Benefit-Risk Assessment to Inform FDA Regulatory Decision on COVID-19 Vaccine

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FDA Structured Benefit-Risk Framework (SBRF)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Therapeutic context

Product profile

Special Considerations for COVID-19 Vaccines (1)

- Given to large healthy population to prevent disease
- Low risk tolerance
- Direct individual benefit
  - Preventing disease and related short and long-term clinical consequence among vaccine recipients
- Public health benefit
  - Preventing disease transmission among the population
  - Reduce economic and societal impact from pandemic
- Risk-benefit distribution among the population
  - The adverse reactions of vaccine may occur among vaccine recipients, while the vaccine benefit extends beyond
- Importance of real-word evidence
  - Disease incidence, vaccine effectiveness, rare adverse effects

Special Considerations for COVID-19 Vaccines (2)

- **Emergency Use Authorization** (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19)
  - Public health emergency is declared by the Secretary of HHS
  - EUA allows an earlier access to Investigational New Drugs (INDs)
  - Incomplete clinical trial- smaller sample size, shorter follow up time, etc.
  - Post EUA requirements- continues phase III trials and safety follow-up, active/passive surveillance, etc.

- **Immuno-bridging to infer vaccine efficacy based on immune biomarker**
  - For extended indications: different age groups, dosing regimen, formulation, concomitant administration with other vaccines
  - Need to confirm vaccine effectiveness post-market

Quantitative Analysis to Support SBRF

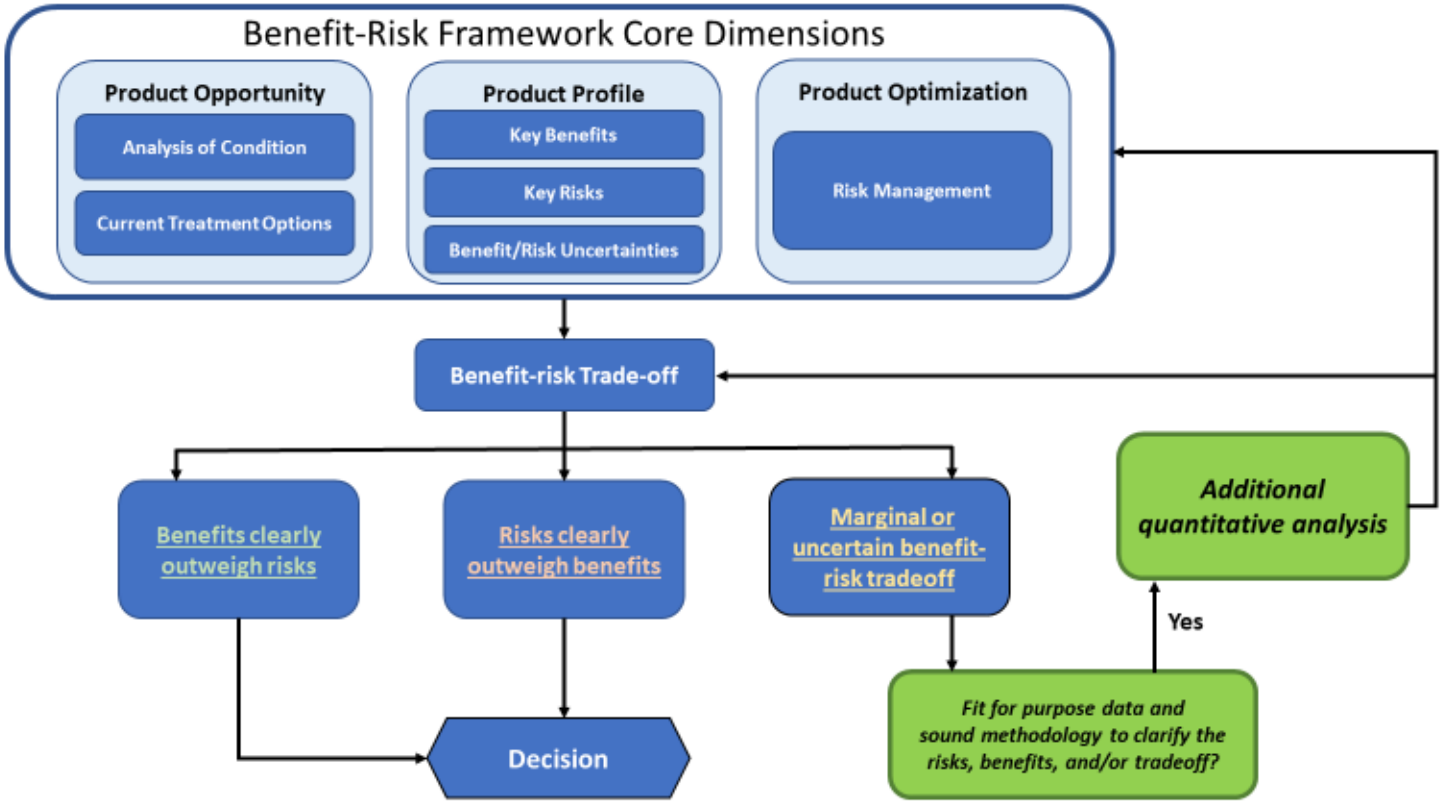


Figure. Decision tree for additional quantitative analysis in benefit-risk assessment for medical products

The Council for International Organizations of Medical Sciences (CIOMS) XII report, 2024

Benefit-Risk Assessment of COVID-19 Vaccine, mRNA (Comirnaty) for Age 16-29 years

Patrick R. Funk, Osman N. Yogurtcu, Richard A. Forshee, Steve A. Anderson, Peter W. Marks, Hong Yang

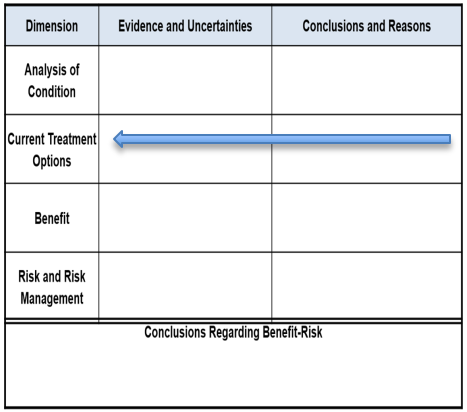
Vaccine, March 2022

Analysis of Condition

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

- 208 million cases and 4.3 million deaths worldwide by August 2021
- 90% cases among age 16 + years of age

Treatment Options



At time of analysis (August 2021)

- No licensed vaccines or anti-viral drugs for COVID-19

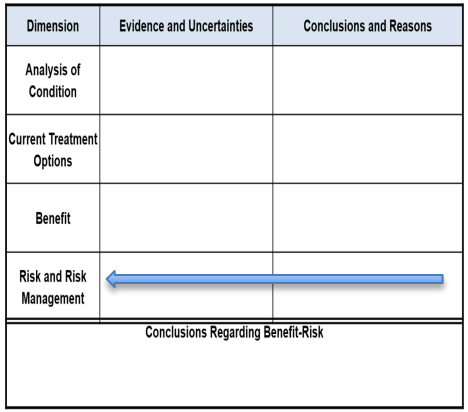
- EUAs of three vaccines:
  - Pfizer-BioNTech Vaccine for 16+ years of age
  - Moderna Vaccine for 18+ years of age
  - Janssen for age 18+ years of age

Benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit	←	
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

- Vaccine Efficacy against confirmed and severe COVID-19 after Dose 2 are 90% and 95%, respectively
- Real-world vaccine protection against disease depends on COVID-19 incidence and circulating virus strains
  - Uncertainty on direction of pandemic
  - Emerge of Delta variant

Risk and Risk Management



- No notable serious adverse events and deaths related to vaccination reported in clinical trials
- Elevated myocarditis/pericarditis case rate identified by post-EUA safety surveillance
  - Clinically significant risk
  - Higher risk among male adolescents
- Risk management options if vaccine is approved:
  - Product label
  - Post-market safety surveillance
  - Post-market requirement/commitment

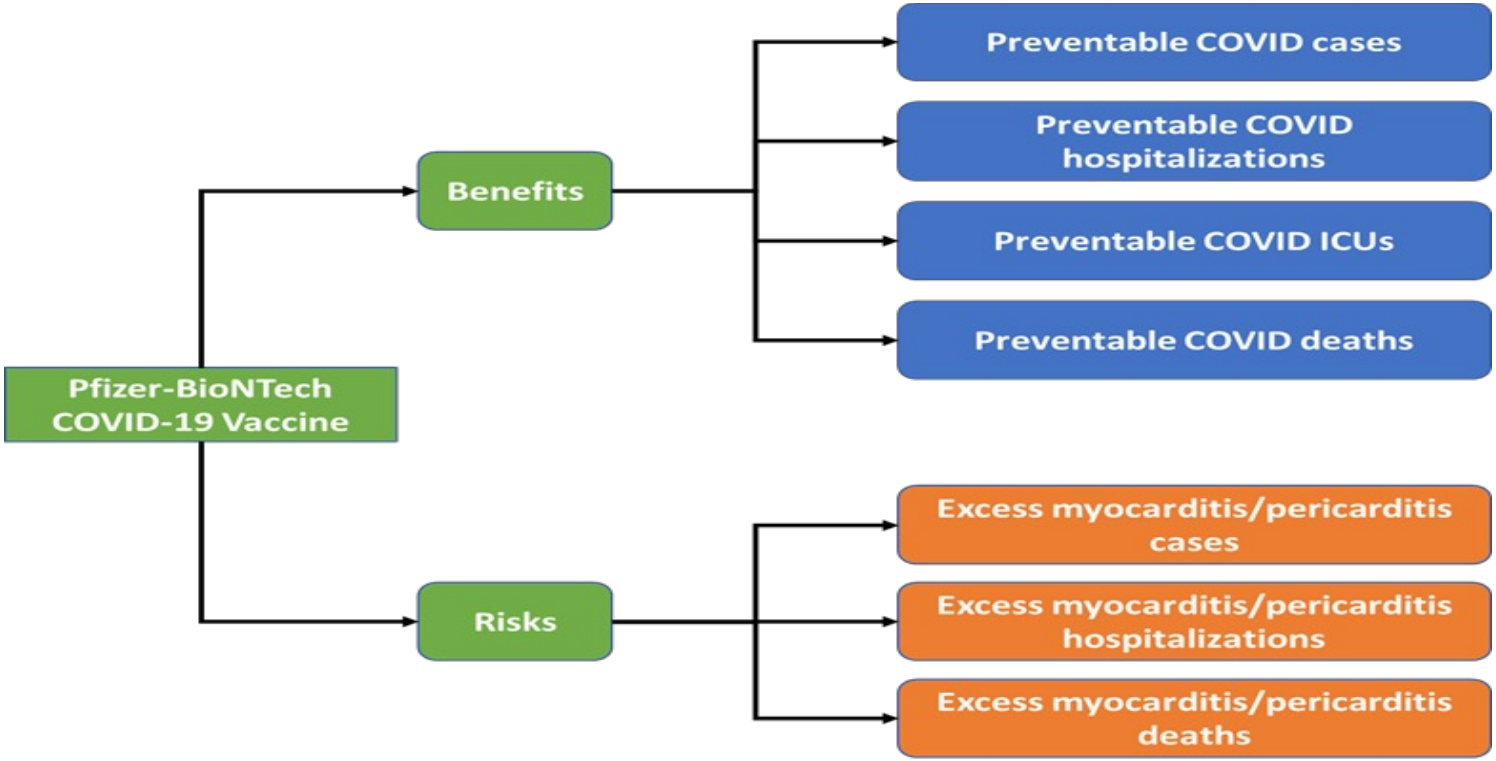
Review Challenges

- Elevated myocarditis/pericarditis case rate, especially among male adolescents
  - Inconsistent case rates and related deaths from limited sources of data

- Vaccine efficacy from clinical trial does not directly translate to vaccine benefit in real-world
  - Unknown direction of pandemics
  - Emerge of Delta variant and uncertainty on vaccine effectiveness

FDA Quantitative Benefit-Risk Assessment of Comirnaty COVID-19 Vaccine

(Per million with two-Doses of vaccine, age 16-18, 19-24 and 25-29 years)



Model Scenarios

Seven model scenarios evaluating the impact on benefits and risks of uncertain **vaccine effectiveness**, **dynamic of pandemic** and **myocarditis death rate**

Common Model Inputs

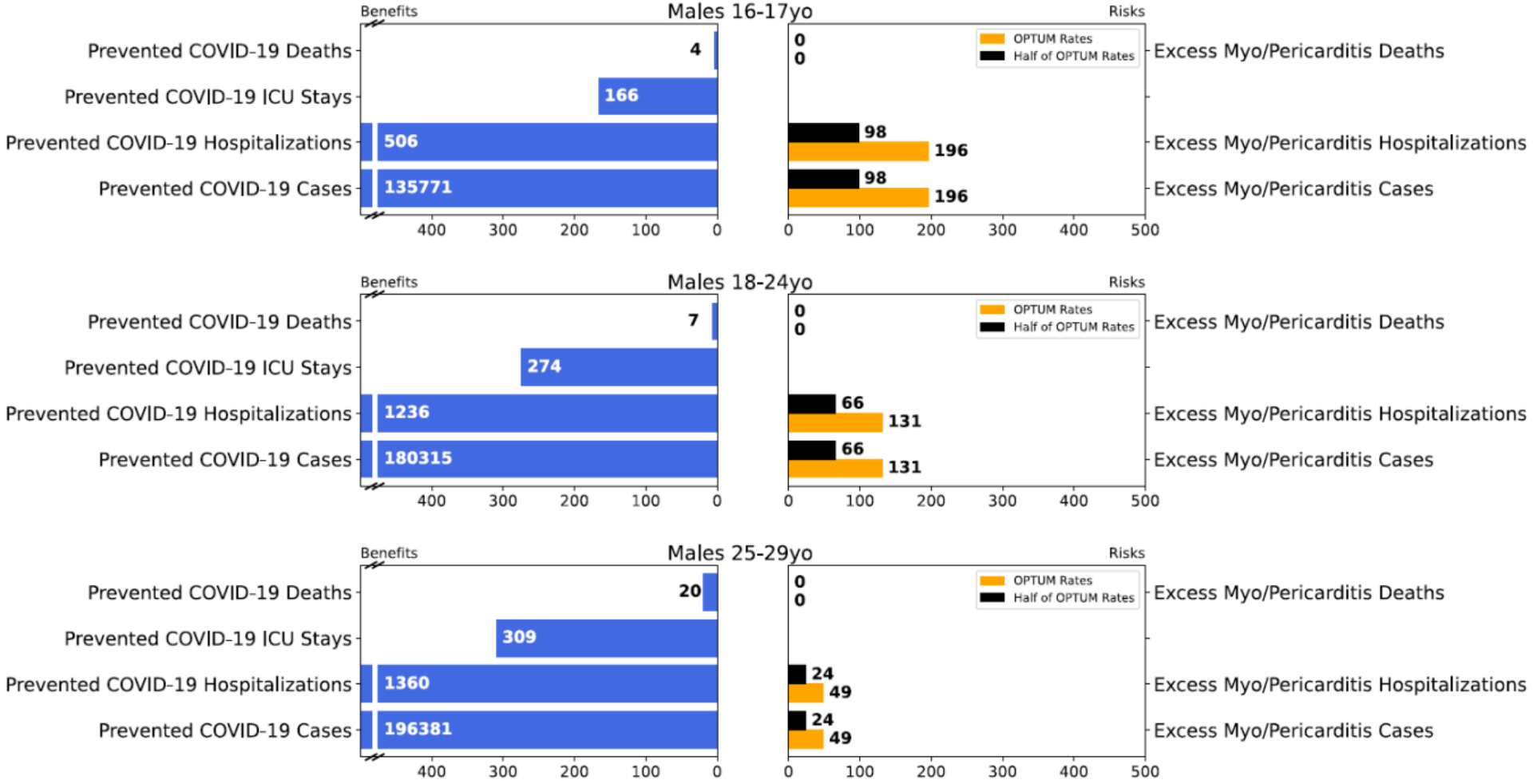
- Protection period[3]: 6 months
- Vaccine effectives[4] against
  - Cases 70%
  - Hospitalization 80%
- Myo/pericarditis rate[5]: FDA BEST/OPTUM and CDC VSD

Two Major Scenarios

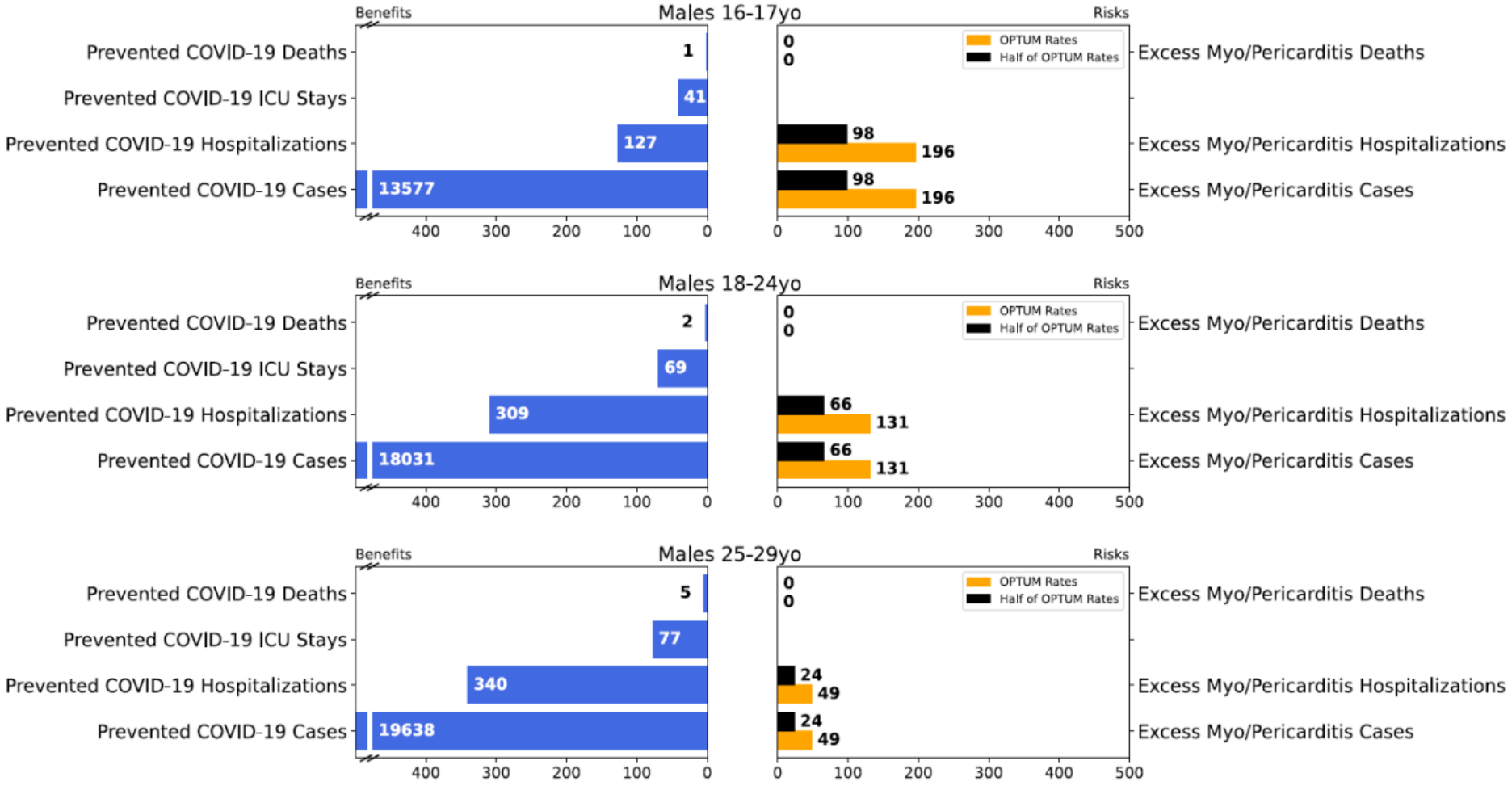
	COVID-19 case incidence[1]	COVID-19 hospitalization incidence[1]	Vaccine attributable myo/pericarditis death rate[2]
Most Likely Scenario	10x @July 10, 2021	4x @July 10,2021	0%
Pessimistic Scenario	@July 10, 2021	@July 10, 2021	0.002%

[1]CDC COVID NET & DataTracker, [2]VAERS data & assumption, [3]Assumption, [4]Real-world evidence, [5]FDA /BESTOPTUM data

Result- Most Likely Scenario (per Million)



Result- Pessimistic Scenario (per Million)



FDA Vaccines and Related Biological Products Advisory Committee, December 10, 2020

Question to VRBPAC:

Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older?

VRBPAC's Votes:

Yes = 17, No = 4, Abstain = 1

Conclusion Regarding Benefit-Risk

Benefits/uncertainty

- Direct benefits: greatly reduces COVID-19 cases, hospital stays, ICUs and deaths
- Indirect benefits: reduce long-term effect of COVID-19 infection, disease transmission, economic and societal impacts
- Uncertainty in dynamic of pandemic, new virus strain, waning of vaccine protection, vaccine protection for subpopulation with comorbidity

Risks/uncertainty and risk management

- Myocarditis and pericarditis risks
- Uncertainty on risks among age groups, long-term effect
- Post-market requirements/commitments: post-market studies and active surveillance on myocarditis/pericarditis

Trade-off and conclusion

- Known and potential benefits outweigh the known and potential risks
- FDA granted BLA approval to COMIRNATY in Nov. 2021

Acknowledgment

- Drs. Patrick Funk, Osman Yogurtcu, Richard Forshee contributed to benefit-risk modeling
- Comirnaty BLA review team's
- FDA BEST partners Acumen and Optum provided data on myocarditis/pericarditis cases
- CDC Vaccine Task Force shared COVID-19 data and information