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

MEMORANDUM

Date: September 13, 2021
To: Ramachandra Naik
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 125742/0: review memo for benefit-risk assessment

Review Memo on Benefit-Risk Assessment of Pfizer Vaccines for Age 16-17 yrs

Reference submission: BLA 125742/0
Reviewers: Hong Yang, Patrick Funk, and Osman Yogurtcu
Date: August 20, 2021

Contents

1. Executive Summary

FDA conducted a benefit-risk assessment to inform the review of the Biologics License Application (BLA) for use of the Pfizer-BioNTech COVID-19 mRNA vaccine (also referred to as BNT162b2) among ages 16 years and older. We assessed the benefits and risks per million individuals who are vaccinated with two complete doses of BNT162b2. The analysis was conducted for the groups stratified by combinations of sex and age (12-15, 16-17, 18-24, and 25-29 years). The model assesses the benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICUs) visits, and deaths, and the risks of vaccine-related excess myocarditis/pericarditis cases, hospitalizations, and deaths. The major sources of data include age/sex specific COVID-19 case and hospitalization incidences reported on COVID NET on July 10, 2021, the myocarditis/pericarditis case rate attributable to vaccine obtained from the OPTUM health claims database, and the vaccine related myocarditis/pericarditis deaths reported through VAERS. We constructed scenarios for both the most likely short-term moving direction of the pandemic and the worst case, which used the most conservative assumptions for all model inputs.

The most likely scenario:

We assumed vaccine protection duration of 6-months, 10x COVID-19 case incidence and 4x COVID-19 hospitalization incidence as of July 10, 70% vaccine efficacy against COVID-19 cases, 80% vaccine efficacy against hospitalization, and no vaccine-related myocarditis death. The model results indicate that, for all age/sex groups and across all model outcomes, the benefits clearly outweigh the risks. For males 16-17 years old—the group with the highest risk of myocarditis/pericarditis—the model predicts that prevented COVID cases, hospitalizations, ICUs, and deaths are 135,771, 506, 166, and 4, respectively. The excess myocarditis/pericarditis cases, associated hospitalizations, and deaths attributable to vaccine are 196, 196, and 0, respectively.

The worst-case scenario:

We used the most conservative assumptions for all the model inputs in this scenario. We assumed 6-months vaccine protection, the COVID-19 case and hospitalization incidence as of July 10, 2021, 70% vaccine efficacy against COVID-19 case, 80% vaccine efficacy against COVID-19 hospitalization, and 0.002% myocarditis/pericarditis death rate.

For males 16-17 years old, the model predicts that prevented COVID cases, hospitalizations, ICUs, and deaths are 13,577, 127, 41, and 1, respectively. The excess myocarditis/pericarditis cases and associated hospitalizations and deaths attributable to the vaccine are 196, 196, and 0, respectively. Even with the conservative assumption on the myocarditis/pericarditis death rate, the model predicted 0 deaths associated with myocarditis/pericarditis. The model predicted a higher number of myocarditis/pericarditis related hospitalizations compared to prevented COVID-19 hospitalizations. However, considering the differential clinical outcomes of the hospitalization from two difference causes, we consider the benefits of the vaccine still outweigh the risks for the highest risk group, males 16-17 years old, under this worst-case scenario.

Our results demonstrate that the benefits of BNT162b2 clearly outweigh its risks for all age and sex

groups we analyzed. However, the benefit-risk estimates are highly uncertain due to the dynamics of pandemics. Other major uncertainties in benefits are vaccine efficacy and duration of protection in the face of emerging virus variants. The major risk uncertainty is the data on vaccine-related myocarditis cases and deaths.

2. Background and regulatory questions

The Pfizer-BioNTech COVID-19 mRNA vaccine (also referred to as BNT162b2) has been recommended for persons 12 years of age and older in the United States under FDA's Emergency Use Authorization (EUA). Since authorization of mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna), real-world evidence has indicated the vaccines are effective in preventing COVID-19 cases and related hospitalizations and deaths. However, increased cases of myocarditis and pericarditis have been reported in the United States associated with mRNA COVID-19 vaccination, particularly in adolescents and young adults (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 BNT162b2 vaccines among ages 16 years and older. The regulatory question to be answered is whether the benefits of vaccination outweigh the risks among various age and sex subgroups being considered for approved use of the vaccine (and in particular, males, age 16-17 years old), considering the potentially elevated myocarditis/pericarditis risk after vaccination suggested 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 complete doses of BNT162b2. The analysis was conducted for the groups stratified by combinations of sex and age (12-15, 16-17, 18-24, and 25-29 years). The model assesses the benefits of vaccine-preventable COVID-19 cases, hospitalizations, intensive care unit (ICUs) visits and deaths, and the risks of vaccine related excess myocarditis/pericarditis cases, hospitalizations, and deaths (Figure 1). The key model inputs include duration of vaccine protection, vaccine efficacy against COVID-19 cases and hospitalizations, age/sex specific COVID-19 case and hospitalization incidence rates, age/sex specific vaccine-attributable myocarditis case rate, and myocarditis death rate (Table 1). To evaluate the impact of uncertainty of these key model inputs on the benefits and risks, low and high values of these model inputs are used for sensitivity analysis.

Our model generates benefit-risk outcomes for seven scenarios (Table 2 and Supplement Table S1) with different combinations of the input values. The three most important scenarios are presented in the main body of this report: Scenario 1, a base scenario using the COVID-19 incidence on July 10; Scenario 2, the most likely scenario; and Scenario 3, the worst-case scenario. Other scenarios are summarized in the supplementary materials of the report.

3.2. Benefits

3.2.1. Calculation of benefits

Our benefit-risk model has four benefit endpoints (Figure 1): preventable COVID-19 cases, hospitalizations, Intensive Care Unit admissions (ICUs), and deaths. To calculate the potential COVID-19 cases preventable by vaccine (C_P), we use Equation 1

$$C_P = \frac{I_C}{P_U} L\ D\ E_C$$	Eq. 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 second vaccine doses administered (fixed at 1 million), and E is the vaccine efficacy against COVID-19 cases. 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 vaccine efficacy against hospitalization (E_H).

$$H_P = \frac{I_H}{P_u} L\ D\ E_H$$	Eq. 2

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 perform these calculations over the individual age and sex groups and combined male and female groups.

3.2.2. Data and assumptions

3.2.2.1. Duration of vaccine protection

We assume the vaccine has at the least 6 months of protection since this is the period examined by Pfizer in their ongoing study (Thomas *et al.,* 2021). The model assesses the benefits for a period of 6 months post 2nd dose of vaccination. For the sensitivity analysis in the supplement, we use a protection period of 12 months as an upper bound. For simplicity, the model does not account for the benefits of partial vaccination (protection between the first and second dose) or the second order benefits of reducing the risk of transmission of COVID-19.

3.2.2.2. Incidences of COVID-19 case, hospitalization, ICU, and death

We assume the incidence rates of COVID-19 case and hospitalization remain constant over the assessment period (next 6 or 12 months). The incidence rates of COVID-19 cases as of week July 10 are obtained from COVID NET for all sex/age groups. Four-week averages of incidence (6/26-7/10) are used due to the variability in rates given

the small numbers of hospitalizations per age/sex groups. The percent of hospitalizations going to ICU and the percent of hospitalized patients who die are estimated based on cumulative rates of hospitalizations, ICUs, and deaths for each sex/age groups reported on COVID NET since March 2020. All the incidence data for these factors are summarized in Table 3. Comparing the incidence from the 2nd week of August with those reported at the lowest point in the summer, we find a 10-time incidence and 4-time hospitalization increase over a 6-week period. Considering the great uncertainty in COVID-19 incidence during the pandemic, we conduct a sensitivity analysis using a 10-times multiplier for case incidence and 4-times multiplier for hospitalization incidence in the sensitivity analysis. The multipliers were derived from the public data in COVID data tracker and COVID NET, respectively, to project the increase in COVID-19 infections/hospitalizations.

3.2.2.3. Unvaccinated population

We estimate the unvaccinated population among each age/sex groups using US census data and "Age groups of people with at least one dose" from COVID data tracker. Data for Texas is not contained in COVID data tracker so we impute proportional vaccination counts based on population averages from the census data. The incidence of COVID-19 cases and hospitalization, described in section 2.2.2.2 "Incidences of COVID-19 case, hospitalization, ICU and death," are converted into the incidence of COVID-19 cases and hospitalizations among unvaccinated individuals of each age/sex group.

3.2.2.4. Vaccine efficacy

We use vaccine efficacy rates of protection against COVID-19 cases of 70% and 90% and vaccine efficacy rates of protection against COVID-19 hospitalizations of 80% and 90% in different scenarios. The high efficacy of 90% represents the lower bound of the confidence interval from the clinical trial data (Oliver *et al*. 2020). The low efficacy of 70% for cases and 80% for hospitalization represents a conservative efficacy rate given the uncertainty of the vaccine's protection against the Delta variant. Early studies on the vaccine's efficacy against cases from the Delta variant suggest 79% in Scotland (Sheikh *et al*., 2021), 87% in Canada (Nasreen *et al*., 2021), and 88% in India (Lopez Bernal *et al*., 2021). To remain conservative in the face of uncertainty in this rapidly changing pandemic, we use a lower bound of vaccine efficacy from these early reports.

3.3. Risks

3.3.1. Calculation of risks

Our benefit-risk model has three risk endpoints (Figure 1): excess myocarditis/pericarditis cases, hospitalizations, and deaths. Estimates of excess cases of myocarditis/pericarditis are calculated by subtracting the background rate of myocarditis in Optum's sample population from 2019 from

the rate of myocarditis in the study window from 12/10/2020 – 07/10/2021. We use Equation 3 to calculate excess cases of myocarditis/pericarditis (M_{Exc}) per one million fully vaccinated individuals.

$$M_{Exc} = \left(M_{Obs1} - M_{Exp1} + M_{Obs2} - M_{Exp2}\right) * F$$	Eq. 3

M_{obs1} and M_{Exp1} are observed and expected myocarditis/pericarditis case rates post dose 1, M_{obs2} and M_{Exp2} are corresponding case rates post dose 2, and F is a multiplier for unit conversion. Expected myocarditis/pericarditis case rates are the predicted background case rate unassociated with vaccine.

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

3.3.2. Data and assumptions

3.3.2.1. Myocarditis/pericarditis attributable to vaccine

We use myocarditis/pericarditis reports data provided by Acumen LLC that are derived from the Optum health claims database (Table 5). Acumen reports cases of myocarditis in 7-, 21-, and 42-day risk windows from each vaccine dose. Our analysis focuses on the 7-day risk window where most cases are found for all groups. The database contains rates of expected ($M_{Exp\ 1}$ and $M_{Exp\ 2}$) and observed (M_{Obs1} and M_{Obs2}) myocarditis/pericarditis in 100k person-years for the 1st and 2nd dose of the vaccine. Converting from 100k person-years in the risk window to one million vaccinated individuals' daily risk, we multiply the rates by a factor F = (7*10)/365. This factor is used to convert the rate per 100k person years to an expected case count for one million full vaccinations assuming a 7-day risk window. Confidence intervals for the myocarditis cases are calculated using the chi-square method for Poisson distribution of rare events (Garwood, 1936).

3.3.2.2. Myocarditis/pericarditis hospitalization and death rate

Almost all adolescent and young adult patients with suspected myocarditis/pericarditis cases are hospitalized and monitored for the condition. In this model, we assume all myocarditis/pericarditis cases are hospitalized, but Vaccine Adverse Events Reporting System (VAERS) data show median stay lengths of one day for observation.

A total of 1,061 myocarditis cases among US <30 years old after vaccination with BNT162b2 are reported through VAERS. Among them, two deaths are reported. The search terms used for query and the narratives for two deaths who had vaccination with BNT162b2 are included in the supplement. Review of the available data by FDA

and CDC indicates that both cases are unlikely to be related to the vaccine. In our model, we assume the death rate related to vaccine is most likely to be zero in the base case and most likely scenarios (Scenario 1 and 2). However, we use 2/1,061 as the death rate for the worst-case scenario (Scenario 3) to account for the very unlikely outcome of these two deaths being attributed to vaccine related myocarditis/pericarditis.

4. Results

This section summarizes the results for three major model scenarios.

4.1. Scenario 1: Base case

Our model scenarios start with the base case that is using the most recent available incidence data on July 10, 2021 and assume a 6-month vaccine protection period, 90% vaccine efficacy against both COVID-19 case and hospitalization, and zero myocarditis/pericarditis death rate.

Figures 2, 3, and 4 summarize the results for analyses of combined male/female, male only, and female only, respectively. The results indicate that benefit-risk is more favorable for male and female combined, female only, and male >18 years old. The model predicted far more prevented COVID-19 cases compared to excess myocarditis/pericarditis for male 12-15 and 16-17 years old, but the model predicted 142 prevented COVID-19 hospitalizations vs. 196 myocarditis/pericarditis hospitalizations for male age 16-17 years old and 122 prevented COVID-19 hospitalizations vs. 179 myocarditis/pericarditis hospitalizations for male 12-15 years old. However, hospitalizations associated with COVID-19 have more severe clinical outcomes than those associated with myocarditis/pericarditis. For this reason, we consider that the benefits of the vaccine outweigh the risks in this scenario even for male age 12-15 and 16-17 years old. See Table 5 for details and the benefit-risk results for 16-17 year olds.

4.2. Scenario 2: Most likely scenario

We constructed a scenario that most likely represents the short-term moving direction of the pandemic. We assume 6-month vaccine protection, and 10X higher COVID-19 case incidence and 4X higher COVID-19 hospitalizations incidence compared to the incidence on July 10. We also assume lower vaccine efficacy (70% against COVID-19 case, 80% against hospitalization) against newly emerging virus variants such as Delta strain. We assumed zero myocarditis death rate based on our best knowledge on the vaccine related myocarditis.

Figures 5, 6, and 7 summarize the results for analyses of combined male/female, male only, and female only, respectively. For all age/sex groups and across all attributes, the benefits clearly outweigh the risks in this scenario. See Table 5 for details and benefit-risk results for 16-17 year olds.

4.3. Scenario 3: Worst case scenario

We also constructed the worst-case scenario using the most conservative assumptions for all the model inputs. We assumed 6-month vaccine protection, the COVID-19 incidence as of July 10, 2021, 70% vaccine efficacy against COVID-19 case, 80% vaccine efficacy against COVID-19 hospitalization, and 0.002% (2/1,061) myocarditis/pericarditis death rate.

Figures 8, 9, and 10 summarize the results for analyses of combined male/female, male only, and female only, respectively. Even with the conservative assumption on

myocarditis/pericarditis death rate, the model predicted 0 deaths associated with myocarditis/pericarditis compared to 1 prevented COVID-19 death for both male 12-15 and 16-17 year old groups. The model predicted 127 prevented COVID-19 hospitalizations vs 196 myocarditis/pericarditis hospitalizations for male age 16-17 years old and 109 prevented COVID-19 hospitalizations vs 179 myocarditis/pericarditis hospitalizations for male 12-15 years old. Considering the differential clinical outcomes of the hospitalization from two different causes, we consider the benefits of the vaccine still outweigh the risks in this "worst case scenario". See Table 5 for details and the benefit-risk results for 16-17 year olds.

5. Conclusions and discussion

Our results demonstrate that the benefits of BNT162b2 clearly outweigh its risks for all age and sex groups we analyzed. Under the base case scenario and the worst-case scenario (Scenario 1 and 3), we predicted a higher number of myocarditis hospitalizations than the COVID-19 hospitalizations among male 16-17 years old; however, considering the differential clinical implications of COVID-19 and myocarditis hospitalization, we consider the benefits of the vaccine still outweigh its risks. Moreover, under all other scenarios including the most likely (Scenario 2), our model predicted that preventable COVID-19 cases, hospitalizations, and deaths exceed the myocarditis cases and related hospitalizations and deaths for all age and sex groups.

We note that COVID-19 incidence highly influences the predicted benefits of the vaccine. If the disease incidence is higher, the benefits of the vaccine will be greater, and vice versa. Therefore, the benefit-risk conclusion may change if the COVID-19 incidence rate becomes very low in the future. Also, "the worst-case scenario" presented here is the worst only among the modelled scenarios. Scenarios worse than Scenario 3 could occur if the data fall outside the ranges of model inputs we used, such as lower COVID-19 incidence than those reported on July 10, lower vaccine effectiveness against COVID-19 cases (<70%) and against hospitalizations (<80%), and shorter vaccine protection duration (<6 months).

6. Limitations

- (BENEFIT) 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. Additionally, estimated benefits of the vaccine would decrease if the vaccine becomes less effective against novel variants of COVID-19. The durability of vaccine protection is another source of uncertainty for the model. Any significant waning of vaccine-induced immunity before 6 or 12 months would reduce the benefit of the vaccine.

- (RISK) There is uncertainty in the myocarditis case and death rates attributable to the vaccine. In the US, two deaths among those less than 30 years old occurred following the administration of BNT162b2 and were evaluated by FDA and CDC. Based on the review of the available clinical information, the causes of death for both cases are not thought to be related to vaccination. To estimate myocarditis/pericarditis risk attributable to the vaccine, health claims data are used, which have inherent limitations such as small sample sizes for these rare outcomes. The cases have not been validated by medical chart review. The crude myocarditis rate in our model was adjusted using myocarditis 2019 background rate, which did not account for COVID-19 infection related risk of myocarditis/pericarditis and may lead to overestimating the risk attributed to the vaccine.

- (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 consider the potential long-term health impacts of COVID-19 or myocarditis. Also, it does not include secondary benefits and risks, such as any potential impact on the public trust in COVID-19 vaccines and the benefit of the vaccine in reducing the viral transmission in the population. In this analysis, we did not investigate the benefits and risks of subpopulations with comorbidity due to limited information. The benefit-risk profile could be different depending on the individual's health condition.

7. Acknowledgements

We thank J. Rosser Matthews, Ph.D., and Katherine Scott, M.D., for editing this Benefit-Risk review memo.

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Table 1. Low and high values model input parameters considered in our sensitivity analysis

Model inputs	Low	High
Vaccine protection period	6 months	12 months
Vaccine efficacy against cases	70%	90%
Vaccine efficacy against hospitalization	80%	90%
COVID-19 case incidence rate	July 10 rate	10X July 10 rate
COVID-19 hospitalization case incidence rate	July 10 rate	4X July 10 rate
Myocarditis death rate	0%	0.002%

Table 2. The three main model scenarios with different combinations of model input values that are shown on Table 1

Scenario	Protection period	Efficacy against cases	Efficacy against hospitalization	COVID-19 case incidence	COVID-19 hospitalization incidence	Vaccine attributable myocarditis death rate
Scenario 1	Low	High	High	Low	Low	Low
Scenario 2 (Most Likely)	Low	Low	Low	High	High	Low
Scenario 3 (Worst Case)	Low	Low	Low	Low	Low	High

Table 3. Vaccine coverage and COVID incidences by sex and age groups

Sex	Age group	Population[1]	Vaccinated population[2]	COVID-19 cases/100k persons[3]	Hospitalizations/100k persons[3]	Percent of hospitalized going to ICU[3]	Percent of hospitalized who die[3]
Female	12-15	8,183,216	2,886,252	37.3	0.671	23.9	0
	16-17	4,119,686	1,985,672	47.9	1.593	19.5	0.7
	18-24	14,923,948	8,033,040	64.6	2.025	8.1	1
	25-29	11,428,122	5,918,524	68.6	2.45	5.9	0.3
Male	12-15	8,535,307	2,815,693	33.1	0.35	31.8	0.9
	16-17	4,300,731	1,826,299	42.9	0.35	32.7	0.7
	18-24	15,633,953	7,217,945	53.3	0.8	22.2	0.6
	25-29	12,036,982	5,592,473	57.8	0.875	22.7	1.5

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

Table 4. Estimated excess number of myocarditis/pericarditis cases for 1 million fully vaccinated individuals with Pfizer BNT162b2 by age and sex. 95% confidence intervals for the rates are shown in brackets

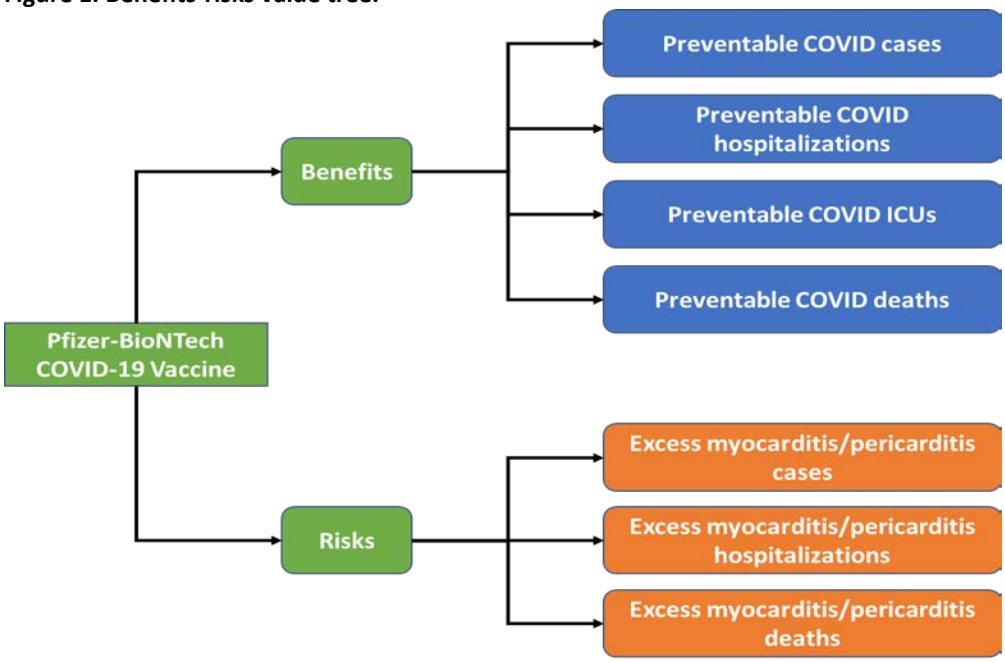
Sex	Age (years)	Rate of excess myocarditis/pericarditis per 1 million fully vaccinated and 95% confidence intervals
Male	12-15	179 [38, 332]
	16-17	196 [36, 424]
	18-25	131 [27, 224]
	26-35	49 [0, 123]
Female	12-15	32 [0, 235]
	16-17	36 [0, 298]
	18-25	57 [9, 147]
	26-35	2 [0, 80]

Source: Optum Database pre-adjudicated claims 12/11/2020 – 07/10/2021

Table 5. Model predicted benefit-risk outcomes of Scenarios 1-3 for the 16-17-year-old groups

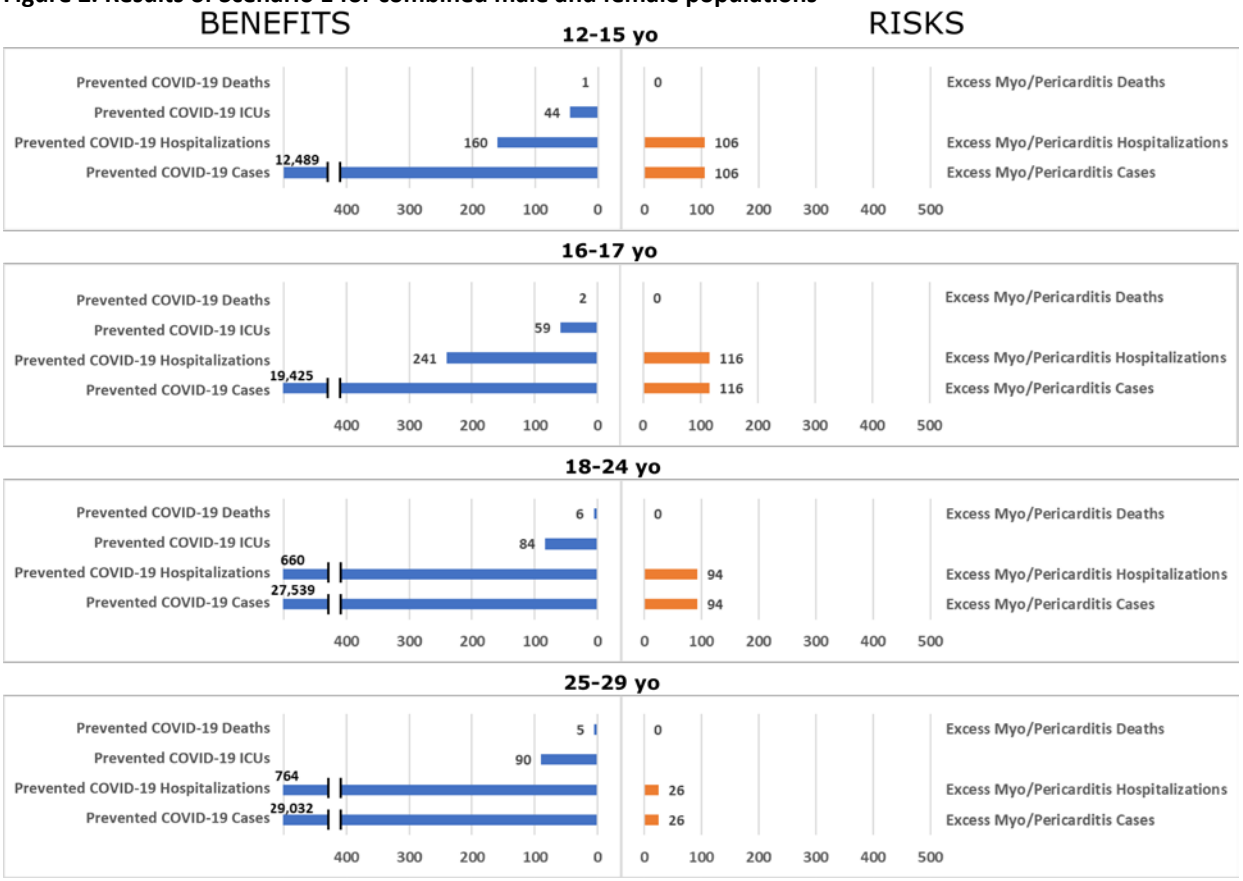
	Benefits				Risks		
Scenario	Prevented COVID-19 Cases	Prevented COVID-19 Hospitalizations	Prevented COVID-19 ICUs	Prevented COVID-19 Deaths	Excess Myocarditis Cases	Excess Myocarditis Hospitalizations	Excess Myocarditis Deaths
Males & Females							
Scenario 1	19,425	241	59	2	116	116	0
Scenario 2	151,080	855	210	6	116	116	0
Scenario 3	15,108	214	52	1	116	116	0
Males only							
Scenario 1	17,456	142	47	1	196	196	0
Scenario 2	135,771	506	166	4	196	196	0
Scenario 3	13,577	127	41	1	196	196	0
Females only							
Scenario 1	21,657	350	68	2	36	36	0
Scenario 2	168,443	1245	243	9	36	36	0
Scenario 3	16,844	311	61	2	36	36	0

Figure 1. Benefits-risks value tree.



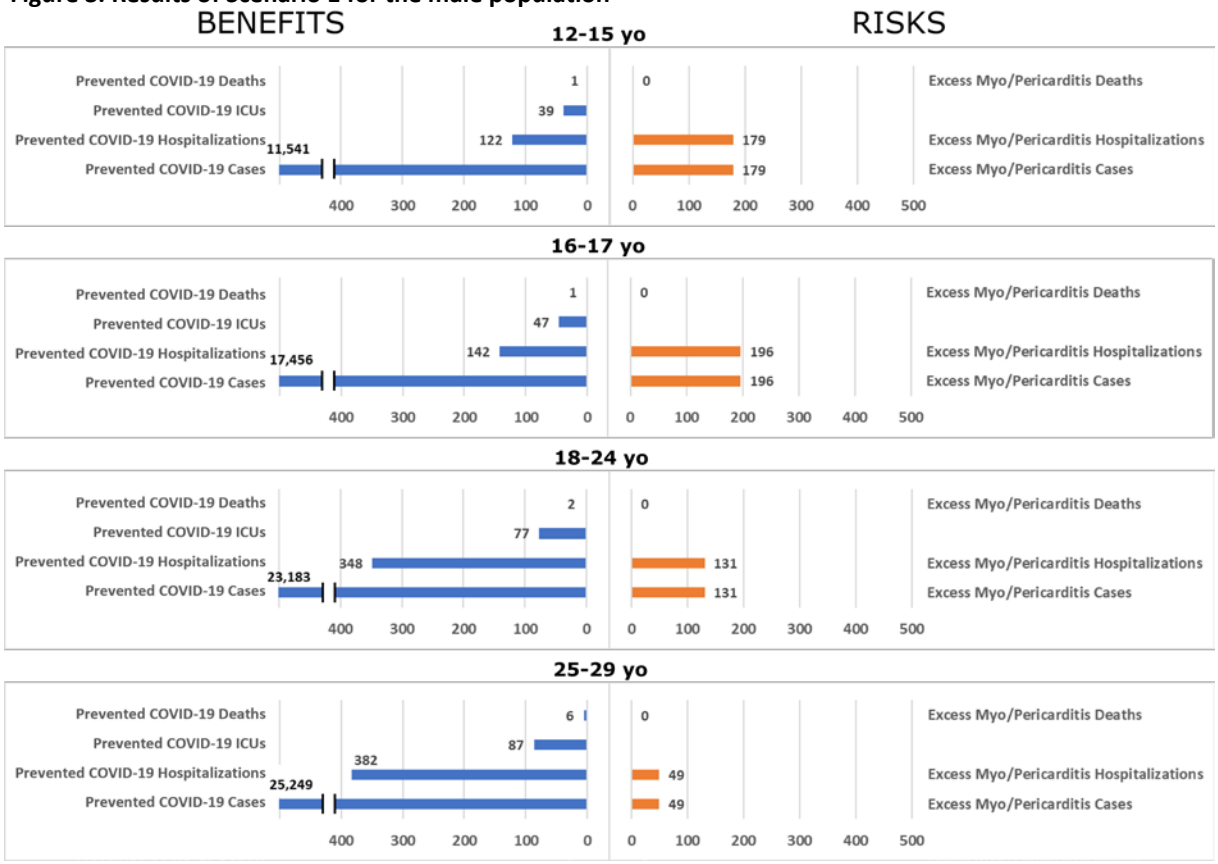
Source : Reviewer Analysis

Figure 2. Results of Scenario 1 for combined male and female populations



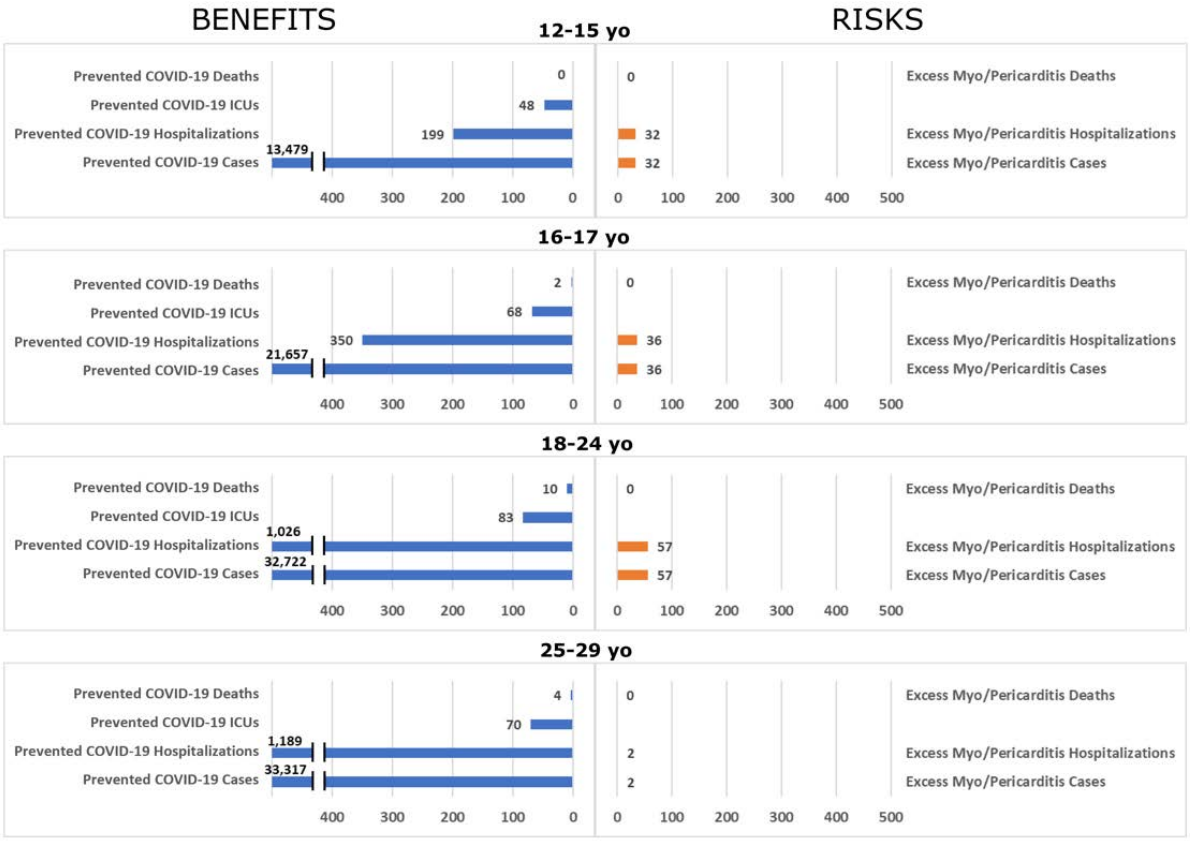
Source: Reviewer Analysis

Figure 3. Results of Scenario 1 for the male population



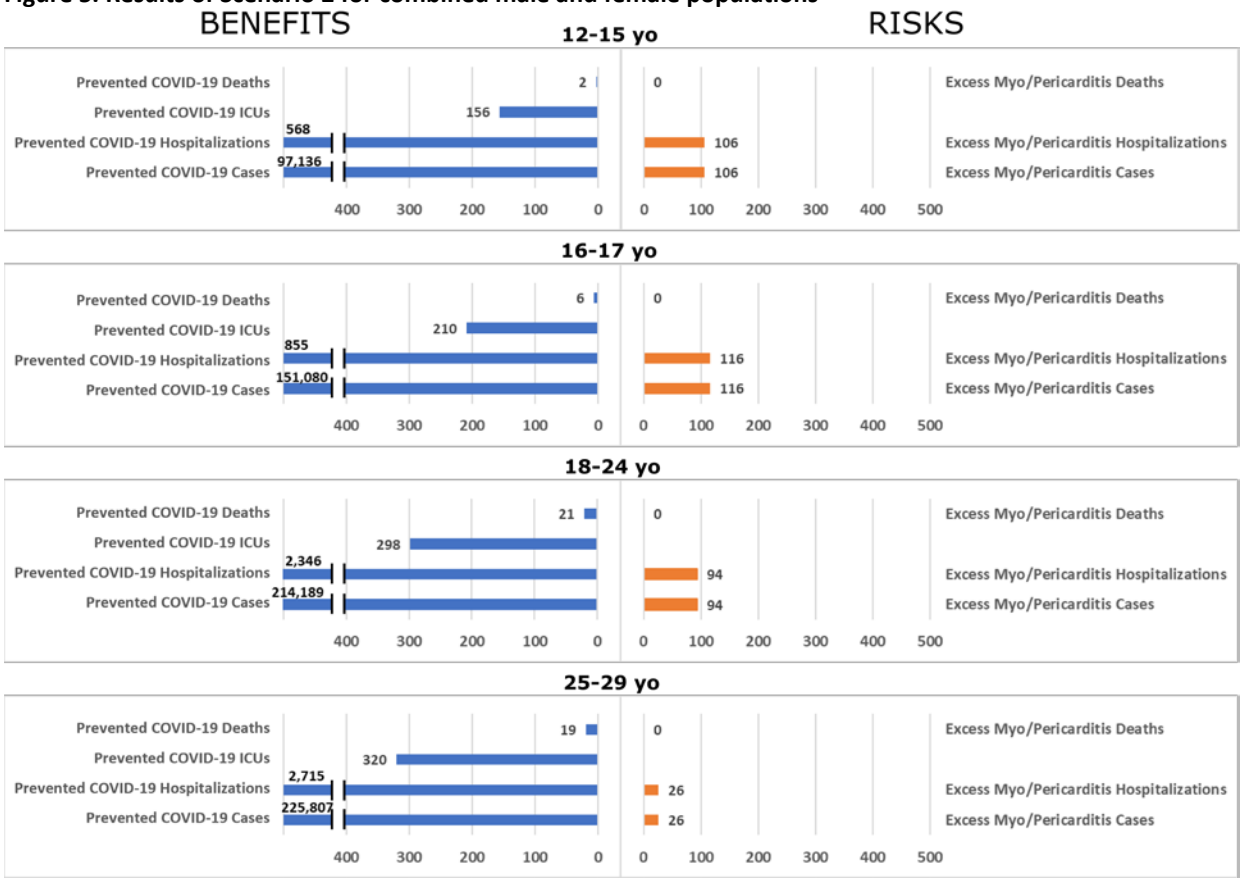
Source : Reviewer Analysis

Figure 4. Results of Scenario 1 for the female population



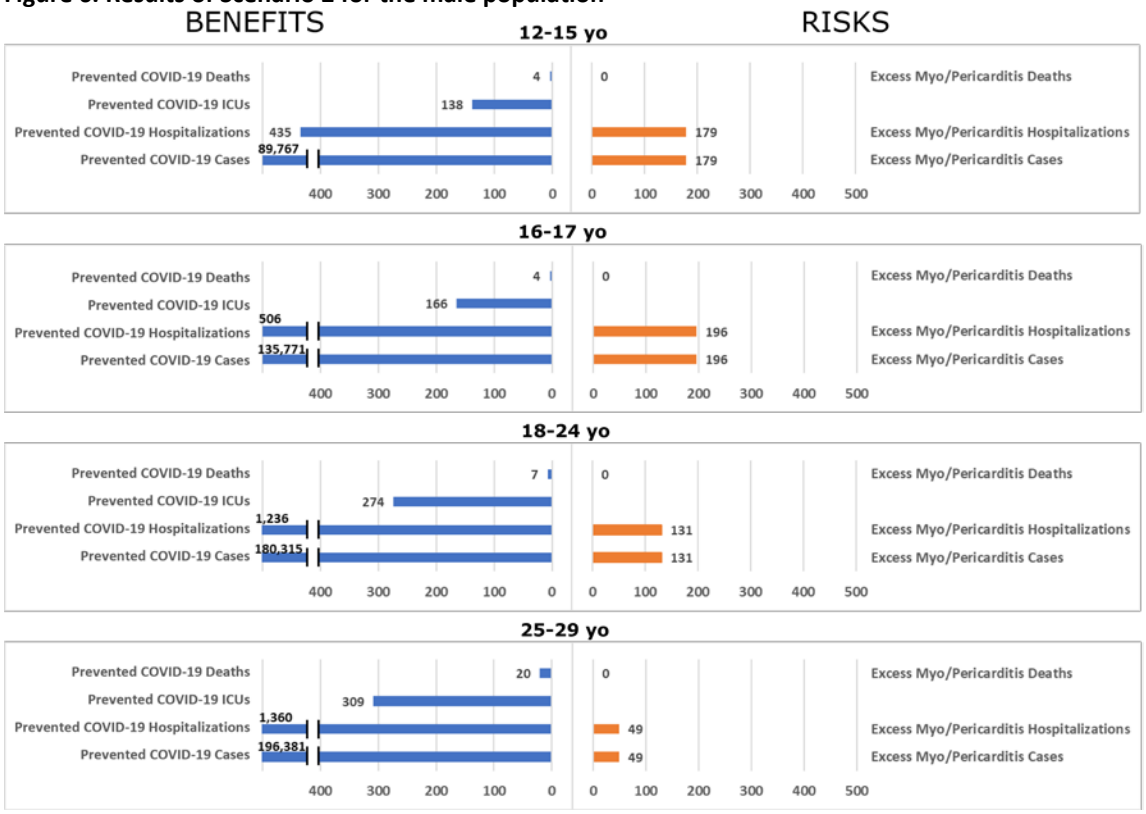
Source : Reviewer Analysis

Figure 5. Results of Scenario 2 for combined male and female populations



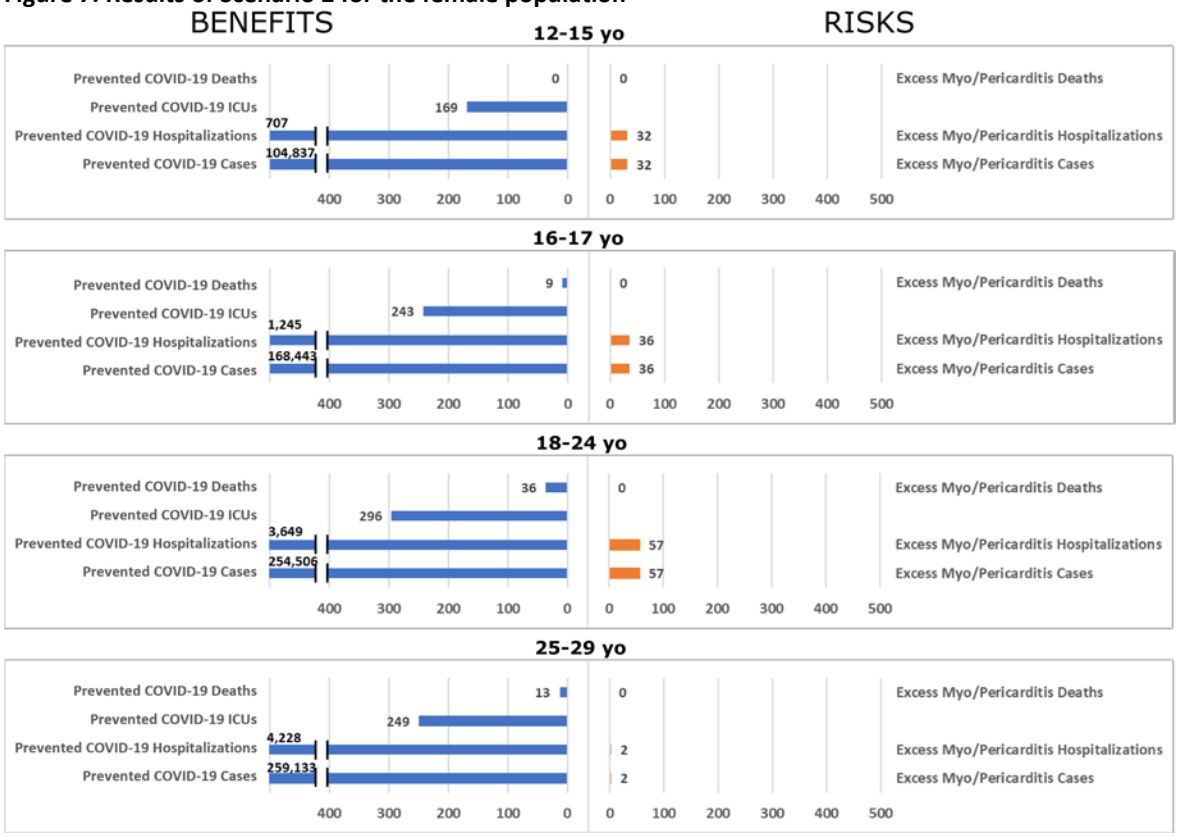
Source : Reviewer Analysis

Figure 6. Results of Scenario 2 for the male population



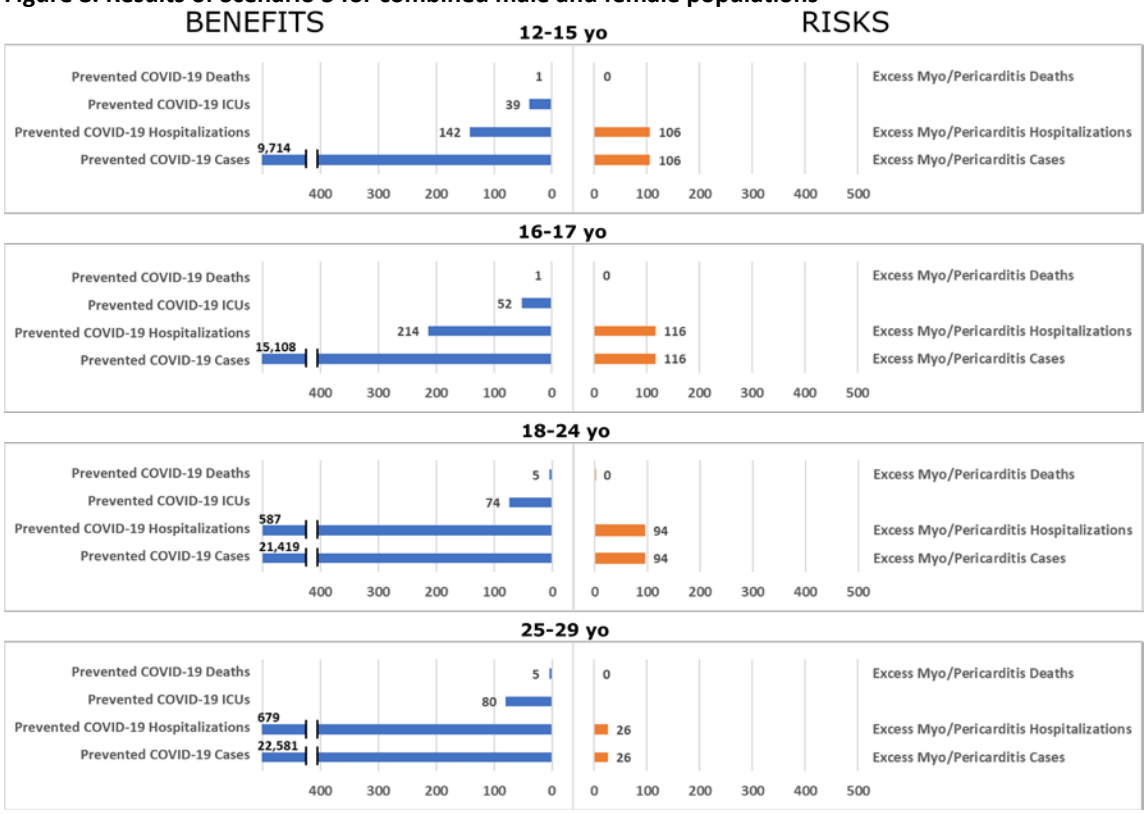
Source : Reviewer Analysis

Figure 7. Results of Scenario 2 for the female population



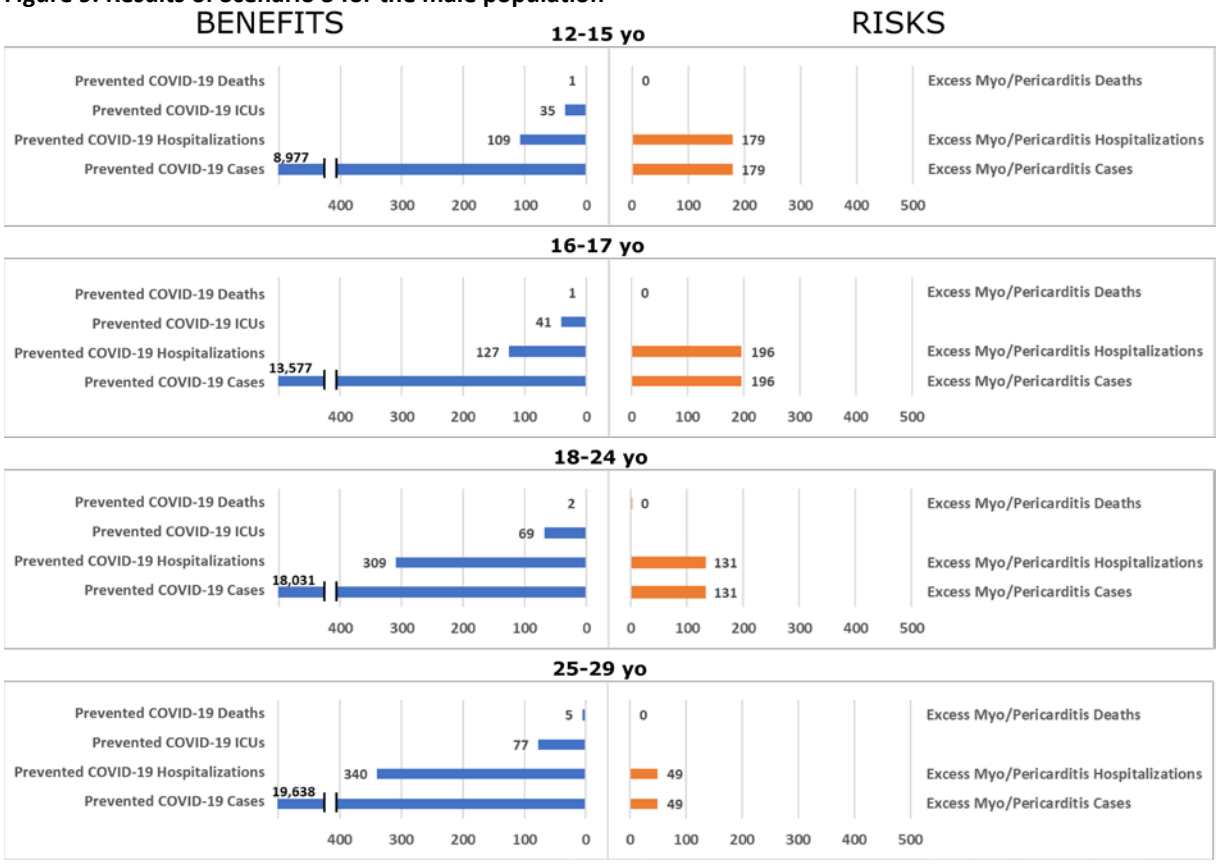
Source : Reviewer Analysis

Figure 8. Results of Scenario 3 for combined male and female populations



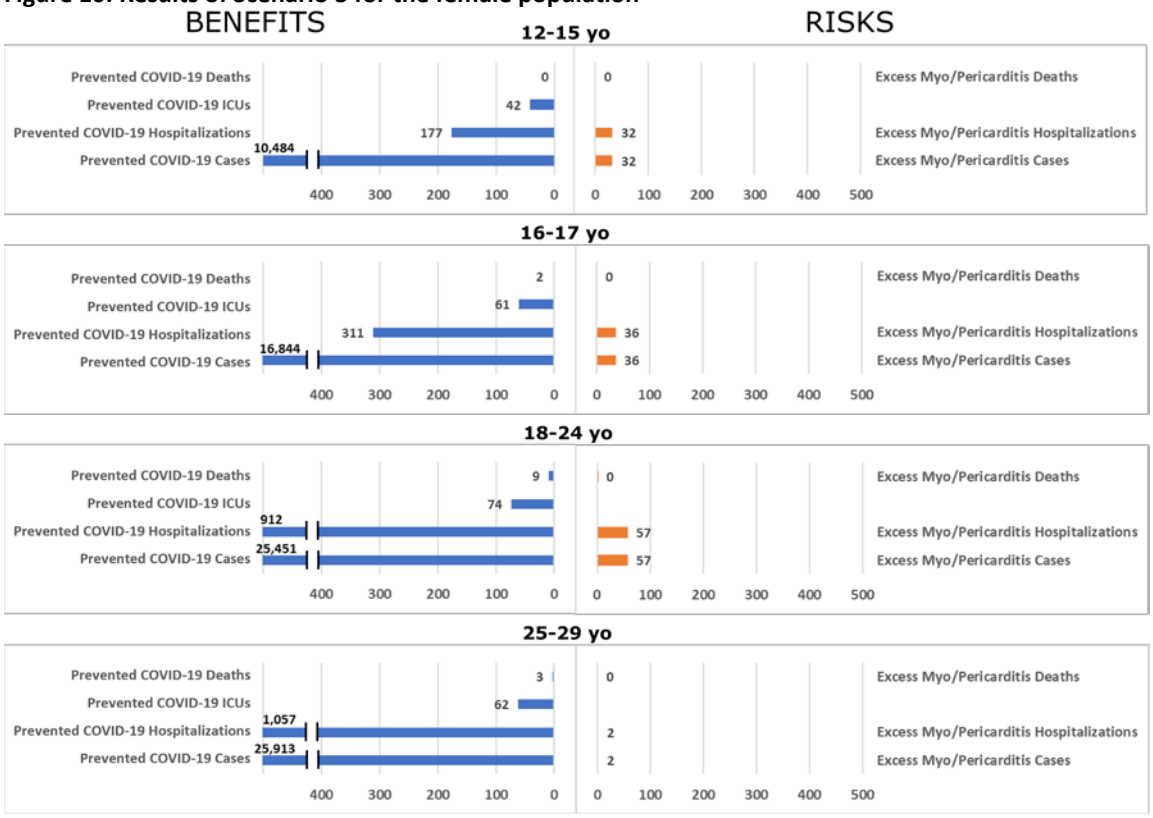
Source : Reviewer Analysis

Figure 9. Results of Scenario 3 for the male population



Source : Reviewer Analysis

Figure 10. Results of Scenario 3 for the female population



Source : Reviewer Analysis

Supplementary Materials

Text S1. Narratives of Myocarditis Death cases and Terms Used in VAERS Search

Table S1. Additional model scenarios with different combinations of model input values that are shown on Table 1 in the main text.

Figure S1: Results of Scenario 4 for combined male and female populations.
Figure S2: Results of Scenario 4 for the male population.
Figure S3: Results of Scenario 4 for the female population.

Figure S4: Results of Scenario 5 for combined male and female populations.
Figure S5: Results of Scenario 5 for the male population.
Figure S6: Results of Scenario 5 for the female population.

Figure S7: Results of Scenario 6 for combined male and female populations.
Figure S8: Results of Scenario 6 for the male population.
Figure S9: Results of Scenario 6 for the female population.

Figure S10: Results of Scenario 6 for combined male and female populations.
Figure S11: Results of Scenario 6 for the male population.
Figure S12: Results of Scenario 6 for the female population.

Text S1. Narratives of Myocarditis Death cases and Terms Used in VAERS Search

Narratives of Myocarditis Death Cases

Pfizer BioNTech Vaccine

VAERS ID 1406840: 13 years old male with attention deficit hyperactivity disorder and developmental coordination disorder experienced flu-like symptoms for (b)(6) days and then was found deceased; onset of symptoms 1-day post-vaccination. The preliminary autopsy report revealed cardiomegaly with biventricular dilatation, bilateral serous pulmonary effusions and serous pericardial effusion, marked pulmonary edema and congestion, and moderate degree of diffuse cerebral edema. COVID-19 and influenza A/B tests were negative. Additional testing on autopsy found this patient died of sepsis due Clostridium septicum.

VAERS ID 1486852: 21 years old female who experienced fever, confusion, seizure, cardiac arrest (b)(6) days post vaccination. Autopsy revealed histology with extensive lymphocytic/plasmocytic myocarditis with rare eosinophils no granuloma. Additional review by pathologists at CDC found the patient had severe myocarditis with intravascular leukocytosis suggestive of sepsis.

Reviewer Comment: Both of these death cases had alternate etiologies likely related to non-COVID-19 infections and were not attributed to vaccine.

VAERS Search Terms

Atypical mycobacterium pericarditis, Autoimmune myocarditis, Autoimmune pericarditis, Bacterial pericarditis, Coxsackie myocarditis, Coxsackie pericarditis, Cytomegalovirus myocarditis, Cytomegalovirus pericarditis, Enterovirus myocarditis, Eosinophilic myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Myocarditis, Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis post infection, Myocarditis septic, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pericarditis helminthic, Pericarditis infective, Pericarditis mycoplasmal, Pleuropericarditis, Purulent pericarditis, Viral myocarditis, Viral pericarditis.

Table S1. Additional model scenarios with different combinations of model input values that are shown on Table 1 in the main text.

Scenario	Protection period	Efficacy against cases	Efficacy against hospitalization	COVID-19 case incidence	COVID-19 hospitalization incidence	Vaccine attributable myocarditis death rate
4	Low	High	High	High	High	Low
5	High	High	High	Low	Low	Low
6	Low	Low	Low	Low	Low	Low
7	Low	Low	Low	High	High	High

Note: Additional scenarios are used to examine the impact of specific changes to model inputs.

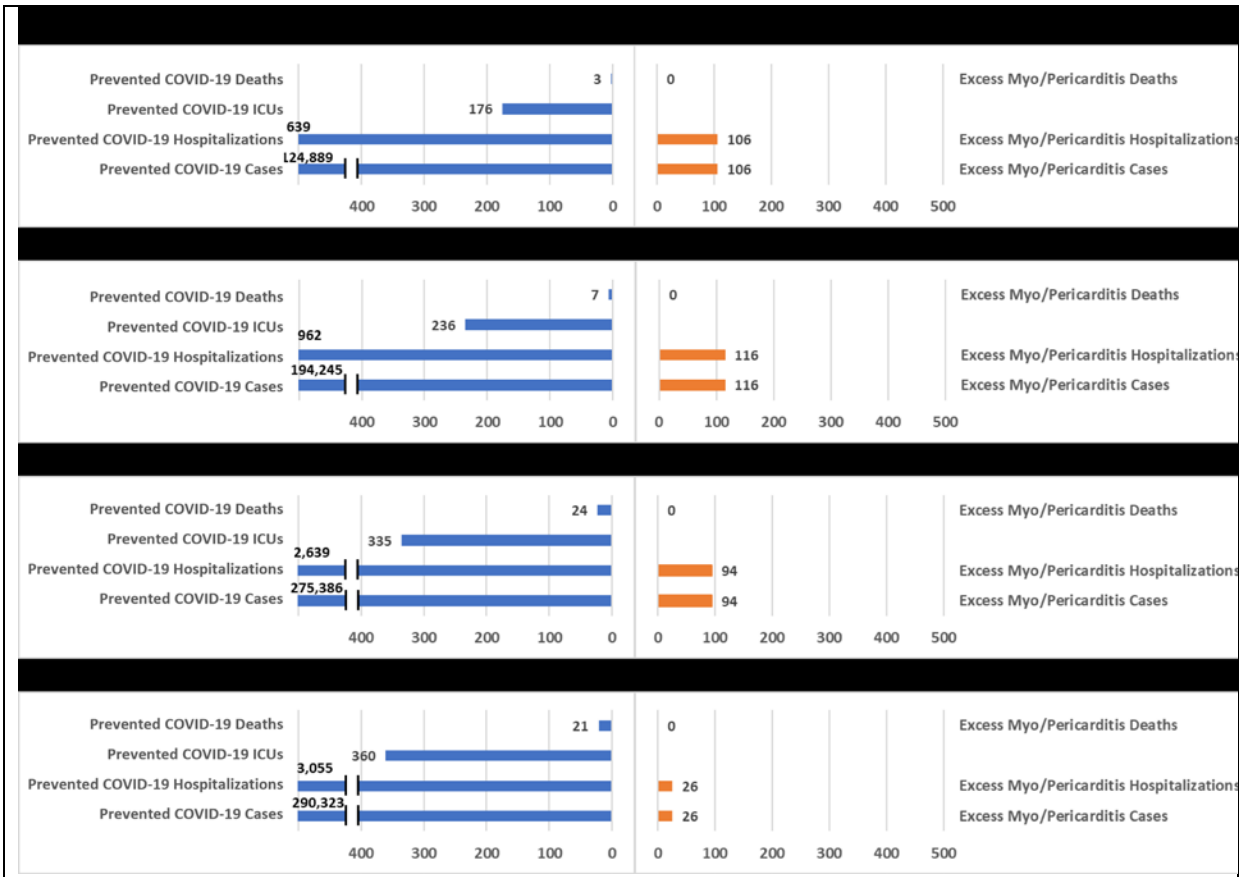


Figure S1: Results of Scenario 4 for combined male and female populations

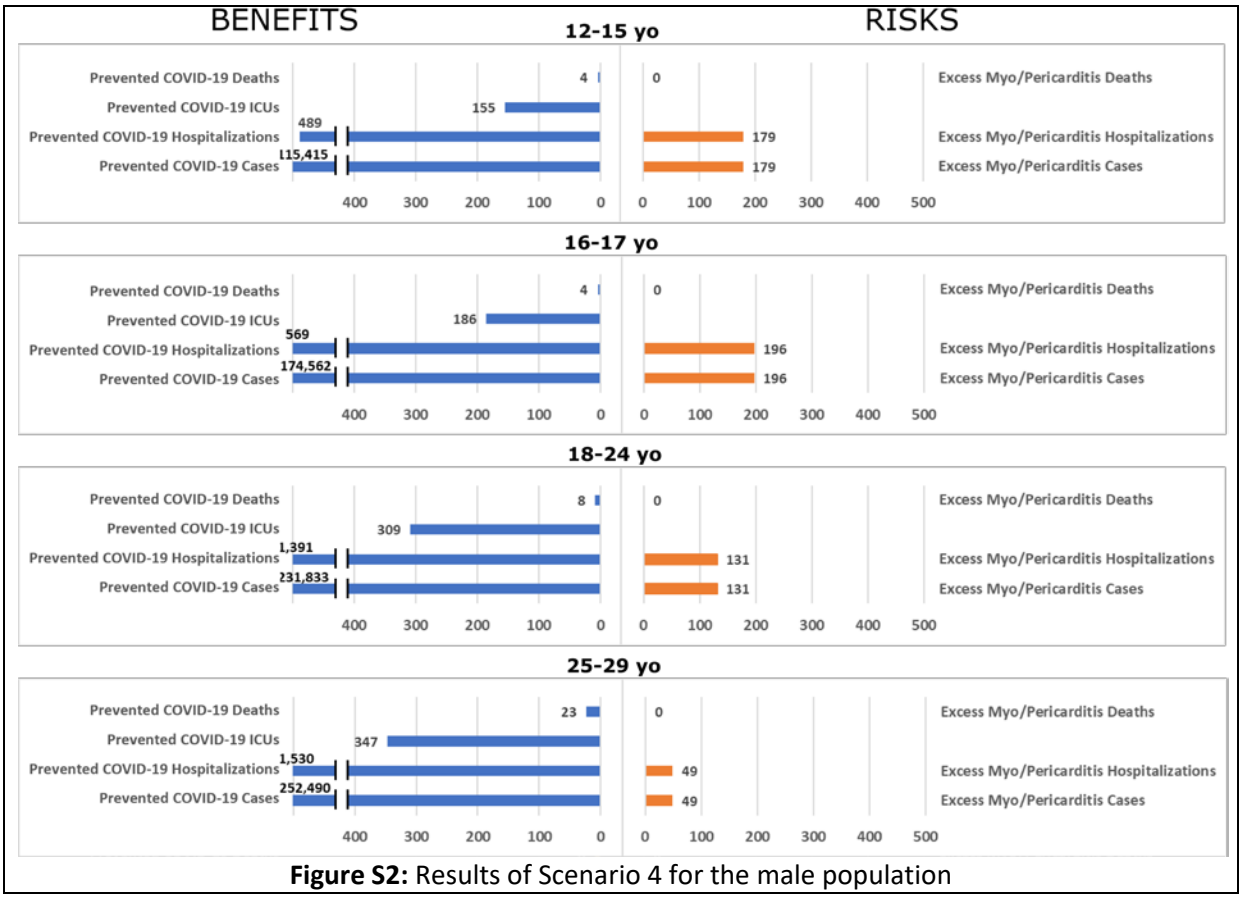


Figure S2: Results of Scenario 4 for the male population

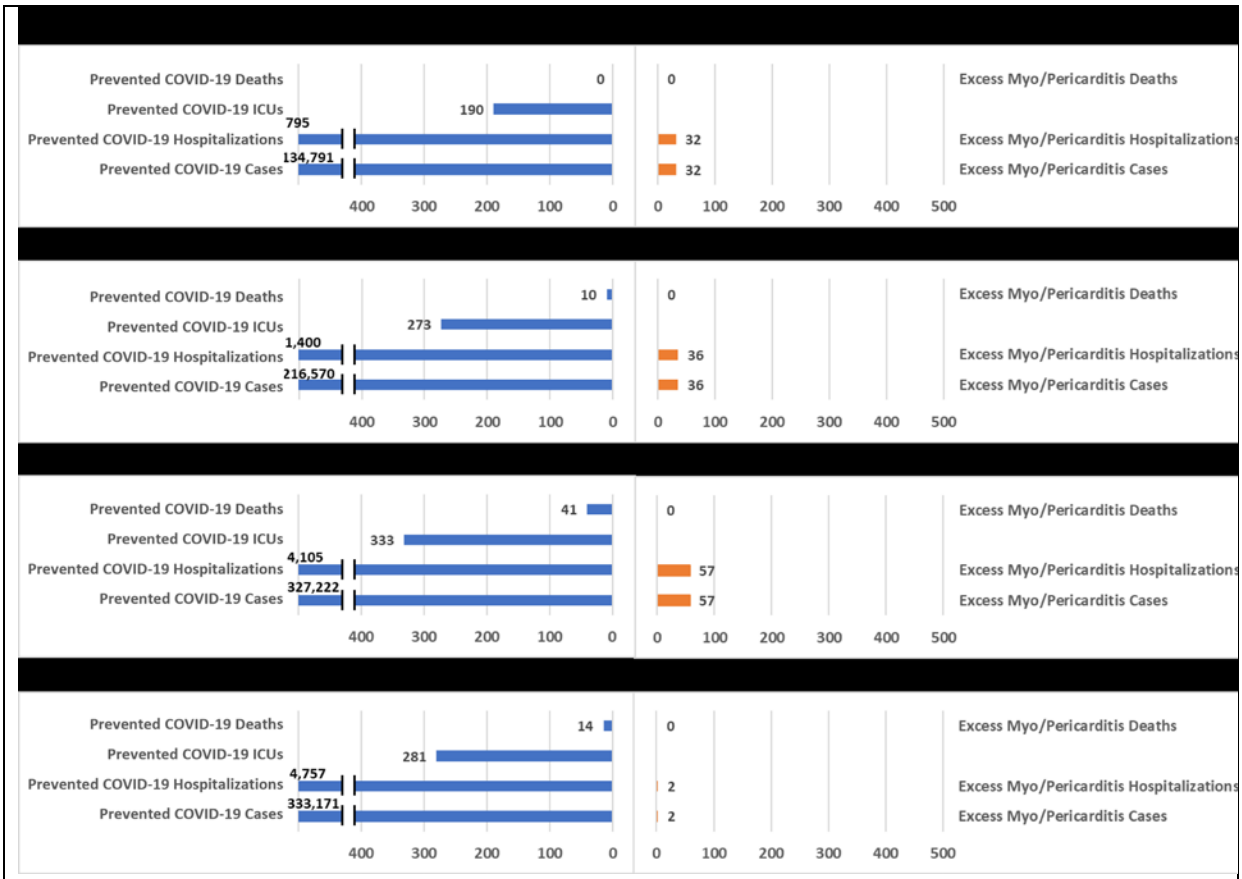


Figure S3: Results of Scenario 4 for the female population

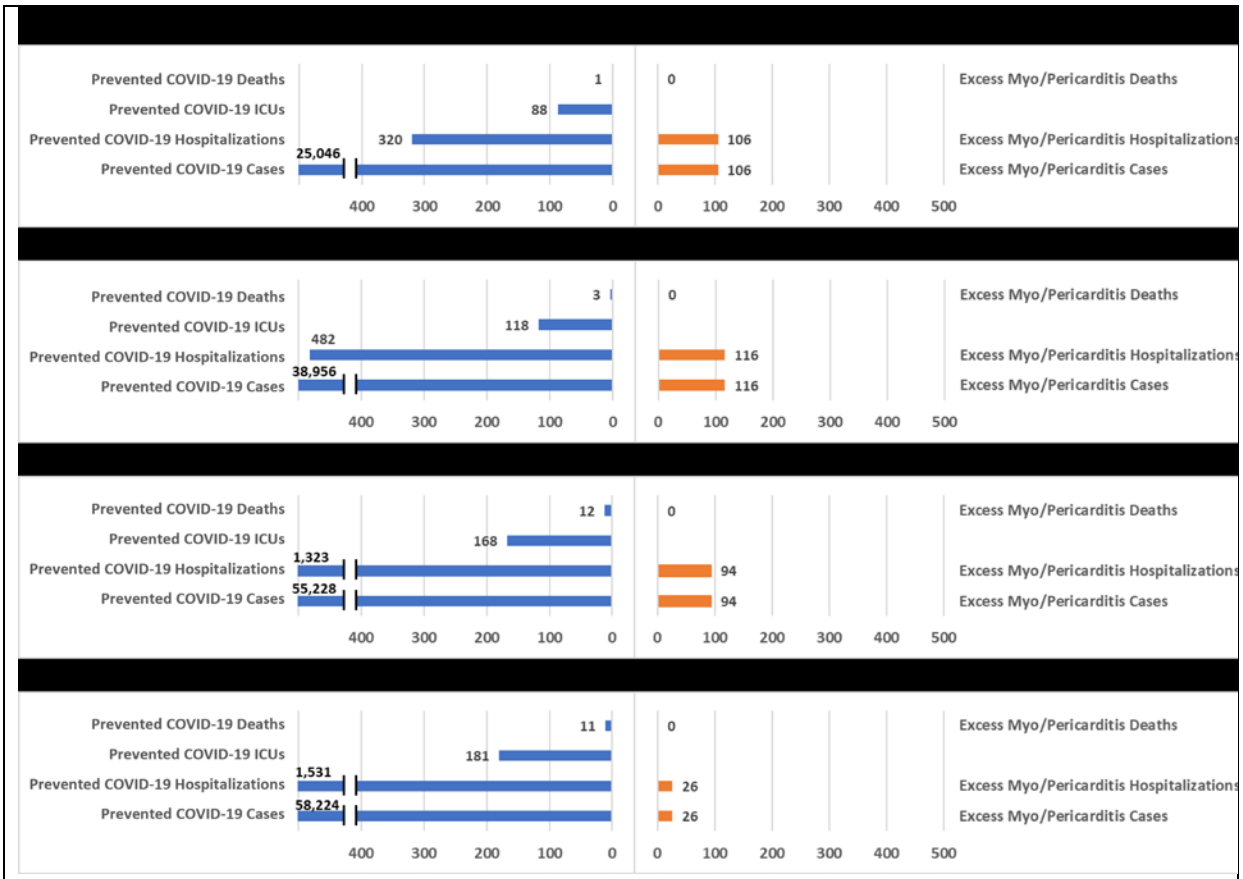


Figure S4: Results of Scenario 5 for combined male and female populations

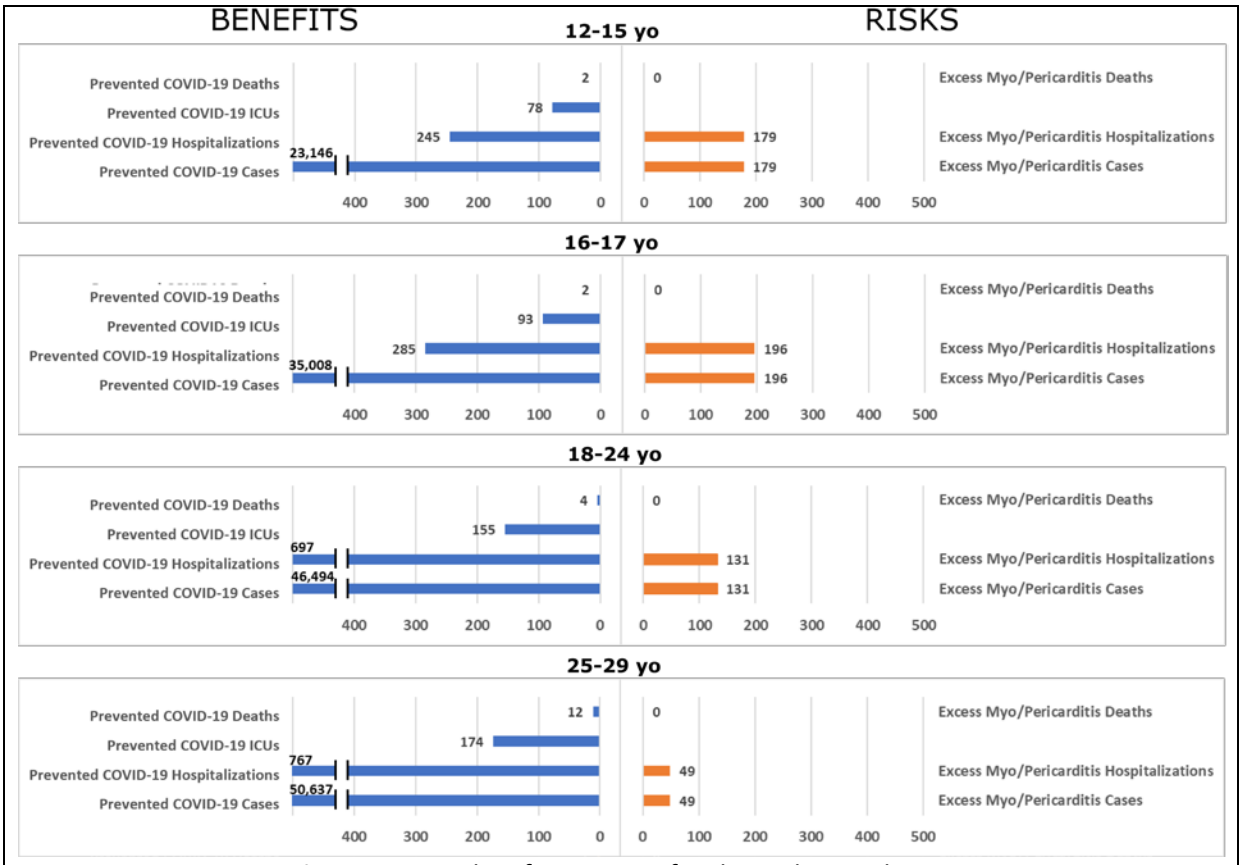


Figure S5: Results of Scenario 5 for the male population

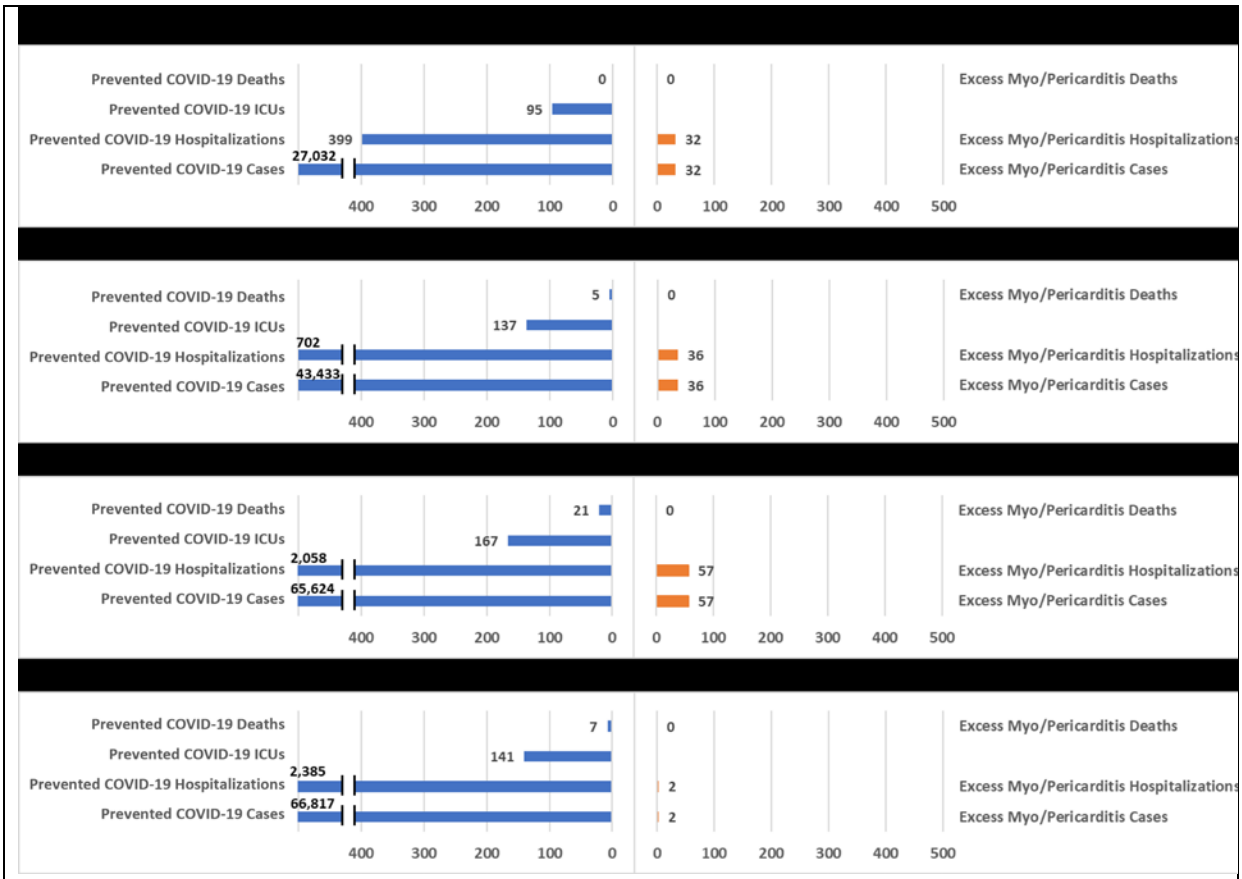


Figure S6: Results of Scenario 5 for the female population

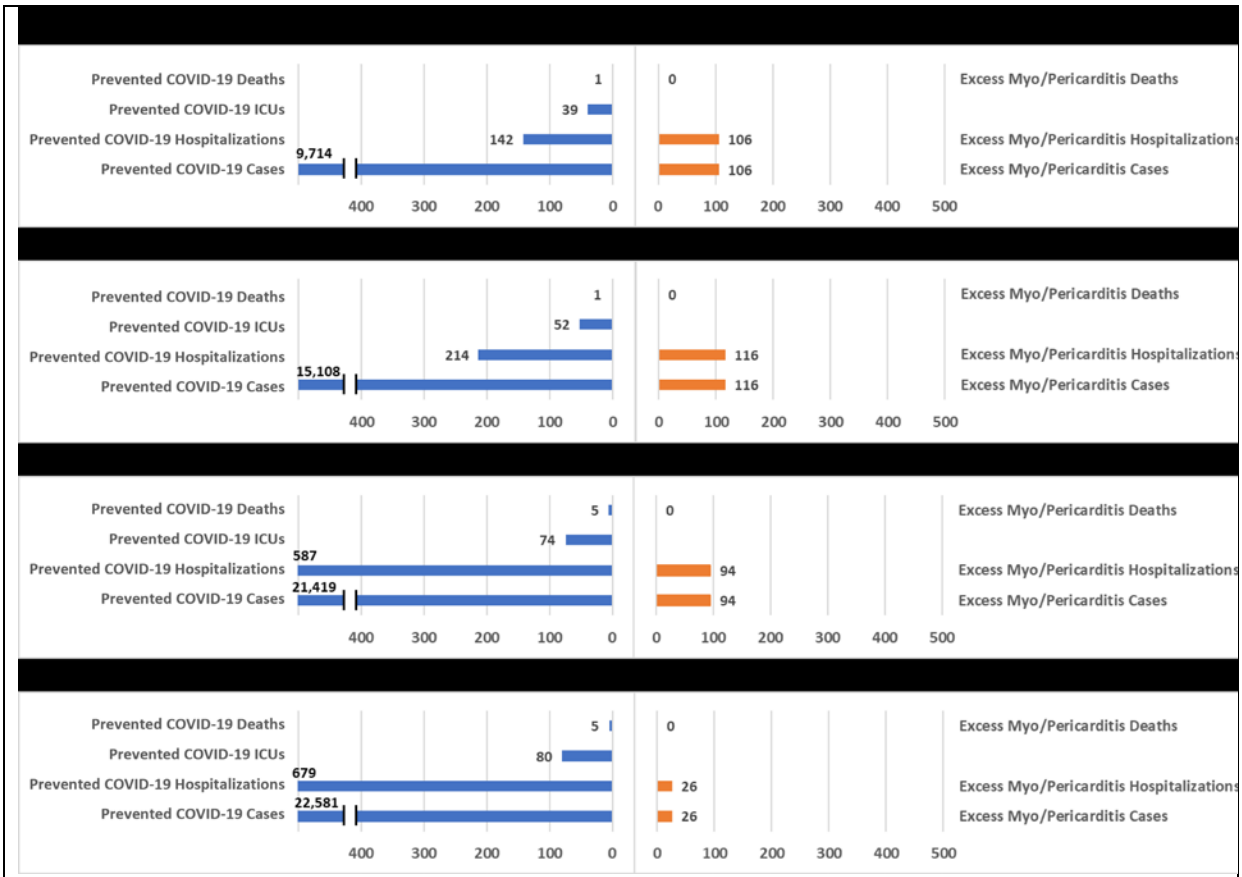


Figure S7: Results of Scenario 6 for combined male and female populations

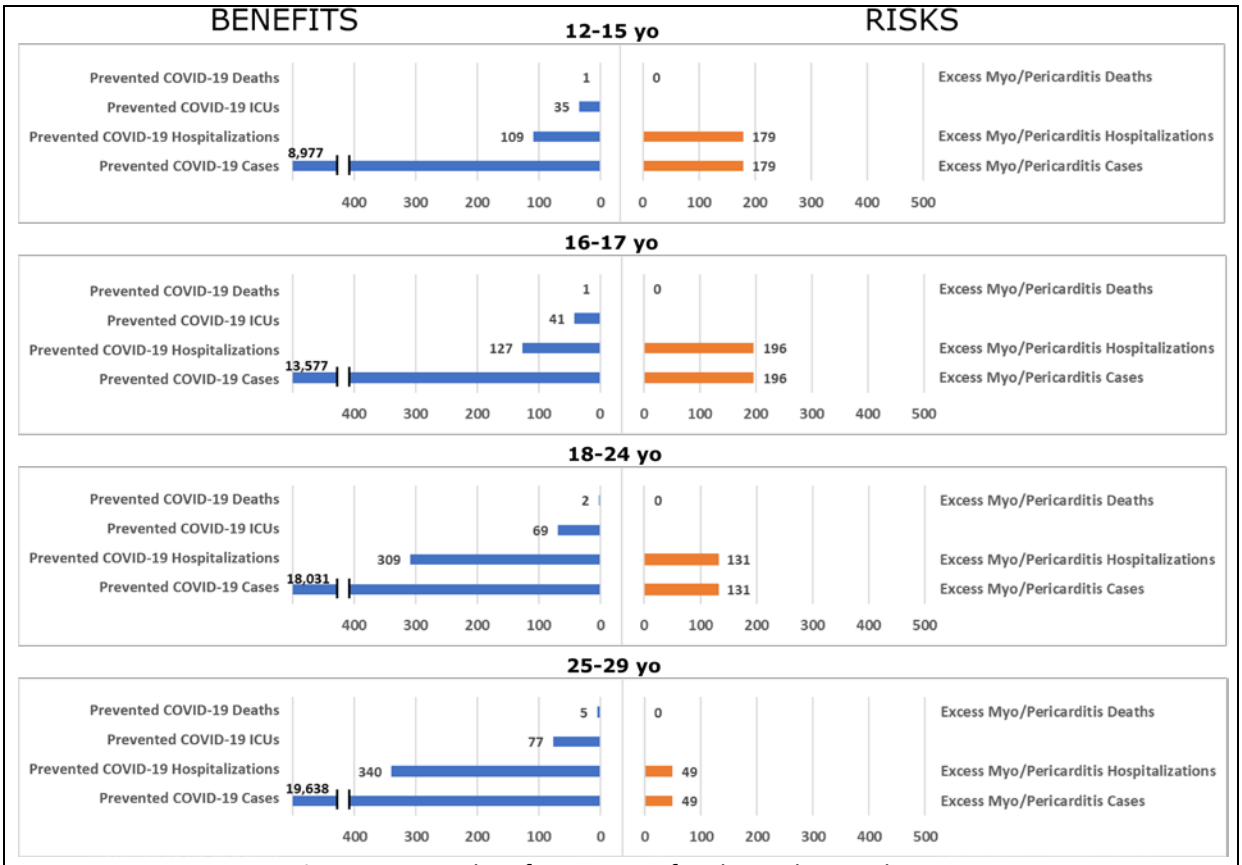


Figure S8: Results of Scenario 6 for the male population

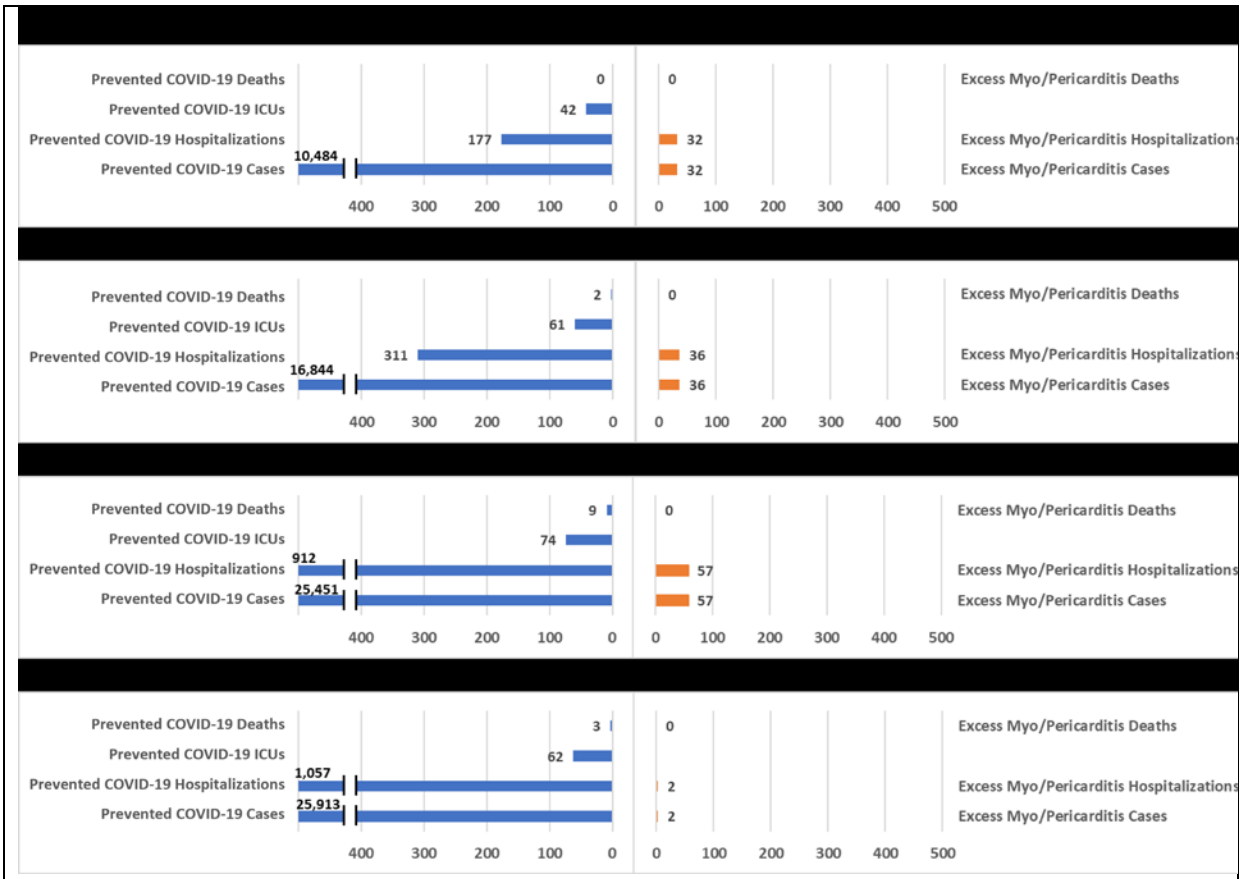


Figure S9: Results of Scenario 6 for the female population

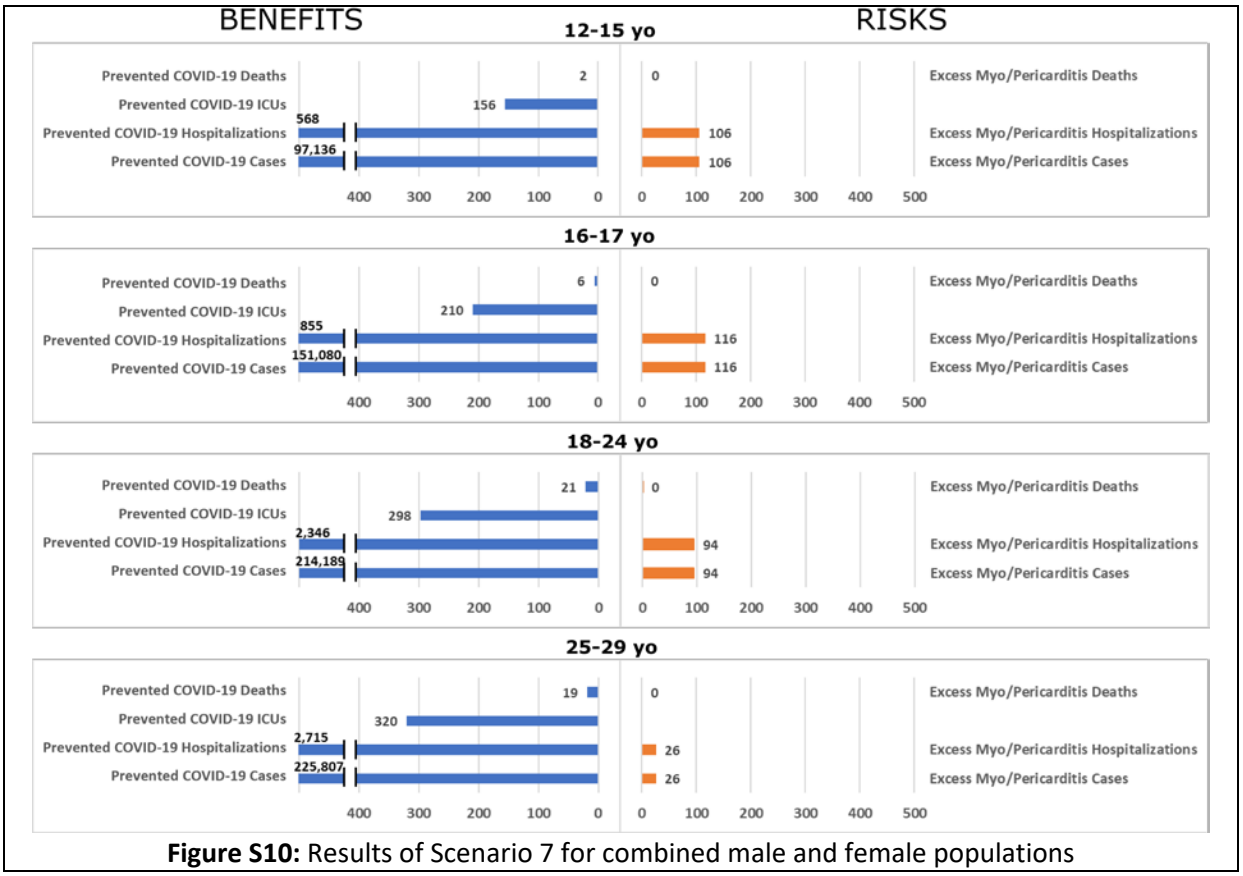


Figure S10: Results of Scenario 7 for combined male and female populations

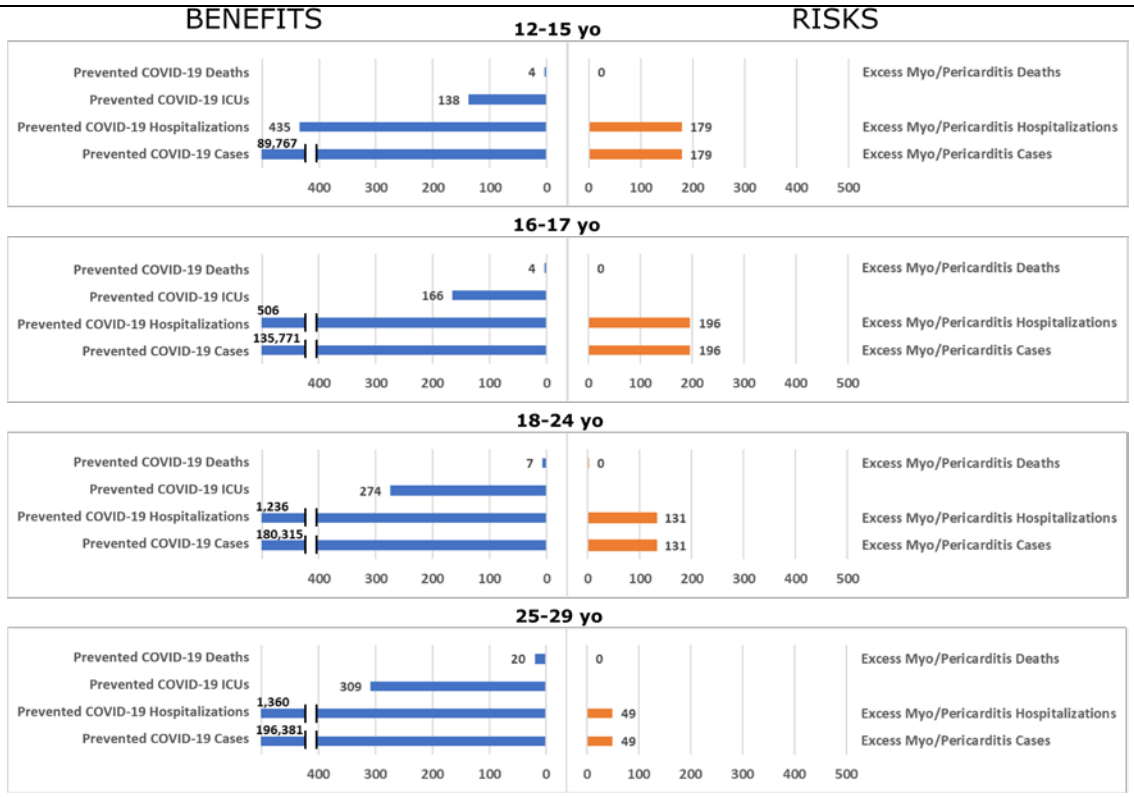


Figure S11: Results of Scenario 7 for the male population

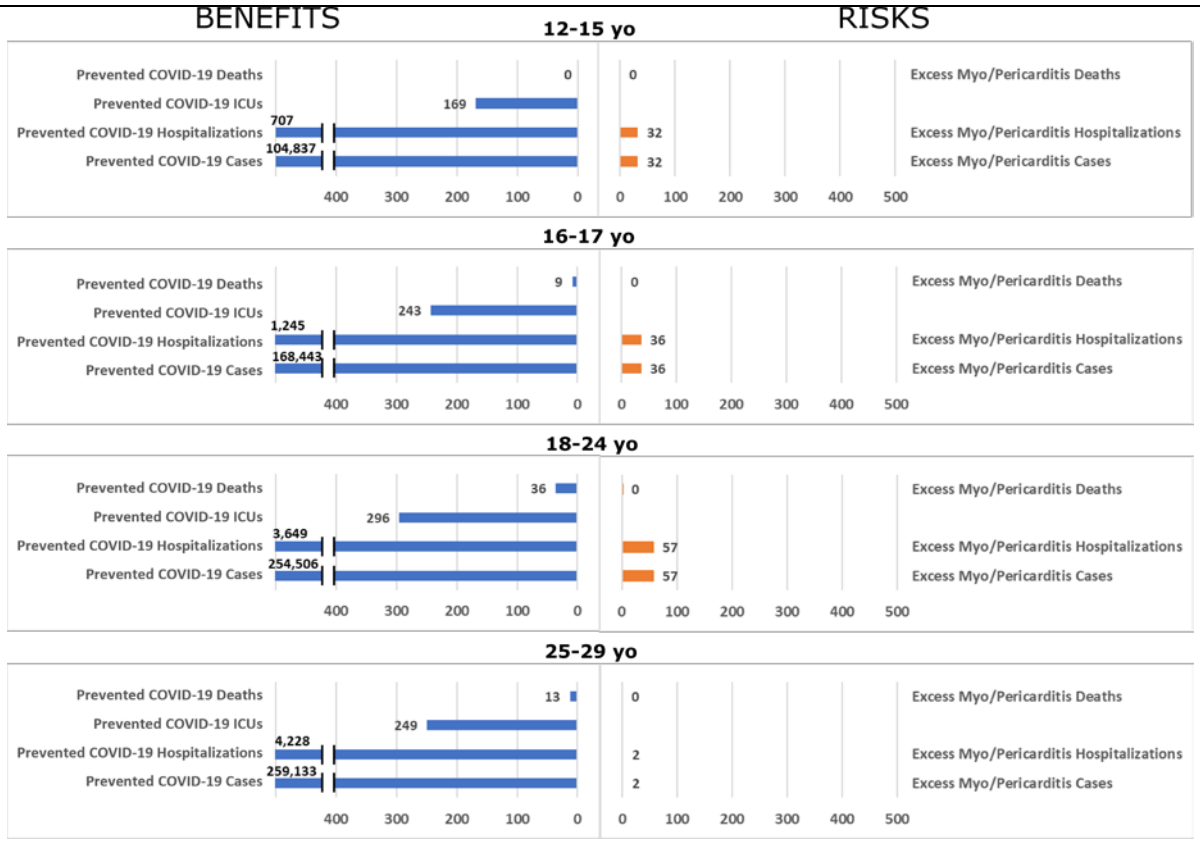


Figure S12: Results of Scenario 7 for the female population