



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: February 10, 2022
To: Sudhakar Agnihothram
From: Hong Yang, Ph.D., Patrick Funk, Ph.D., and Osman N. Yogurtcu, Ph.D.
Analytics and Benefit-Risk Assessment Team
OBE

Through: Richard Forshee, Ph.D.
Acting Deputy Office Director
OBE

Re: STN 125752/0: review memo for benefit-risk assessment

Review Memo on Benefit-Risk Assessment of Spikevax for Ages 18 and Above

Reference submission: BLA 125752/0

Reviewers: Hong Yang, Patrick Funk, and Osman Yogurtcu

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Contents

1. Executive Summary.....	3
2. Background and regulatory questions.....	5
3. Methods.....	6
3.1. Model Overview	6
3.2. Calculation of Benefits.....	6
3.3. Benefits Data and Assumptions.....	7
3.4. Rates of vaccine-attributable myocarditis/pericarditis.....	8
3.5. Risks Data and Assumptions.....	8
4. Results.....	10
5. Conclusions and discussion	11
6. Limitations.....	12
6.1. Estimation of Benefits	12
6.2. Estimation of Risks.....	12
6.3. Benefit-Risk Balance.....	13
References	14
List of Tables.....	15
List of Figures.....	15

1. Executive Summary

FDA conducted a benefit-risk (B-R) assessment to inform the review of the Biologics License Application (BLA) for use of Spikevax (also referred to as mRNA-1273 vaccine or Moderna COVID-19 mRNA vaccine) among individuals ages 18 years and older. The model assesses the benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions, and deaths, and the risks of vaccine-related myocarditis/pericarditis cases, hospitalizations, ICU admissions and deaths. We assessed the benefits and risks per million individuals who are vaccinated with two complete doses of mRNA-1273 vaccine. The analysis was conducted for the male population stratified by age (18-25, 26-35, 36-45, 46-55 and 55-64 years). The major sources of data include age specific COVID-19 case and hospitalization incidences reported in December, 2021 [CDC COVID Data Tracker and COVID-NET], average COVID ICU and death rates from March 2020 to October 2021 [COVID-NET], the vaccine effectiveness (VE) against Delta and Omicron virus strains based on US [Jones 2021] and UK studies [UKHSA], respectively, the age specific myocarditis/pericarditis case rates attributable to vaccine obtained from the CBER Biologics Effectiveness and Safety System (BEST) health claims databases, and the rates of vaccine related myocarditis/pericarditis hospitalizations and ICU admissions reported through Vaccine Safety Datalink (VSD) system [Klein 2021]. We constructed six model scenarios (Table 1) to evaluate the benefits and risks of the vaccine and the impacts of uncertainty associated with the future dynamic of the pandemic, VE against emerging virus variants and rates of myocarditis/pericarditis case associated with the vaccine.

Our results support that the benefits of mRNA-1273 vaccine clearly outweigh its risks for all the model scenarios. For Scenario 1 (base and most likely scenario) we assumed the COVID-19 incidence to be that of the week of December 25, 2021 [COVID Data Tracker and COVID-NET], 30% VE against cases and 72% VE against hospitalization with Omicron dominant strain based on a large UK study [UKHSA], and vaccine attributable myocarditis/pericarditis rates as the mean of meta-analysis results from four BEST system databases. The model predicted that vaccinating one million males 18-25 years of age (the age/sex group with the highest risk of myocarditis/pericarditis attributable to vaccine) with two primary series doses of mRNA-1273 vaccine would prevent 76,326 COVID-19 cases, 1,755 hospitalizations, 421 ICU admissions and 4 deaths due to COVID-19 and would cause 148 vaccine-attributable myocarditis/pericarditis cases, 127 hospitalizations and 0 ICU admissions. No death due to vaccine attributed myocarditis/pericarditis is expected. See Table 2 for the complete results of all the scenarios.

Modeling was not conducted for females and individuals 65 years of age and older due to limitations of the data, as there are too few cases of myocarditis/pericarditis after vaccination in these groups to reliably estimate myocarditis/pericarditis rates. However, this evidence indicates that males and females 65 years of age and older and females of all ages have a lower risk of vaccine-associated myocarditis. Consequently, it is reasonable to expect that the benefit-risk balance of vaccination with the Moderna COVID-19 Vaccine in these demographic groups would be even more favorable compared with males 18-64 years of age. Therefore, we conclude the benefits of mRNA-1273 vaccine outweigh its risks for the overall indicated population. However, uncertainties in the dynamics of the pandemic (disease incidence and emerging variants), VE for emerging variants, and rate of vaccine attributed myocarditis/pericarditis are important limitations of our analysis. Another limitation of this benefit-risk assessment is that it does

not assess potential long-term adverse effects due to either COVID-19 or vaccine attributable myocarditis/pericarditis.

2. Background and regulatory questions

The Moderna COVID-19 mRNA vaccine has been authorized for use in persons 18 years of age and older in the United States under Emergency Use Authorization (EUA). Since authorization of mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna), real-world evidence from the pre-Omicron period has indicated the vaccines are effective in preventing COVID-19 cases and related hospitalizations and deaths. However, cases of myocarditis and pericarditis associated with mRNA COVID-19 vaccines have been reported in the United States, particularly in adolescents (for whom the Pfizer-BioNTech vaccine is authorized) and young adult males [Marshall *et al.* 2021; Shay *et al.* 2021; Watkins, *et al.*, 2021]. FDA conducted a benefit-risk assessment to inform regulatory decisions related to the Biologics License Application (BLA) for use of mRNA-1273 vaccine among individuals 18 years of age and older. The regulatory question addressed by our analyses is whether the benefits of vaccination outweigh the risks for the target population, considering the uncertainties of the evolving pandemic (changes in disease incidence and emergence of new variants) and the risk of myocarditis/pericarditis after vaccination, most strikingly among young males, identified by post-authorization safety surveillance.

3. Methods

3.1. Model Overview

We assessed the benefits and risks per million individuals who are vaccinated with two primary series doses of mRNA-1273 vaccine. The analysis was conducted for the male population stratified by age: 18-25, 26-35, 36-45, 46-55 and 55-64 years. We did not model benefits and risks for individuals 65 years of age and older, due to the lack of data on the rate of vaccine-attributable myocarditis/pericarditis in this population. Females were also not included since the reported vaccine-attributable cases of myocarditis/pericarditis for female age groups were rare, leading to an unstable case rate. The model assesses the benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions, and deaths, and the risks of vaccine related myocarditis/pericarditis cases, hospitalizations, ICU admissions, and deaths (Figure 1). The key model inputs include duration of vaccine protection, vaccine effectiveness (VE) against COVID-19 cases and hospitalizations, age specific COVID-19 case and hospitalization incidence rates, age specific vaccine-attributable myocarditis case rate, hospitalizations, ICU admissions, and death rate.

Our model generates benefit-risk outcomes for six different scenarios (Table 1) to provide a sensitivity analysis of the uncertainties related to three major model inputs, COVID-19 incidence (Scenarios 1, 2 and 3), VE (Scenarios 1 and 4), and vaccine-attributable myocarditis/pericarditis rate (Scenarios 1, 5 and 6). Scenario 1 is the base scenario. For the remaining scenarios, only one of the three major model inputs from Scenario 1 is modified at a time (summarized in Table 1).

3.2. Calculation of Benefits

Our benefit-risk model has four benefit endpoints (Figure 1): preventable COVID-19 cases, hospitalizations, ICU admissions, and deaths. To calculate the potential COVID-19 cases preventable by vaccine (C_P), we use Equation 1, where I_C is the COVID-19 case incidence rate, P_U is the proportion of the population that is at risk (i.e., unvaccinated), L is the duration of vaccine protection, D is the number of individuals with two doses administered (fixed at 1 million), and E_C is the VE against COVID-19 cases.

$C_P = \frac{I_C}{P_U} L D E_C$	Eq. 1
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For preventable COVID-19 hospitalizations (H_P), we use a similar equation (Equation 2) in which we consider the COVID-19 hospitalization incidence rate (I_H) and VE against hospitalization (E_H).

$H_P = \frac{I_H}{P_U} L D E_H$	Eq. 2
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The preventable COVID-19 ICUs (I_P) and preventable COVID-19 deaths (D_P) are fractions of H_P , such that $I_P = f_{IH} H_P$ and $D_P = f_{DH} H_P$.

We performed these calculations for each of the different age groups.

3.3. Benefits Data and Assumptions

3.3.1. Duration of vaccine protection

We estimated protection over a 5-month period after completion of the 2-dose primary series, since a 5-month interval between completion of the primary series and booster dose is authorized by FDA and recommended by CDC. For simplicity, the model does not account for benefits of partial vaccination and also assumes a constant VE during the 5-month period post 2nd dose. We assumed the incidence rates of COVID-19 case and hospitalization remain constant over the assessment period (within 5 months post the 2nd dose). For Scenarios 1, 4, 5 and 6, the incidence rates of COVID-19 cases from the week of December 25, 2022 were obtained from COVID-NET for all male age groups. The hospitalization rates for these scenarios were the average rate for the week of December 11, 2021 collected by COVID-NET. The percent of hospitalizations with ICU admission and the percent of hospitalized patients who die were estimated based on the cumulative rates of hospitalizations, ICU admissions, and deaths for each male age group from March 2020 to October 2021 provided by the CDC (collected by COVID-NET). We used the average (from March 2020 to December 2021) and the lowest US COVID-19 incidence rate (June 2021) in Scenarios 2 and 3, respectively. All the incidence related model inputs are summarized in Table 3.

3.3.2. Unvaccinated population

We estimated the unvaccinated population among each male age group using US census data and “Age groups of people with at least one dose” from the COVID data tracker. The incidence of COVID-19 cases and hospitalization shown on Table 3 were converted into the incidence of COVID-19 cases and hospitalizations among unvaccinated individuals of each age group.

3.3.3. Vaccine effectiveness

We assumed Omicron as the dominant strain in Scenarios 1, 2, 3, 5 and 6 and assumed averages of 30% VE against COVID-19 cases and 72% VE against COVID-19 hospitalizations during the 5-month period post 2nd dose. The data from a UK surveillance report was used to derive these VEs for Omicron [UKHSA]. For Scenario 4 we assume Delta as the dominant strain and used averages of 80% VE against cases and 90% VE against hospitalizations [Jones 2021]. Many studies conducted in the US and other countries during the Delta dominant period showed consistently high VE of mRNA-1273 vaccine against both COVID-19 cases and related hospitalization [Jones 2021 and Oliver 2021].

3.4. Rates of vaccine-attributable myocarditis/pericarditis

Our benefit-risk model has four risk endpoints (Figure 1): vaccine-attributable myocarditis/pericarditis cases, hospitalizations, ICU admissions, and deaths. Estimates of vaccine-attributable cases of myocarditis/pericarditis (per 1 million person-days with a risk window of 7 days post vaccination) are based on a meta-analysis of four health claims databases in BEST, which combined four data partners DP1-4 with data starting from December 10, 2020 (Table 4). Data cutoff dates for the sources are as follows: DP1 (August 21, 2021), DP2 (July 10, 2021), DP3 (July 31, 2021), and DP4 (June 30, 2021). The age specific vaccine-attributable incidences of myocarditis/pericarditis were calculated by dose 1 and 2. For this analysis we used the sum of incidences for dose 1 and 2 as the model input. For Scenarios 1, 2, 3, and 4 we used the mean meta-analysis predicted myocarditis/pericarditis rate for each male age group, while for Scenario 5 we use the 2.5th percentile rate and for Scenario 6 we used the 97.5th percentile rate. We used Equation 3 to calculate total myocarditis/pericarditis (M_{Pred}) per one million fully vaccinated individuals.

$M_{Pred} = (M_{Pred1} + M_{Pred2}) * F$	Eq. 3
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M_{Pred1} is the meta-analysis predicted myocarditis/pericarditis case rates post dose 1, M_{Pred2} is the corresponding meta-analysis predicted case rates post dose 2, and F is a multiplier to convert the unit from 1 million person-days to 1 million fully vaccinated persons assuming all the cases occur within a 7-day window post each dose of vaccination.

The number of myocarditis hospitalization (M_H) and deaths (M_D) are fractions of predicted myocarditis/pericarditis cases (M_{Pred}), such that $M_H = M_{Pred} * F_{HM}$ and $M_D = M_{Pred} * F_{DM}$.

3.5. Risks Data and Assumptions

3.5.1. Myocarditis/pericarditis attributable to vaccine

We used myocarditis/pericarditis incidence data for male age groups provided by Acumen LLC and derived from four BEST health claim databases (Table 4). Acumen reports meta-analysis results for the incidence of myocarditis case rates by vaccine dose 1 and 2 for the risk window of 7 days. The reported cases of myocarditis/pericarditis attributable to vaccine among female age groups and male and female age 65 years or above are rare, leading to unstable estimates of case rates. Therefore, we are not able to provide reliable estimates of the risks for females in all age groups and individuals 65 years of age and above.

3.5.2. Myocarditis/pericarditis hospitalization, ICU admission and death

VSD data [Klein 2021] shows that 86% of myocarditis cases are hospitalized and none require admission to the ICU for ages 18-29 years. The rate for hospitalization falls to 77%

for ages 30-39 years. Since the age ranges in VSD differ from those in our analysis, we made an adjustment for our age ranges. We used hospitalization rates of 86% for ages 18-25 years, 81.5% (the midpoint between ages 18-29 years and ages 30-39 years in VSD data) for ages 26-35 years, and 77% for ages 36 years and above in our analysis. The hospitalizations were mainly for monitoring and precautionary purposes. Vaccine Adverse Events Reporting System (VAERS) data show a median of a one day stay during hospitalization. No death confirmed to be caused by vaccine-attributable myocarditis/pericarditis has been identified. In this model, we assumed a zero death rate due to myocarditis/pericarditis attributed to vaccine.

4. Results

Our results support that the benefits of mRNA-1273 vaccine clearly outweigh its risks for all the model scenarios. For Scenario 1 (base scenario), the model predicted that vaccination of 1 million males 18-25 years of age with two primary series doses of mRNA-1273 vaccine would prevent 76,326 COVID-19 cases, 1,755 hospitalizations, 421 ICU admissions and 4 deaths due to COVID-19, while causing 148 vaccine-attributable myocarditis/pericarditis cases, 127 hospitalizations and no ICU admissions. No death due to vaccine attributed myocarditis/pericarditis is expected. These results represent the benefit-risk of the groups with the highest potential myocarditis/pericarditis risk under the current scenario (Omicron dominant, most recent peak incidence and the mean rate of vaccine-attributable myocarditis/pericarditis case), and we consider that the benefits of vaccine clearly outweigh the risks. The results for all six model scenarios are summarized in Table 2, and we consider that the benefits of vaccine clearly outweigh the risks for each of the additional 5 scenarios as well. Scenarios 1, 2 and 3 represent the uncertainty in the case incidence (the week of December 25, 2021, average and the lowest incidence) in the future pandemic, Scenarios 1 and 4 represent the uncertainty in VE against the emerging variants (Omicron vs Delta), and Scenarios 1, 5 and 6 represent the uncertainty in the incidence rate of vaccine-attributable myocarditis/pericarditis.

5. Conclusions and discussion

Our results support that the benefits of mRNA-1273 vaccine clearly outweigh its risks for all the model scenarios for all males 18-64 years of age. Furthermore, based on consistent evidence that indicates a lower risk of vaccine-associated myocarditis in females of all ages and in males 65 years and older, it is reasonable to expect that the benefit-risk balance of vaccination with Moderna in these demographic groups would be even more favorable compares with males 18-64 years of age. Therefore, we conclude the benefits of mRNA-1273 vaccine outweigh its risks for the overall target population.

6. Limitations

6.1. Estimation of Benefits

- In this analysis we conducted sensitivity analyses to test the incidence rate at the recent peak, average, and low level during the pandemic. However, the constant COVID-19 incidence rate assumption in our model generates high uncertainty on the estimate of benefits, considering the uncertain dynamics of the pandemic. Furthermore, the percent of hospitalizations resulting in ICU admission and the percent of hospitalized patients who die are estimated based on cumulative rates of hospitalizations, ICU admissions, and deaths for each age group reported on COVID-NET from March 2020 to October 2021 (pre-Omicron period). This rate may have changed since Omicron surged, but the more recent data is not yet available. The rate of ICU admission and death associated with Omicron may be lower compared to Delta, which may lead to overestimation of the benefits.
- Estimated benefits of the vaccine would decrease if the vaccine becomes less effective against novel variants of COVID-19. In this analysis, we evaluated the impact of different VEs for Omicron and Delta strains. However, there is uncertainty associated with future new variants or composition of the variants. Furthermore, the 30% VE for Omicron used in this analysis was obtained from a UK study. A similar US study with a smaller sample size showed a 23% VE for Omicron. However, we do not expect that this difference in VE estimates would change our B-R conclusion.
- The durability of vaccine protection is another source of uncertainty for the model. In this analysis we assumed a 5-month protection period after completion of two primary doses of mRNA-1273 vaccine. Any significant waning of vaccine-induced immunity within 5 months post 2nd dose would reduce the benefit of the vaccine.

6.2. Estimation of Risks

- Females of all ages and both males and females age 65 years or older were not included in this analysis due to the rarity of cases of myocarditis/pericarditis leading to an unstable estimate of case rate. However, the benefit-risk for females and individuals 65 years of age or older is expected to be more favorable compared to male age 18-25 years, for whom clear favorable benefit-risk was demonstrated by this analysis.
- There is uncertainty in the risk of myocarditis cases attributable to the vaccine. To estimate myocarditis/pericarditis risk attributable to the vaccine, health claims data are used, which have inherent limitations such as small sample sizes due to rare events among age groups. The reported cases in BEST have not been validated by medical chart review, and therefore may be an overestimate. To address some of these limitations, the crude myocarditis rate in our model was adjusted using the myocarditis background rate in 2019, meta-analysis of four claims databases was conducted to increase the sample size, and a sensitivity analysis was conducted to test the confidence interval of the estimated vaccine-attributable myocarditis/pericarditis

case rate.

6.3. Benefit-Risk Balance

- Some benefit-risk endpoints in our assessment are difficult to compare directly, for example, hospitalizations from COVID-19 and myocarditis hospitalizations.
- This benefit-risk assessment does not include potential long-term adverse effects due to either COVID-19 or myocarditis and second-order benefits and risks, such as any potential impact on the public trust in COVID-19 vaccines.
- In this analysis, we did not investigate the benefits and risks for specific subpopulations, such as those with comorbidities, due to limited information for these populations. The benefit-risk profile could be different depending on an individual's health condition.

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List of Tables

Table 1 Six model scenarios with varying COVID-19 incidence rates, vaccine effectiveness against cases and hospitalization, and myocarditis/pericarditis rates.....	16
Table 2 Benefit-risk outcomes per million males vaccinated with 2 primary series doses of mRNA-1273 vaccine under each of six scenarios described in Table 1.....	17
Table 3. Vaccine coverage and COVID incidences by age groups (Male population only).	18
Table 4. Estimated rates of vaccine-attributable myocarditis/pericarditis cases, by age subgroup, for 1 million fully vaccinated male individuals with mRNA-1273 vaccine.	19

List of Figures

Figure 1. Benefits-risks value tree.....	20
Figure 2. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 1.....	21
Figure 3. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 2.....	22
Figure 4. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 3.....	23
Figure 5. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 4.....	24
Figure 6. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 5.....	25
Figure 7. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 6.....	26

Table 1 Six model scenarios with varying COVID-19 incidence rates, vaccine effectiveness against cases and hospitalization, and myocarditis/pericarditis rates.

	COVID-19 Incidence	Vaccine Effectiveness	Vaccine-attributable Myocarditis Risk
Scenario 1	As of December, 2021	Omicron dominant: 30% against cases 72% against hospitalization	Mean of BEST meta-analysis
Scenario 2	Average COVID-19 pandemic incidence	Same as Scenario 1	Same as Scenario 1
Scenario 3	Lowest COVID-19 pandemic incidence (June 5, 2021)	Same as Scenario 1	Same as Scenario 1
Scenario 4	Same as Scenario 1	Delta dominant: 80% against cases 90% against hospitalization	Same as Scenario 1
Scenario 5	Same as Scenario 1	Same as Scenario 1	2.5 th percentile of BEST meta-analysis
Scenario 6	Same as Scenario 1	Same as Scenario 1	97.5 th percentile of BEST meta-analysis

Table 2 Benefit-risk outcomes per million males vaccinated with 2 primary series doses of mRNA-1273 vaccine under each of six scenarios described in Table 1.

	Ages	BENEFITS				RISKS			
		COVID	COVID	COVID	COVID	Myo/Peri	Myo/Peri	Myo/Peri	Myo/Peri
		Cases	Hospitalizations	ICUs	Deaths	Cases	Hospitalizations	ICUs	Deaths
Scenario 1	18-25yo	76,326	1,755	421	4	148	127	0	0
	26-35yo	72,389	2,591	663	75	43	35	0	0
	36-45yo	76,964	5,188	1,370	145	29	22	0	0
	46-55yo	71,916	10,374	3,040	643	23	18	0	0
	56-64yo	53,856	10,678	3,503	1,025	23	17	0	0
Scenario 2	18-25yo	31,286	1,399	336	3	148	127	0	0
	26-35yo	29,742	1,851	474	54	43	35	0	0
	36-45yo	36,099	3,515	928	98	29	22	0	0
	46-55yo	41,331	7,058	2,068	438	23	18	0	0
	56-64yo	33,737	7,291	2,392	700	23	17	0	0
Scenario 3	18-25yo	5,594	735	176	1	148	127	0	0
	26-35yo	5,387	914	234	27	43	35	0	0
	36-45yo	6,382	1,434	378	40	29	22	0	0
	46-55yo	6,829	2,580	756	160	23	18	0	0
	56-64yo	5,378	2,640	866	253	23	17	0	0
Scenario 4	18-25yo	203,537	2,193	526	4	148	127	0	0
	26-35yo	193,038	3,238	829	94	43	35	0	0
	36-45yo	205,238	6,485	1,712	182	29	22	0	0
	46-55yo	191,777	12,967	3,799	804	23	18	0	0
	56-64yo	143,617	13,348	4,378	1,281	23	17	0	0
Scenario 5	18-25yo	76,326	1,755	421	4	76	65	0	0
	26-35yo	72,389	2,591	663	75	12	10	0	0
	36-45yo	76,964	5,188	1,370	145	14	10	0	0
	46-55yo	71,916	10,374	3,040	643	12	9	0	0
	56-64yo	53,856	10,678	3,503	1,025	11	9	0	0
Scenario 6	18-25yo	76,326	1,755	421	4	289	249	0	0
	26-35yo	72,389	2,591	663	75	153	124	0	0
	36-45yo	76,964	5,188	1,370	145	63	49	0	0
	46-55yo	71,916	10,374	3,040	643	46	36	0	0
	56-64yo	53,856	10,678	3,503	1,025	46	36	0	0

Table 3. Vaccine coverage and COVID incidences by age groups (Male population only).

Age group	Population¹	Vaccinated population²	Daily COVID-19 cases/100k persons²	Daily Hospitalizations/ 100k persons³	Percent of hospitalized going to ICU³	Percent of hospitalized who die³
18-25	18,075,261	11,150,165	64.13	0.61	24.0	0.2
26-35	23,566,099	14,378,360	61.89	0.92	25.6	2.9
36-45	20,777,760	14,478,672	51.17	1.44	26.4	2.8
46-55	20,613,664	15,792,132	36.89	2.22	29.3	6.2
56-64	20,395,650	14,960,870	31.47	2.60	32.8	9.6

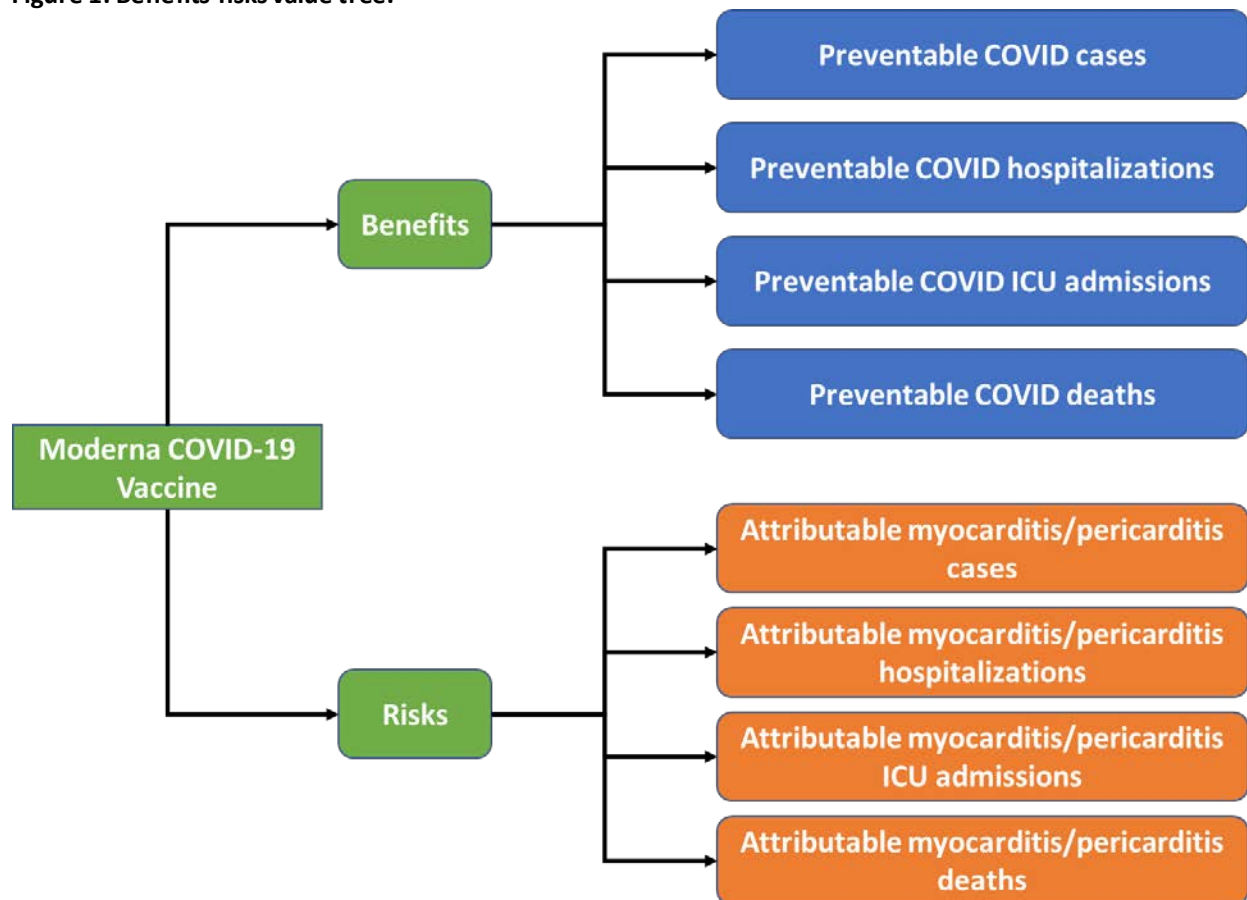
Source: 1-CDC Wonder, 2-COVID Data Tracker, 3-COVID-NET

Table 4. Estimated rates of vaccine-attributable myocarditis/pericarditis cases, by age subgroup, for 1 million fully vaccinated male individuals with mRNA-1273 vaccine. DP1-4 stands for CBER BEST data partners 1 through 4.

Dose	Age Group	Moderna mRNA-1273 Adjusted Rate per 1M Doses Point Estimate and 95% CI	Data Source
Dose 1	18-25	19.7 [8.1, 48.0]	DP1-4
	26-35	11.5 [3.9, 33.7]	DP1, DP2, and DP4
	36-45	5.8 [2.2, 15.8]	DP2 and DP3
	46-55	10.7 [4.9, 23.5]	DP1 and DP4
	56-64	13.0 [7.4, 23.1]	DP1-4
Dose 2	18-25	127.8 [67.8, 241.2]	DP1-4
	26-35	31.8 [8.5, 118.9]	DP1-4
	36-45	23.1 [11.3, 47.2]	DP1-4
	46-55	12.5 [6.9, 22.8]	DP1-4
	56-64	9.6 [3.9, 23.3]	DP1-4

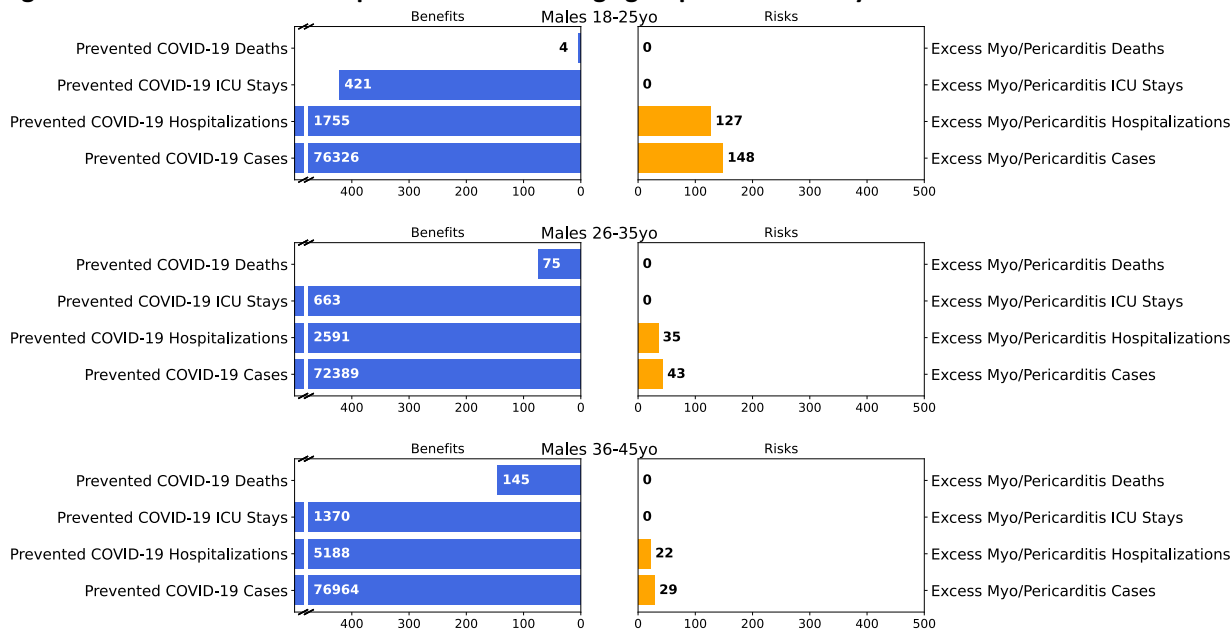
Source: BEST System Database

Figure 1. Benefits-risks value tree.



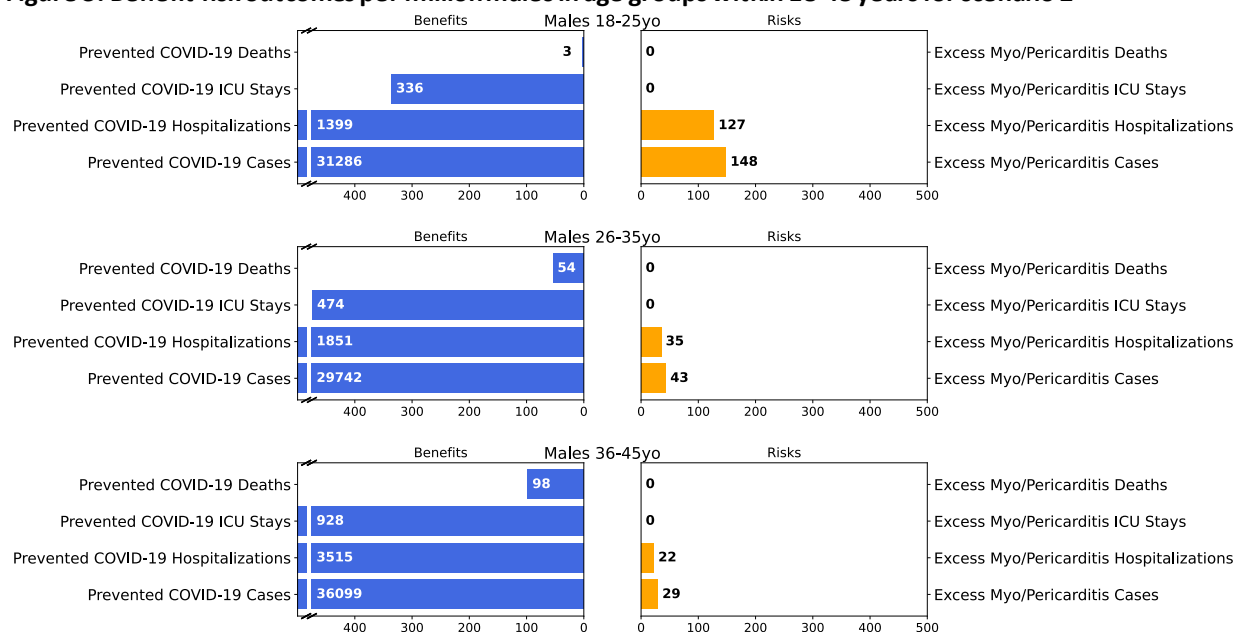
Source: Reviewer Analysis

Figure 2. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 1



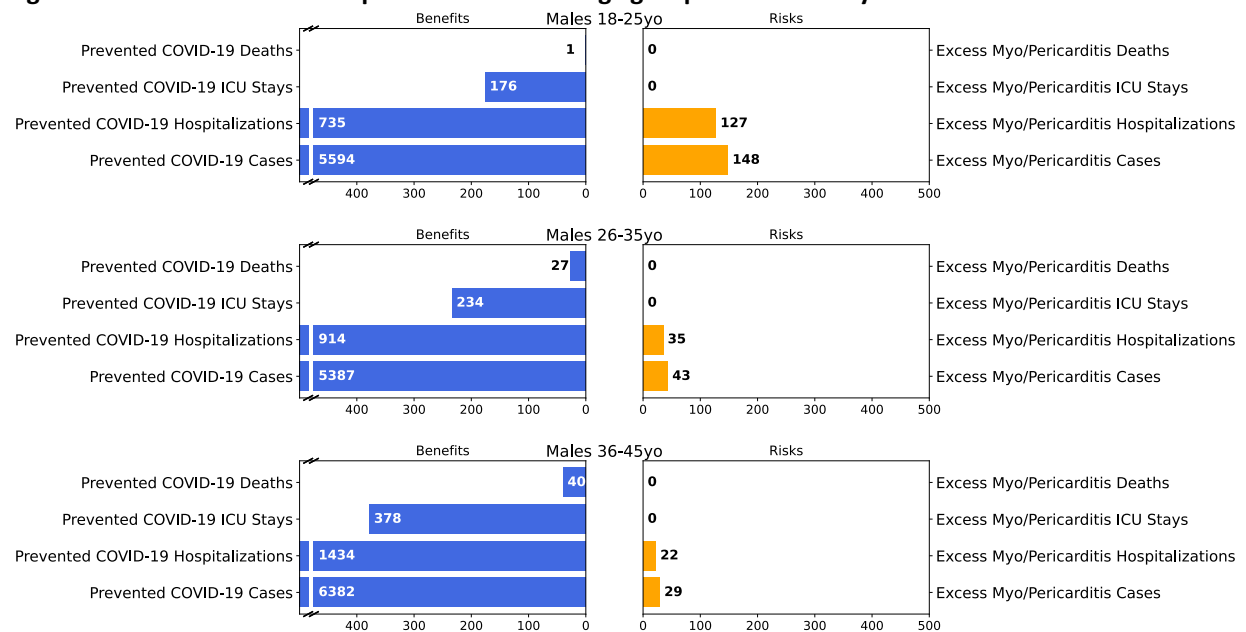
Source: Reviewer Analysis

Figure 3. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 2



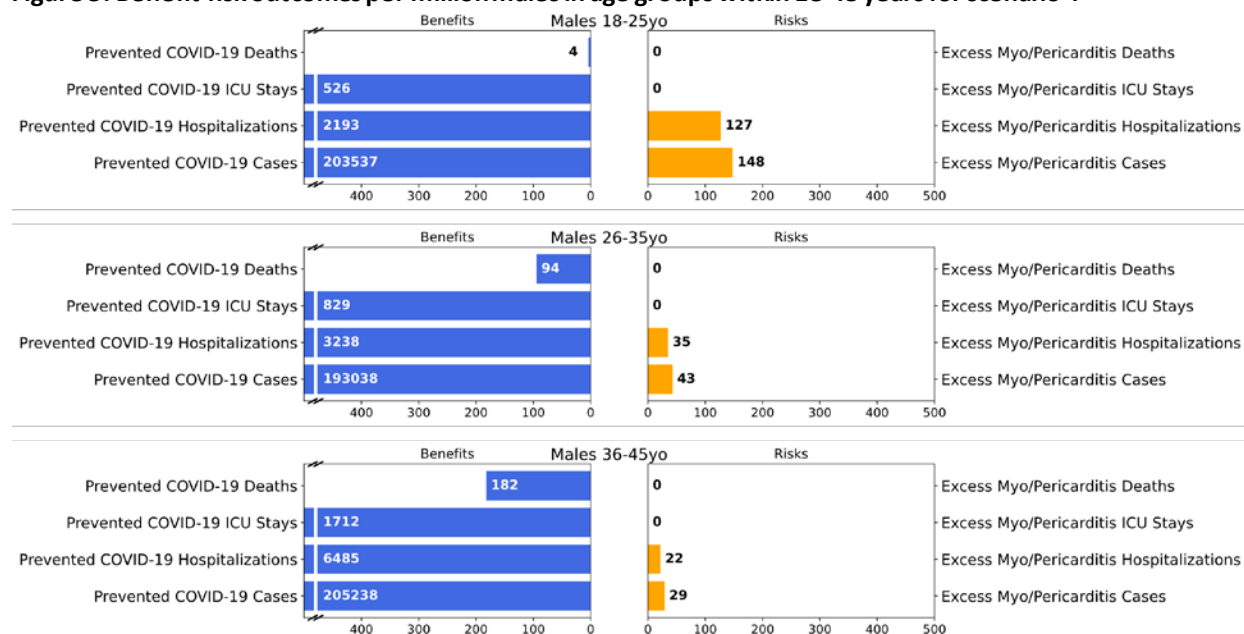
Source: Reviewer Analysis

Figure 4. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 3



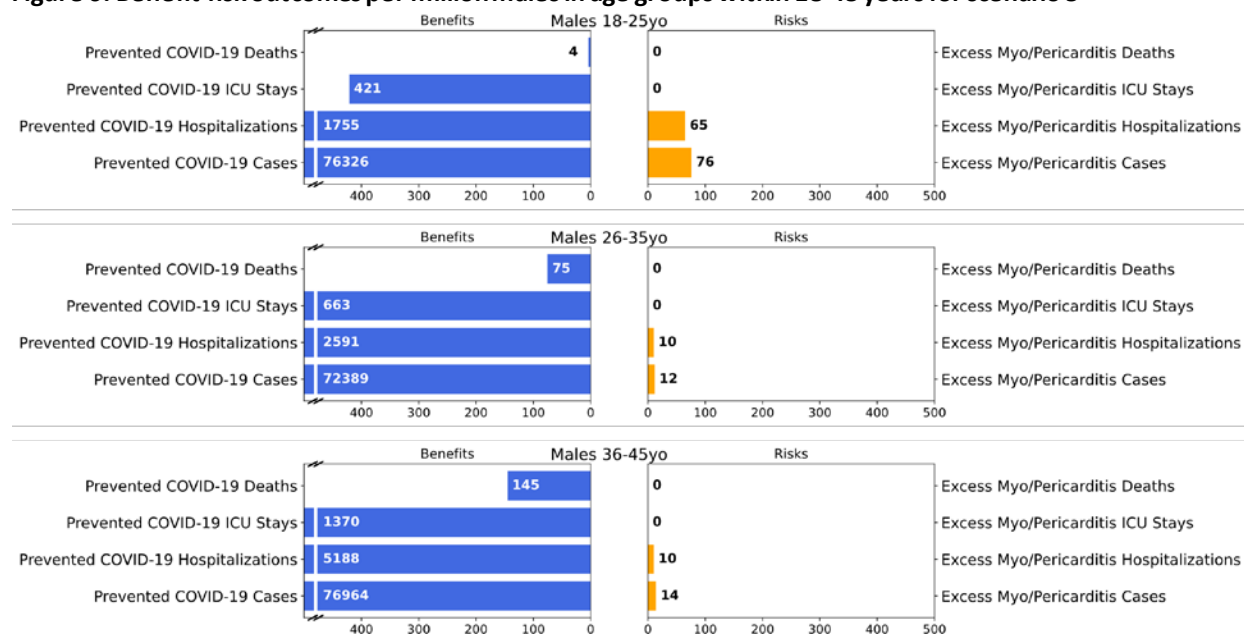
Source: Reviewer Analysis

Figure 5. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 4



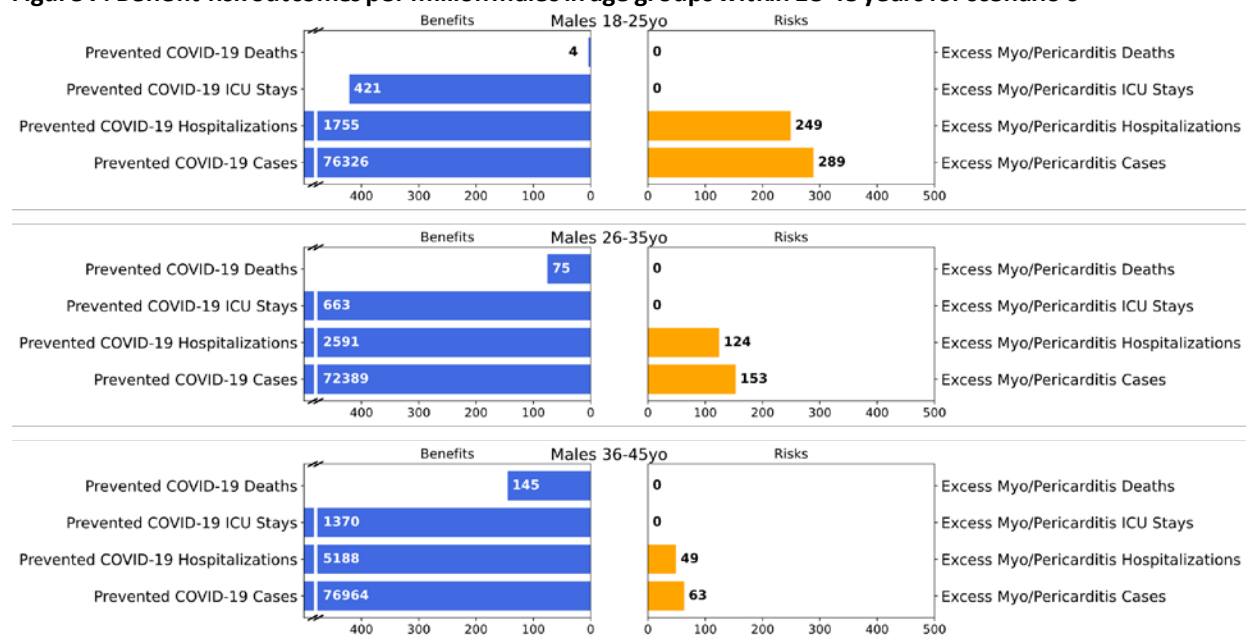
Source: Reviewer Analysis

Figure 6. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 5



Source: Reviewer Analysis

Figure 7. Benefit-risk outcomes per million males in age groups within 18-45 years for scenario 6



Source: Reviewer Analysis