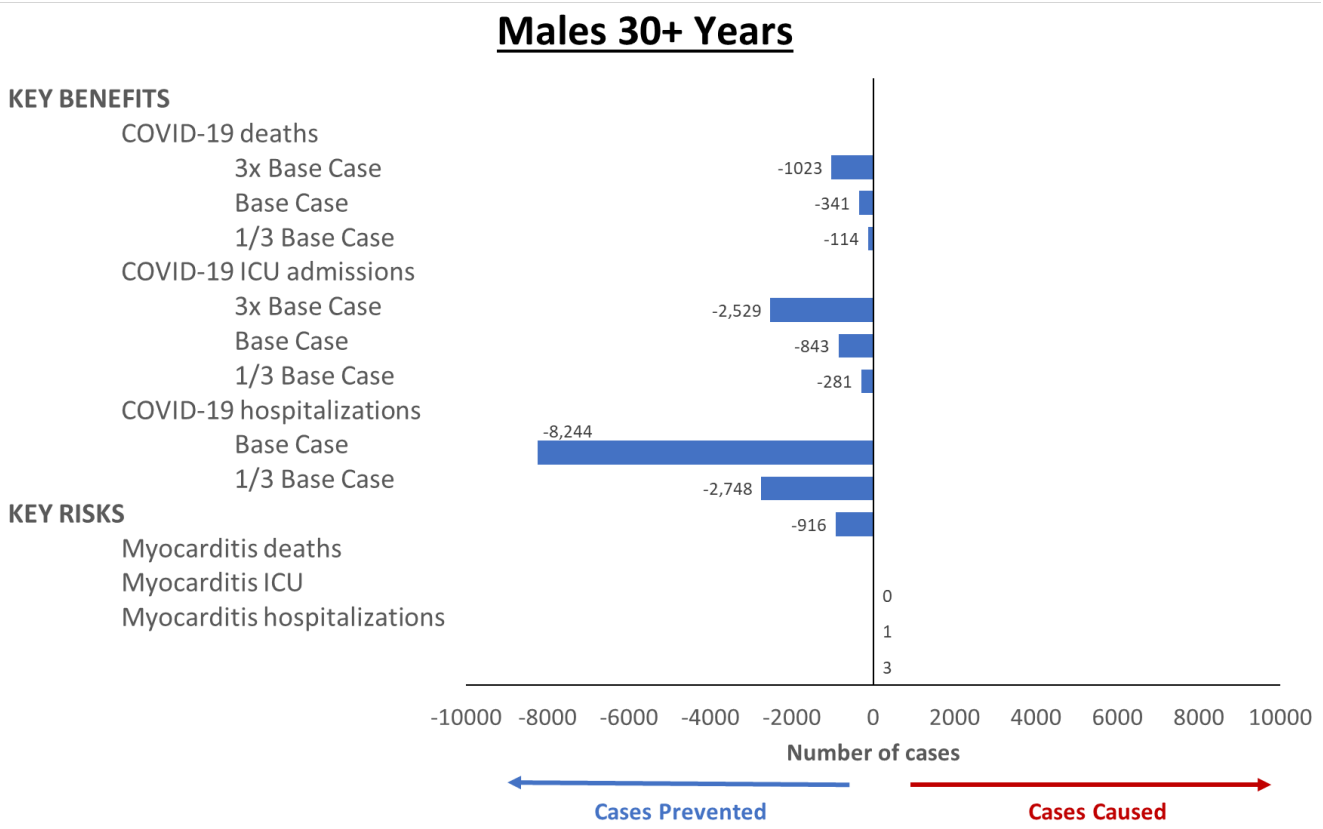
* **Benefits:** events prevented by vaccination, **Risks:** events expected following vaccination

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



* **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



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

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

Section 8: Integrated B-R Assessment

For the base case analysis, during a period of relatively low COVID-19 incidence in the US compared to earlier in the pandemic (~6 / 100,000 / day vs. peak of ~60 / 100,000 / day), the benefits of mRNA COVID-19 vaccination outweigh the risks for all male age groups. Benefits outweigh risks to the greatest extent in males > 30 years of age (e.g. per 1,000,000 persons receiving a 2nd dose of mRNA vaccine, 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 benefits also outweigh the risks, though to a lesser degree than for >30 year (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 2nd dose mRNA vaccines vs. no vaccine 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.

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